Deep Brain Stimulation of Two Unconventional Targets in Refractory Non-Resectable Epilepsy

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Posterior hypothalamus · Caudal zona incerta

Abstract
Introduction: Several deep brain targets have been assessed for the treatment of unresectable refractory epileptic conditions. Adrian Upton in 1985 proposed deep brain stimulation (DBS) of the anterior nucleus of the thalamus for the treatment of seizures and psychosis [Cooper I.S., Upton A.R.: Biol Psychiatry 1985;20:811–813]. Francisco Velasco, in 1987, introduced DBS of the thalamic centromedian nucleus, proposing its employment for Lennox-Gastaut syndrome and for multifocal epilepsy. Other proposed targets are the subthalamic nucleus, caudate nucleus, Forel fields and mammillo-thalamic tract. We employed DBS for stimulating 2 ‘unconventional targets’, the posterior hypothalamus (pHyp) and caudal zona incerta (CZi), for the treatment of 2 patients with multifocal epilepsy and behavioural comorbidity, and 2 patients with sensorimotor focal seizures, respectively. Such patients did not meet criteria for resective surgery. Material and Methods: In our institution, between January 2003 and May 2004, we started DBS in 2 epileptic patients. The former patient was affected by multifocal epilepsy, and the second one by refractory partial motor and secondary generalized seizures. The chosen targets were the pHyp in the former case and the CZi in the latter. The encouraging results obtained led us to replicate such a favourable experience in 2 more patients, 1 with focal motor epilepsy once again (resulting in status epilepticus) and the other with behavioural comorbidity and multifocal epilepsy. Results: A significant reduction in seizure frequency was observed, and the 2 patients with behavioural comorbidity also showed a dramatic improvement in their disruptive behaviour. The patient with motor focal seizures showed a 70% reduction in seizure frequency, and in the last patient remission from status epilepticus was obtained. Conclusion: Our data confirm DBS of deep brain structures modulates the functional activity of the cerebral cortex as suggested by Adrian Upton in 1985. In the reported series, deep-brain stimulation of 2 unconventional targets belonging to the reticulo-cortical system (the brainstem-diencephalon functional system including structures that act as remote controls in modulating cortical excitability) was found to be effective in controlling otherwise refractory multifocal (pHyp) and focal sensorimotor (CZi) epilepsy when resective surgery was not feasible.

Introduction
Epilepsy is considered a clinical condition due to hypersynchronous discharges of cortical neuronal pools. Nevertheless, a significant amount of data [1–8] points to the role of subcortical structures that modulate the cortical activity and seizure threshold. The so-called ‘centren-
cephalic epilepsy' is possibly facilitated by altered interactions between the cortex and the subcortical structures. These considerations have led to many attempts to treat refractory epilepsy with deep brain lesions within the relay nuclei of the basal ganglia, including the centromedian nucleus of thalamus, the caudate nucleus, the subthalamic nucleus (STN) and the mesencephalic reticular formation. During the 1970s, stereotactic lesions were performed on many basal ganglia nuclei to treat unresectable and refractory epilepsy. Favorable results were often reported; however, the lack of homogeneous selection criteria and the amount and variety of the targeted anatomical areas made any kind of definitive conclusions and guidelines impossible. In spite of the preliminary attempts by Cooper and Upton [2] to perform neuromodulation in the treatment of refractory epilepsy, the surgical field of drug-resistant epilepsy remained strictly confined to the resection of the epileptogenic area. Refractory epilepsy due to multifocal epileptogenic foci or unresectable foci located in eloquent areas remained as 2 untreated fields until the introduction of vagal nerve stimulation (VNS) in the 1990s. The incidence of medically refractory patients, who cannot be treated by resective surgery, is estimated to be about 15% of all epileptic patients [3].

The deep brain stimulation (DBS) era, pioneered by Adrian Upton and Irwin Cooper [6] (1985) and Francisco Velasco [8] (1987) led to the reconsideration of some of the ‘old’ targets: the chronic stimulation of the anterior nucleus and centromedian nucleus of the thalamus have shown to be successful in patients affected by seizures of limbic origin, and by Lennox-Gastaut epilepsy and multifocal epilepsy, respectively. The chronic stimulation of anterior thalamic nuclei was effective in a heterogeneous population of refractory epileptic patients, and a multicentre trial was carried out to validate such a target (the SANTE study) [5]. Several case reports and small studies also suggested the therapeutic role of STN high-frequency stimulation (HFS) in simple partial motor and myoclonic seizures [1]. Potential indications for DBS may overlap the indications for VNS, which represents a less invasive procedure, and may act in a similar way through antidromic modulation of the brainstem and thalamic nuclei [9]. The improvement of resective surgery techniques and the results of VNS restrict the indications for DBS; nonetheless, the good results of the aforementioned studies open the way to exploring new deep brain targets, the stimulation of which could act as a kind of ‘remote control’ through the reticulo-cortical system [7].

Three years ago at our institute, we treated 2 patients identified respectively with multifocal epilepsy and refractory simple partial motor and secondary generalized seizures. The chosen targets were respectively the posterior-medial hypothalamus (pHyp) and the caudal zona incerta (CZi). The encouraging results obtained from these 2 patients led us to replicate the positive results in 2 more patients. In this paper, we detail the results obtained in these 4 patients, discuss issues regarding target choice and suggest a future perspective on DBS in the treatment of epilepsy.

**Material and Methods**

**Target Choices**

The pHyp was the target of choice for 2 patients affected by multifocal epilepsy. The rationale for this choice was based on the following reasons:

- Experimental data suggesting the control of seizures induced by posterior hypothalamus stimulation in the rat pentylene-tetrazol model [4].
- Comorbidity with disruptive behaviour that is known to benefit from pHyp DBS [10].
- Previous reports of seizure control obtained by radio-frequency lesions within the pHyp in refractory epileptic patients [11].
- Evidence of involvement of the tuberomammillary region of the hypothalamus in the post-ictal seizure protection phenomenon in rats [12].

The CZi was targeted in 2 patients affected by refractory seizures originating in the frontal motor cortex. The rationale for this choice was based on the following reasons:

- Previously reported experience of successful stimulation of the STN. In fact, Benabid et al. [13] targeted the STN nucleus with a posterior trajectory through the posterior subthalamic area, which lies very close to the CZi. We avoided the direct stimulation of STN nucleus itself to avoid the well-known behavioural implications of STN stimulation in Parkinson’s disease patients [14].
- CZi connections to the thalamic and subthalamic nuclei involved in the control of movements and frontal motor cortex [15, 16].
- Experimental data suggesting the modulating role of CZi stimulation on the motor cortical system [17].

**Patients**

Patient 1 is a 36-year-old man who suffered from birth anoxia followed by a progressive cognitive and motor delay and myoclonic epilepsy which began in early childhood. No concomitant genetic or metabolic pathologies were disclosed. At the age of 21 years, he began to present atonic and myoclonic seizures, both of which were followed by falls. In the same period, he developed disruptive behaviour with regard to both people and objects. Secondary generalized tonic-clonic seizures were also observed. The interictal EEG performed at that time showed independent multifocal spikes. Medical treatment, including neuroleptics (chlor-
promazine, thioridazine, clotiapine) and antiepileptics (carbamazepine, clonazepam, phenobarbital, valproate), was not effective. At 25 years, this patient’s behaviour and his epilepsy worsened until 2 years before admission at our institute. He started alternating between episodic rages with acting out and a drug-induced drowsiness. Cerebral MRI showed mild T1 and T2 signal alteration of the basal frontal cortex. Blood examinations disclosed liver failure suggestive of the toxic effects of medication. This is the clinical picture that led us to perform a pHyp deep brain stimulation.

Patient 2 is a 28-year-old right-handed woman who was admitted to our institute for post-traumatic drug-resistant epilepsy. When she was 6 months old, she sustained a severe head injury. Focal motor seizures involving the left hemibody were observed and antiepileptic treatment was started (phenobarbital). At the age of 11 years, seizure frequency dramatically increased from monthly to more than daily. Her seizures were characterized by an initial sensation of ‘electric’ current involving the left upper limb, followed by clonic jerks with a Jacksonian march without the loss of consciousness. Despite various antiepileptic drugs (phenobarbital, carbamazepine, valproic acid, phenytoin, lamotrigine), seizure frequency did not decrease.

The patient was admitted to our institute when she was 25 years old. The neurological examination revealed a mild left hemiparesis. At that time, seizures still occurred daily and an average of 180 episodes per month was reported. The brain MRI showed a large intracerebral malacic area, primarily involving the right frontal lobe and, partially, the primary motor cortex. The electroclinical data suggested the involvement of the primary sensory motor cortex in the genesis of the seizures. For this reason, the surgical resection of the epileptogenic cortex was not considered. Instead CZi DBS was suggested for this patient.

Patient 3, 20-year-old male, experienced the onset of seizures at the age of 2 years, when his parents started to notice the presence of episodes of sudden laughter with involuntary contractions of the left hemiface and homolateral gaze deviation. Subsequently, episodes of sudden loss of consciousness with falls began to appear. He underwent neurological and neuropsychological examinations, and the diagnosis of partial cryptogenetic epilepsy was made. Brain CT and MRI were normal. EEG disclosed bilateral independent paroxysmic activity in the central regions of both hemispheres. With time, seizures assumed a multi-weekly frequency and persisted despite many pharmacological attempts (valproate, carbamazepine, phenobarbital, phenytoin, carbamithium, topiramate) to control them. A psychological evaluation documented the presence of a severe psychotic syndrome that tended to evolve into heteroaggressive and disruptive behaviour towards people and objects. The mean frequency of 3 times a week for generalized seizures with sudden loss of consciousness and falling was established; the mean frequency of 8 per day for seizures with sudden laughing and involuntary contractions of the left hemiface and homolateral gaze deviation was observed. According to the electroclinical features, resective surgery was not indicated while pHyp DBS was considered.

Patient 4, a 22-year-old woman, in whom the disease began at the age of 18 years with focal myoclonic jerks of the right facial muscles that soon resulted in epilepsy partialis continua. A brain MRI showed a mild left fronto-polar atrophy. After one year, despite antiepileptic drug treatment and subsequent high-dose steroids, the symptoms worsened with the appearance of a mild right facial motor deficit. A repeat brain MRI showed slight progression of the left focal atrophy. Four years later, the patient developed a focal motor status epilepticus. Neurological deficits were still limited to a mild paresis of the right face and of the ipsilateral upper limb with pyramidal signs. EEG recordings showed slow focal activities entered on the fronto-central regions. In order to control epilepsy partialis continua, the patient was admitted to an intensive-care unit and high doses of benzodiazepine were administered. Plasmapheresis cycles and medical treatment including azathioprine and IgM vena cycles were unable to control seizures. Cortical and subcortical biopsies of the left frontal lobe were suggestive of Rasmussen encephalitis. Given the good level of cognitive, motor and language functions, we decided to perform a left CZi DBS.

Surgery
Before intervention, a brain volumetric high-definition MRI was performed; this allowed us to obtain a precise visual localization of the anterior commissure/posterior commissure line. At the time of surgery and under general anaesthesia, the patients underwent positioning of the Leksell G frame. A volumetric (2 mm thick) brain CT was obtained under such stereotactic conditions. CT and MR were then merged together using an automated technique based on a mutual-information algorithm (Framelink 4.0, Stealth Station; Medtronic, Minn. USA).

The coordinates of the electrode tip for targeting the posterior hypothalamus were: 5 mm below the midcommissural plane (z), 3 mm behind the commissural point (y) and ± 2 mm lateral to the midline (x). The coordinates of the electrode tip for targeting the CZi were: 2 mm below the midcommissural plane (z), 6 mm behind the midcomissural point (y) and ± 13 mm lateral to the midline (x).

For the hypothalamic target, 2 four-contact electrodes (3389; Medtronic) were inserted through a 3-mm coronal paramedian twist-drill hole (fig. 1) for each patient.

For the CZi target, a monolateral parieto-occipital trajectory was chosen (fig. 2) for each patient.

The stimulation was bilateral for pHyp and unilateral for CZi.

For the localization of both pHyp and CZi, we relied on: (1) indirect targeting by the determination of target coordinates registered at the midcommissural point on the Schaltenbrand and Wharen atlas for CZi and on the Franzini atlas for pHyp [10]; (2) final targeting adjustment by visualization of the simulated trajectories and target areas on merged pre-operative MRI and CT images obtained with the Framelink 4 software; (3) intraoperative microrecording of single units activity: for pHyp we principally relied on our previous observations of a periodical burst pattern of discharge at around 17 Hz in the posterior hypothalamic region in pathological aggressive patients [Cordella et al., in press], and for CZi we relied on previous reports about the discharge pattern of such anatomical regions previously reported in Parkinson’s disease patients [18].

We performed scalp EEG in patient 3 during surgery (this was the only case in which we performed such an examination); it demonstrated an abrupt disappearance of epileptic spikes from fronto-polar and temporal cortex (fig. 3) after macrostimulation at the planned anatomical target on the right side with the following parameters: 2.0 mA, 90 μs, 100 Hz, contact 0 as cathode and contact 1 as anode.
Fig. 1. a–c Post-operative brain CT/MRI merged examinations of patient 3, treated with bilateral pHyp DBS. d Axial section of the Franzini atlas at 5 mm below the anterior commissure/posterior commissure plane showing the location of the electrode's active contacts on both sides (Medtronic 3389; contact number 0) in the pHyp (brown) as little white crosses on red circles. Relationships with the red nucleus (RN; pink) and the STN (cyan) are shown. ZI = Zona incerta.
In all cases, after surgery the post-operative stereotactic CT was merged with the pre-operative MRI to confirm the correct electrode placement and to locate the exact position of each contact with respect to the planned target. All of the post-operative radiological examinations confirmed that the planned portion of the lead transfixed the intended target volume. Subclavicular pulse generators (Soletra, Medtronic) were then placed and connected to the subcutaneous lead, which were subsequently connected to the definitive brain electrodes.

The active contacts were 0 and 1 for pHyp chronic stimulation and 2 and 3 for CZi chronic stimulation (fig. 1, 2). The choice of the active contacts was planned before surgery according to the trajectory and the final position of the electrode tip (fig. 1), so that the electrode ‘transfixed’ the anatomical volume of interest.

After the intervention, the patients underwent regular monthly follow-up visits during the first 3 months after surgery and then every 3 months thereafter. At each visit, different stimulation amplitudes were tried in order to obtain an optimal seizure control level. The stimulation parameters were 90 μs, pulse width, 100 Hz (patient 4) and 185 Hz (patients 1–3) and 1.5–3.5 V. The only parameter that was changed with time was the amplitude, which was progressively increased, while concomitantly checking for side effects, which we observed to be a medial ocular deviation of the ipsilateral eye at voltages higher than 4 V in patients 1 and 3 (pHyp) and contralateral upper limb paresthesias at voltages higher than 3 V in patients 2 and 4 (CZi). We did not observe any adverse effects at the therapeutic stimulation parameters. At the end of the stimulation adjustment period, the chosen stimulation parameters were:

- Patient 1: 1.5 V, monopolar with contacts 0 and 1 as cathodes, 90 μs, 185 Hz (pHyp).
- Patient 2: 2.0 V, monopolar with contacts 1 and 2 as cathodes, 90 μs, 185 Hz (CZi).
- Patient 3: 3.5 V, monopolar with contacts 0 and 1 as cathodes, 90 μs, 185 Hz (pHyp).
- Patient 4: 2.0 V, monopolar with contacts 1 and 2 as cathodes, 90 μs, 100 Hz (CZi).

**Results**

For all 4 patients, the results were collected by daily seizure diaries kept and constantly updated by parents who could also carefully observe any current changes in the patient’s pathological behaviour (particularly in cases 1 and 3).

**Postero-Medial Hypothalamus**

**Case 1.** After the intervention (2003), and then at the 3-month follow-up visit, the parents reported remission of aggressive and disruptive behaviours toward people, but the persistence of disruptive behaviour towards objects. During the first month, secondary generalized sei-
seizures had disappeared. The other seizures started to decrease gradually and progressively in intensity and frequency over time, starting in the first month after surgery (30% reduction), until a total of a 75% reduction of seizures was obtained at a 6-month interval. This percentage of improvement related to both the myoclonic seizures and the atonic seizures with falling was stable within a year after surgery. The entire symptomatology began to worsen after the depletion of the battery of the implanted pulse generator in 2007. The initial positive results recurred when the batteries were surgically replaced.

Case 3. Intraoperative scalp EEG showed the disappearance of epileptic spikes from the fronto-polar and temporal cortex (fig. 3). One month after the intervention (July 2007), the behaviour consistently improved with the disappearance of aggressive bouts. At the 2-month follow-up, gelastic seizures had completely disappeared. Complex partial seizures started to improve from the second month after surgery (30% reduction), and at 6 months they decreased by 80%; the number of seizures with falling began to decrease by the third month after surgery (40% reduction) until an 80% reduction was reached at 6 months. This level persisted after 9 months.

Caudal Zona Incerta

Case 2. After the intervention (2004), the patient started to improve from the first month (reduction by 20% of the frequency of partial motor seizures) and then progressively over time. At 6-months post-intervention, the reduction was 70%. The stable improvement was observed at the 1-year follow-up visit: the overall rate of seizures had decreased by 85%. The left hemiparesis was observed to be unchanged over time and no worsening had occurred.

Case 4. Immediately after the intervention (November 2007), the status epilepticus ceased, and scattered episodes of partial motor seizures of the right hemiface and upper limb still occurred daily (being controlled by benzodiazepines). The patient became conscious and was dismissed from the intensive-care unit, assisted ventilation was no longer required. The total amount of antiepileptic drugs was also reduced, but the patient still presents with several hemifacial motor seizures unaffected by the electrical stimulation. This is in contrast to the dramatic effect of DBS in relieving the status epilepticus, but related to the persistence of the inflammatory encephalitis that was confirmed by an open biopsy of the frontal cortex.

In terms of quality of life, improvement was even higher in both groups. The decrease of falling seizures was so high in the 2 patients who underwent pHyp stimulation that both were able to regain a sort of autonomy in walking and personal attendance. The first patient was able to attend a therapeutic community due to the reduction of both epileptic seizures and the bouts of violent behavior, which had occurred independently. The second pHyp-stimulated patient obtained a consistent control of seizures and a dramatic improvement in terms of his violent aggressive behaviour.

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Table 1. Clinical and neuroradiological seizure characteristics and follow-up of the operated patients (numbered as in the text)

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Etiology</th>
<th>Age at surgery years</th>
<th>Neurologic examination</th>
<th>Type of seizure</th>
<th>MRI</th>
<th>Follow-up</th>
<th>Post-operative seizure reduction rate %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>post-anoxia</td>
<td>36</td>
<td>severe cognitive impairment; intractable aggressiveness</td>
<td>atonic and myoclonic followed by falls</td>
<td>bilateral basal frontal cortex atrophy</td>
<td>5 years</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>head injury</td>
<td>28</td>
<td>mild left hemiparesis</td>
<td>left focal motor</td>
<td>right posterior frontal encephalomalacia</td>
<td>4 years</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>idiopathic</td>
<td>20</td>
<td>severe cognitive impairment; intractable aggressiveness</td>
<td>gelastic; versive, loss of consciousness and falls</td>
<td>normal</td>
<td>9 months</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>Rasmussen encephalitis</td>
<td>22</td>
<td>mild paresis of the right face and ipsilateral upper limb</td>
<td>epilepsy partialis continua</td>
<td>progressive left fronto-polar atrophy</td>
<td>6 months</td>
<td>status epilepticus disappearance</td>
</tr>
</tbody>
</table>

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The first of the CZi-stimulated patients regained autonomy in daily activities and started to attend school again; the second cZI stimulated patient was able to be withdrawn from assisted ventilation in the intensive-care unit, where she had been placed for over 2 months due to the need for major sedation to control status epilepticus.

Results on seizure control, follow-up and stimulation parameters are summarized in table 1 and figure 4.

**Discussion**

We reported the results of DBS on 2 different targets with different therapeutic indications and results. The findings of this protocol may, in the future, be compared to those obtained by VNS that is nowadays considered the treatment of choice in almost all of refractory unresectable epilepsy syndromes.
Our results suggest HFS DBS of ‘centrencephalic’ targets (characterized by widespread cortical projections) as a viable treatment able to control seizures in conditions such as status epilepticus of Rasmussen encephalitis. The HFS of CZi also allowed long-term improvement of partial motor seizures in the patient affected by long-lasting post-traumatic epilepsy originating from the motor cortex. The target choice in these 2 cases was based on a literature review and analysis, mostly from data of the so-called ‘lesional’ era that targeted the main motor pathways (such as posterior limb of the internal capsule) and the sensory pathways (ventro-lateral nucleus of the thalamus) to treat epilepsy partialis continua [19].

The CZi lies posterior to the STN, close to the Forel fields and beneath the lemniscal fibers and the pyramidal motor bundle within the cerebral peduncle and superiorly to the substantia nigra (fig. 2). The zona incerta receives afferents from globus pallidus internus, substantia nigra pars reticulata [16, 20] and several cortical areas [15], and is considered as one of the relay stations of the ascending reticular activating system [16, 21–23]. The zona incerta sends efferents to the specific thalamic nuclei [21], to the basal ganglia output nuclei [20] to the reticular thalamic nuclei [24] and to the mid-brain extrapyramidal area [20]. The chronic electrical stimulation of this area may interact with all these systems, and may modulate the threshold of epileptic seizures of the somatosensory cortex [5]. We cannot rule out that the chronic stimulation of other deep brain targets would be equally effective in the control of this kind of seizure (e.g. STN, the centromedian nucleus, VL and mesencephalic reticular formation).

In our opinion, the stimulation of brain structures that interact with the reticulo-thalamo-cortical pathways (the reticulo-thalamo-cortical system has been hypothesized to include some diencephalic and mesencephalic structures that interact to modulate the degree of vigilance and the cortical excitability) [7, 25, 26] may modify the threshold of epileptic seizures introducing a ‘noise’ signal into the network that controls cortical neurons activity and synchronization. The radio frequency lesions of the past were neutralized over time by the development of new circuits and a sort of neural plasticity, which abolished the therapeutic role of the stereotactic lesions. The effects of DBS seem to be more difficult to neutralize, as demonstrated by the long-standing positive results obtained in the treatment of movements disorders. Our choice of implanting an electrode within the CZi was supported by its critical role in the modulation of the somatosensory cortex and by the aim of searching for a node of a complex bidirectional network where therapeutic levels of electrical stimulation could be delivered without the induction of major side effects, including interactions with the limbic system, which may happen with STN HFS [14]. The posterior approach was preferred to optimally involve the CZi, which lies posterior to STN, and to avoid trajectories through the frontal cortex (mostly affected by encephalitis in one case, and altered by traumatic and post-surgical scaring in the second case).

The choice of target in the second group of patients was easier because of the need to treat the specific behaviour of comorbidity in both patients. Moreover, the data of Sano et al. [11] clearly suggest the involvement of pHyp in the control of multifocal epilepsy. It must be noted that recently reported experimental data confirms the role of pHyp in the control of seizures due to the activation of histaminergic projection on the cortex [12]. In the experimental model, the antiepileptic effect of pHyp stimulation gave superior results, whether in reference to the stimulation of the anterior thalamus or to the stimulation of the mammillo-thalamic tract. Our results confirmed the hypotheses at the origin of target choice. Both the value and safety of the reported targets for DBS in 2 different patterns of refractory epilepsy are noted. In conclusion, we consider the positive results obtained in this small group of patients as a prerequisite to plan a prospective study to evaluate HFS DBS in selected patients with refractory unresectable epilepsy, i.e. CZi DBS in patients with focal sensorimotor seizures and pHyp DBS in patients with behavioural comorbidity and/or multifocal seizures.

We are well aware, however, that DBS should be confined nowadays to extremely severe epileptic conditions; nevertheless, it may become a valid alternative to VNS if the overall results are confirmed in a larger study of patients. New ‘unconventional’ targets could potentially be identified and available, with expected results possibly superior to the rates of expected seizure control currently obtained by VNS [27] (which is 50% seizure reduction in 50% of treated patients) in medically refractory patients who cannot be treated by resective surgery.
References