Deep brain stimulation of the posteromedial hypothalamus: indications, long-term results, and neurophysiological considerations

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Object. The aim of this study was to review the indications for and results of deep brain stimulation (DBS) of the posterior hypothalamus (pHyp) in the treatment of drug-refractory and severe painful syndromes of the face, disruptive and aggressive behavior associated with epilepsy, and below-average intelligence. The preoperative clinical picture, functional imaging studies, and overall clinical results in the literature are discussed.

Methods. All patients underwent stereotactic implantation of deep-brain electrodes within the pHyp. Data from several authors have been collected and reported for each clinical entity, as have clinical results, adverse events, and neurophysiological characteristics of the pHyp.

Results. The percentage of patients with chronic cluster headache who responded to DBS was 50% in the overall reported series. The response rate was 100% for short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing and for chronic paroxysmal hemicrania, although only 2 patients and 1 patient, respectively, have been described as having these conditions.

None of the 4 patients suffering from refractory neuropathic trigeminal pain benefited from the procedure (0% response rate), whereas all 5 patients (100%) affected with refractory trigeminal neuralgia (TN) due to multiple sclerosis (MS) and undergoing pHyp DBS experienced a significant decrease in pain attacks within the first branch of cranial nerve V. Six (75%) of 8 patients presenting with aggressive behavior and mental retardation benefited from pHyp stimulation; 6 patients were part of the authors' series and 2 were reported in the literature.

Conclusions. In carefully selected patients, DBS of the pHyp can be considered an effective procedure for the treatment of refractory trigeminal autonomic cephalalgias, aggressive behavior, and MS-related TN in the first trigeminal branch. Only larger and prospective studies along with multidisciplinary approaches (including, by necessity, neuroimaging studies) can lead us to better patient selection that would reduce the rate of nonresponders. *(DOI: 10.3171/2010.5.FOCUS1094)*

Key Words   •   posterior hypothalamus   •   deep brain stimulation   •
cluster headache   •   aggressive behavior   •   trigeminal autonomic cephalalgia

Deep brain stimulation of the pHyp was the first application in which the choice of target was motivated by neuroimaging functional data.[28] Activation of the pHyp during cluster headache pain attacks was observed during PET,[38] the original observation that led to the placement of deep brain electrodes within the pHyp to

inhibit the pathologically activated neuronal pool in patients with CCH.

The targeted brain volume for chronic high frequency stimulation within the pHyp was really the same target that Sano and colleagues[44] used in 1966 in using radiofrequency lesions to treat pathologically aggressive and disruptive behavior.

These 2 observations supported the rationale for the choice of pHyp DBS in patients affected with severe pain syndrome of the face and in patients presenting with disruptive behavior.

Since the first reported series in 2003,[16] several authors have used chronic stimulation of the pHyp to treat rare and severe syndromes refractory to conservative therapies. More specifically, the series reported in the literature include 51 patients affected with CCH,[3,6,11,14,31,45,47]

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8 patients with aggressive and disruptive behavior,[20,23,26] 5 patients with TN due to demyelinating disease,[18] 2 patients affected by SUNCT,[29,32] 1 patient with CPH,[53] and 4 patients with neuropathic pain of the face (Table 1).[18]

Although the overall number of patients surgically treated since the first pHyp implant is not very large, we can analyze a consistent amount of data from either published studies or our own experience. The topics addressed and discussed here are focused on the main aspects of pHyp DBS, including indications, percentage of responders, long-term results, side effects, and hypotheses about the mechanisms of its action.

Posterior Hypothalamus DBS for CCH

General Considerations

Cluster headache is characterized by disabling, strictly unilateral painful attacks mostly perceived in the retroorbital area. These headaches are accompanied by autonomic signs such as miosis, lacrimation, conjunctival injection, nasal congestion, and rhinorrhea. The prevalence of the disorder is estimated to be < 1%, and it mostly affects males (M/F ratio between 2.5 and 7.1).[34,50] Fischera et al.[13] reported a lifetime prevalence of 124 cases per 100,000 persons and a 1-year prevalence of 53 cases per 100,000 persons.

Pain attacks typically last 15–180 minutes, occur daily, and are continuous or spaced out by remission periods of < 1 month.[22] In contrast, in the episodic form, attacks occur during a period ("cluster period") of 6–12 weeks interrupted by remission periods lasting up to 12 months.

Conventional conservative treatment of CCH consists of prophylactic therapy (verapamil, methysergide, lithium carbonate, melatonin, gabapentin, sodium valproate, and corticosteroids) and abortive therapy (triptans, inhaled 100% oxygen, indomethacin, and opiates). In 10–20% of patients with CCH, conservative therapy does not satisfactorily control the symptoms, and so pain attacks become severely debilitating.[25]

Inclusion Criteria for DBS in the Literature

The reports published in the literature include 46 patients with drug-resistant CCH who underwent surgical intervention with DBS of the posterior hypothalamic area and whose follow-up examination data are available.[3,6,11,14,31,45,47] The report of 1 of these studies[11] is an abstract, and so the study is not considered in this review. Thus, the number of patients in our review is 44.

Initial guidelines for inclusion criteria for DBS of the pHyp in CCH were proposed by Leone et al.:[30] 1) the presence of diagnostic criteria for CCH according to the International Headache Society;[22] 2) inadequate relief from prophylactic therapy, including verapamil, lithium, sodium valproate, methysergide, topiramate, gabapentin, nonsteroidal antiinflammatory drugs such as indomethacin, and corticosteroids; and 3) CCH lasting at least 2 years, with strictly lateralized pain attacks. Sillay and coworkers[47] expanded this criteria by also including: 1) at least 6 debilitating headache episodes per week rated by patients as at least 6 on a visual analog scale of 1–10; 2) unsatisfactory relief from abortive therapy, including oxygen, sumatriptan, and opioids; 3) failure of occipital nerve stimulation therapy for at least 1 year; and 4) completion of daily headache diaries over a period of 1 month prior to surgery. The latter criterion should be considered as strictly dependent on the design of the study that these authors performed in 2009.[47]

Exclusion criteria included the following: 1) general

TABLE 1: Summary of literature on studies published to date on pHyp DBS*

Authors & Year	No. of Patients	Pathology	pHyp Stereotactic Coordinates			Mean FU (mos)	No. of Responders
			X	Y	Z		
Leone et al., 2008	16	CCH	±2	−3	−5	48	10
Fontaine et al., 2010	11	CCH	±2	−3	−5	10	6
Bartsch et al., 2008	6	CCH	±2	−3	−5	17	3
Sillay et al., 2010	5	CCH	±2	−3	−5†	11	3
Schoenen et al., 2005	4	CCH	±2	−6	−8	14.5	2
D'Andrea et al., 2006	3	CCH	±2	−3	−5	30	2
Brittain et al., 2009	2	CCH	±2	−6	−8	11	2
Leone et al., 2005	1	SUNCT	±2	−3	−5	60	1
Lyons et al., 2009	1	SUNCT	±2	−3	−5	12	1
Walcott et al., 2009	1	CPH	±2	−3	−5	18	1
Franzini et al., 2009	6	AB	±2	−3	−5	36	4
Hernando et al., 2008	1	AB	±2	0	−2	18	1
Kuhn et al., 2008	1	self-mutilation	±2.5	−2	−2.5	4	1
Franzini et al., 2007	5	TN in MS	±2	−3	−5	41	5
Franzini et al., 2008	3	neuropathic TP	±2	−3	−5	4	0

* AB = aggressive behavior; FU = follow-up; TP = trigeminal pain.
† Authors refined the site of the intended target by locating it 4–5 mm posterior to the mammillothalamic tract and medial to the anterior border of the red nucleus.

or neurological pathological conditions increasing the risk of positioning of deep brain electrodes, such as intraparenchymal lesions, coagulopathy, severe cardiological or pulmonary diseases, or the need for anticoagulant drugs; 2) inability to perform brain MR imaging; 3) pregnancy; and 4) severe or inadequately treated psychiatric comorbidity.

Among the studies published, the main criterion for defining a patient as "a responder" to DBS was a 50% reduction in the frequency or intensity of pain attacks.

Case Studies

Belgian Study. Schoenen and coworkers[45] enrolled 6 patients for DBS treatment who had fulfilled the following criteria: 1) age of 25–55 years; 2) CCH persisting for 2 or more years; 3) 4 or more attacks per week; 4) resistance or intolerance to adequate trials with verapamil, steroids, methysergide, lithium, and/or ergotamine; and 5) no disabling medical or psychiatric disorders.

French Multicenter Study. Fontaine et al.[14] conducted a systematic study aimed at assessing the efficacy of DBS of the pHyp for the treatment of severe and drug-refractory CCH. The study was a prospective, double-blind crossover trial including 11 patients selected on the following criteria: 1) disease duration > 3 years; 2) resistance to drug treatment with up to 960 mg/day of verapamil, plasma levels of lithium ranging from 0.6 to 1 mEq/L; 3) daily pain attacks; 4) absence of substance abuse or dependence; 5) age of 18–65 years; 6) normal brain MR imaging studies; and 7) no contraindications to surgery or anesthesia.

German Study. Bartsch et al.[3] described 6 patients who were considered eligible for DBS according to the above-mentioned criteria established by Leone et al.[30]

British Study. Brittain and coworkers[6] reported on 2 patients fulfilling the diagnostic criteria for CCH who underwent the implantation of deep brain electrodes in the pHyp.

American Study. Sillay and coworkers[47] reported on 8 patients who submitted to DBS for CCH, although follow-up data were available for only 5 of them. The inclusion criteria consisted of an extended version of those suggested by Leone in 2004[30] and have been mentioned before.

Italian Study. Our center detailed the first series in 2003,[16] and since then 16 patients with CCH have undergone DBS. Our inclusion criteria to date have been as follows: 1) diagnosis of CCH made by 2 independent neurologists specializing in headaches; 2) conservative prophylactic and abortive treatments already tried in adequate dosages both alone or in combination therapy (verapamil, lithium carbonate, methysergide, valproate, topiramate, gabapentin, melatonin, pizotifen, indomethacin, and steroids); and 3) normal neuroradiological examination, including brain CT, MR imaging studies of the craniocervical junction, and venous angiographic sequences. It is important to note that since 2005, we have also included chronic stimulation of the greater occipital nerve

for the therapeutic algorithm; the dual-channel IPG that is implanted can be later connected to the DBS electrodes in case of inefficacy of peripheral nerve stimulation.

Among the 16 patients who were surgically treated, 14 were men and 2 were women; the mean duration of the chronic phase of CCH was 2 years. All of our patients suffered from multiple daily pain attacks and had tried all of the aforementioned drugs, alone or in combination, without benefit. The prolonged use of steroids in some patients had produced some severe drug-related complications such as chronic intestinal bleeding, bone demineralization with aseptic necrosis of the femoral head, fluid retention with heart failure, arterial hypertension, weight increase, psychosis, and glaucoma.

Surgery and Target Choice

The surgical planning described here is used at our institute.

The planning procedure is performed with the aid of a Leksell head frame (Eleckta) with the patient under local anesthesia. A preoperative set of MR images (generally axial, volumetric, fast spin echo inversion-recovery T1-weighted with Gd and T2-weighted sets) is obtained to acquire high-definition images for precisely defining the location of anterior and posterior commissures and midbrain structures below the commissural plane (mammillary bodies and red nucleus). Magnetic resonance images are then merged with CT scans obtained under stereotactic conditions after positioning the head frame. The fusion of the 2 imaging sets is performed using an automated technique based on a mutual-information algorithm (Frame-link 4.0, Sofamor Danek Stealthstation, Medtronic). The merged images as well as every single slice of the imaging set were coregistered with the Schaltenbrand stereotactic atlas to obtain AC-, PC-, and MCP-related coordinates in millimeters.

After the stereotactic procedure, bilateral (Soletra, Medtronic, Inc.) or dual-channel monolateral (Kinetra, Medtronic, Inc.) IPGs are positioned into subclavicular subcutaneous pockets and connected to brain electrodes for chronic electrical stimulation.

Postoperative brain CT or MR imaging constitutes a useful tool both for assessing the accuracy of electrode placement and correlating the extent of the clinical benefit or adverse effects. The two sets of images can be merged, taking advantage of the lower degree of image distortion with CT and the more precise defined gray-white matter boundaries provided by MR imaging.[12]

Belgian and British Studies. Coordinates for the pHyp were 2 mm lateral to midline, 6 mm behind the MCP, and 8 mm below the intercommissural plane, according to indications by Leone et al. as reported in 2001.[28]

French Multicenter Study, German Study, and Italian Study. Coordinates were 2 mm lateral to the midline, 3 mm posterior to the MCP, and 5 mm inferior to the midcommissural plane.

American Study. The initial stereotactic coordinates were 2 mm lateral to the midline, 3 mm posterior to the MCP, and 5 mm inferior to the midcommissural plane,

but the authors refined the site of the intended target by locating it 4–5 mm posterior to the mammillothalamic tract and medial to the anterior border of the red nucleus by visualizing the region of interest using 1.5-T brain MR imaging.

The posterior hypothalamic target addressed by these coordinates was the same volume that was lesioned by Sano and coworkers in 1970.[43] Anyway, it is important to consider that in 1 previously described patient,[17] the targeting procedure based exclusively on the MCP or AC-PC plane was the basic cause of electrode misplacement, and such misplacement was due to the anatomical variability of the angle between the brainstem's major axis and the intercommissural plane. To correct this problem we took into account a new anatomical landmark that was incorporated into the final targeting procedure; we named this landmark the "IPP."[20] It is localized in the apex of the interpeduncular cistern 8 mm below the AC-PC plane at the level of the maximum diameter of the mammillary bodies. The definitive coordinates of the target, taking into account this correction point, were 2 mm lateral to the midline, 2 mm posterior to the IPP (instead of 3 mm posterior to the MCP), and 5 mm below the AC-PC plane (Fig. 1). A dedicated program and atlas have been developed and are freely available on the Internet to help in choosing the proper coordinates of this target (http://www.angelofranzini.com/BRAIN.HTM).

Intraoperative Microrecordings in the pHyp

Single-unit recordings are performed through a high impedance microelectrode to corroborate the neuroanatomical maps planned to target the nucleus of interest. This method is currently used to map the subthalamic nucleus (that is, in Parkinson disease), thalamic nuclei (that is, in pain), and the globus pallidus (that is, in dystonia). To date, such is not the case for the pHyp. In fact, just a few papers have dealt with the electrophysiological properties of pHyp neurons in pain[3,7,19,40,41,45] and behavior disorders.[8,23] Moreover, just a few have attempted to quantify the firing discharge properties;[3,8,9,40] the remaining illustrated only the raw electrophysiological traces.[20,23,41,45]

Microrecordings within the pHyp were performed in proximity to the stereotactic coordinates as suggested by us in 2003—specifically, 2 mm lateral to the commissural line, 3 mm posterior to the MCP, and 5 mm below the commissural line. All authors recorded single-unit activity with the patients fully awake and in a pain-free state. Cordella et al.[8] have described data sampled within the pHyp of 2 patients with behavioral disorders, both under general anesthesia due to the difficulty in controlling their behavior.

All data sampled in patients with TACs describe a low-frequency, tonic, and nonoscillatory discharge pattern (Fig. 2A). Differences occurred in the mean firing rate: Cordella et al.[9] described a mean discharge rate of 24 Hz in 3 patients; Bartsch et al.,[3] a mean firing rate of 17 Hz (range 13–35 Hz) in 6 patients; and Sani et al.,[40] a mean firing rate of 13 Hz in 6 patients. The firing discharge did not show variations as to tactile, motor, autonomic, and emotional stimulations in all of the tested neurons.

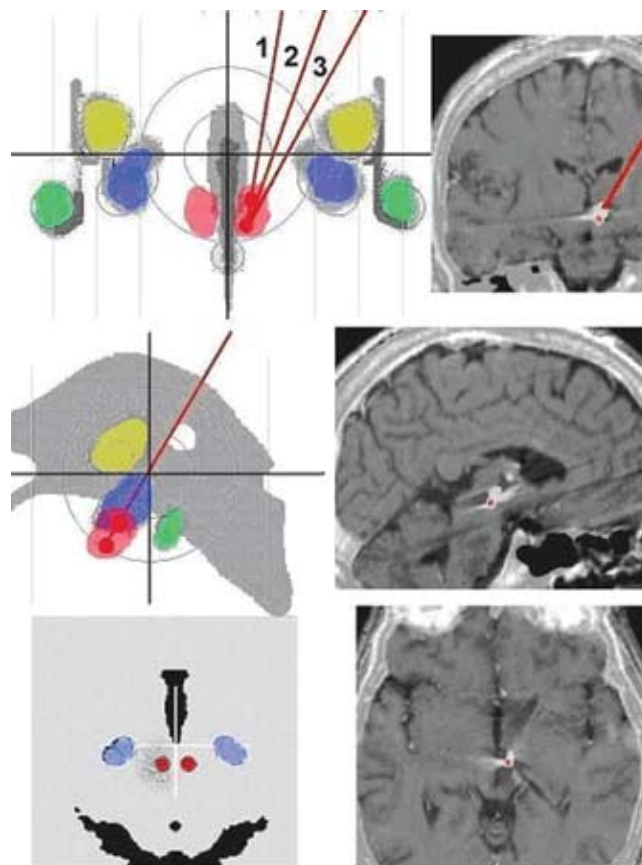Recently, Brittain et al.[6] recorded LFPs within the

Fig. 1. **Left:** Virtual ventriculography plates showing the target (pHyp: *pink* and *red*) in coronal *(upper)*, sagittal *(center)*, and axial *(lower)* sections as part of surgical planning. Trajectories are numbered 1, 2, and 3 in the anteroposterior ventricular representation showing the different angles used to reach the target. Trajectories can change according to the ventricular shape and dimensions and the presence of vessels within the precoronal frontal cortex at the entry point. **Right:** Postoperative CT images merged with preoperative MR images showing the definitive location of an electrode in coronal *(upper)*, sagittal *(center)*, and axial *(lower)* planes.

pHyp of 2 patients with CCHs. The LFPs represent aggregate synaptic activity within the vicinity of the DBS macroelectrode, whereas microelectrodes typically represent the action potential firing of isolated neurons. In 1 of these 2 patients, it has been possible to record data during a cluster attack. The pain attack was associated with an increase in the relative LFP power and specifically a distinct 16- to 22-Hz peak in neural activity. The presence of a specific neural rhythm was the first direct evidence of pHyp involvement during the cluster pain as indirectly described in neuroimaging studies.[40] It is relevant that the stereotactic coordinates used to target the pHyp in this latter report were distinct from those previously mentioned and were 6 mm posterior, 2 mm lateral, and 8 mm inferior to the MCP. This difference, along with the intrinsic differences between the single-unit recordings and the LFPs, might be a reason for the dissimilarities between the various reports.

Cordella et al.[8] described single-unit activity in 2 patients affected by behavioral disorders. In 1 patient who also had traumatic brain injury, the discharge pattern had
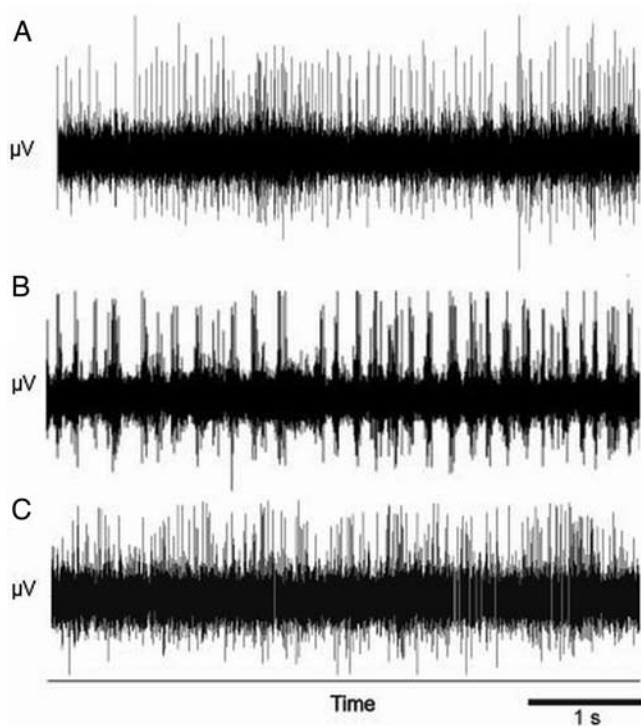
Fig. 2. Oscilloscope snapshots from intraoperative pHyp microrecording. **A:** Trace showing a low-frequency, tonic, nonoscillatory discharge pattern in a patient affected by CCHs. **B:** Trace showing a low frequency rate (19 Hz) discharge pattern with phasic oscillations at around 7–8 Hz in a patient with aggressive behavior associated with multifocal refractory epilepsy. **C:** Trace showing a low-frequency (10 Hz) discharge pattern in a patient with aggressive behaviors and traumatic brain injury. Tonic activity without significant oscillations is evident.

a low-frequency rate (10 Hz) and was tonic with no oscillations. In the other patient, who presented with gelastic epilepsy associated with behavioral disorder, there was a low-frequency rate (19 Hz) with phasic oscillations at around 7–8 Hz (Fig. 2B and C).[8] These findings might suggest how the discharge pattern of neurons in the pHyp should be evaluated with reference to the presence of concurrent pathology or behavioral states. Nevertheless, the number of analyzed units remains small. Indeed, the statement of any pathophysiological hypothesis is still hazardous and likely to sound like mere speculation; however, it is possible to safely make some observations. 1) Posterior hypothalamus neurons are spontaneously active. Indeed, the recording of single-unit activity within this nucleus is feasible. 2) It is possible to attempt to characterize the firing rate and pattern. 3) In awake patients with TACs the firing rate ranges between 13 and 24 spikes/second, with a tonic and not an oscillatory firing pattern. 4) In patients under general anesthesia and with aggressive behavior, the firing rate ranges between 10 and 19 spikes/second. 5) The patient with aggressive behavior and associated epilepsy showed phasic oscillations at around 8 Hz. 6) There is no clear evidence of the neurophysiological characteristics of either the superior or inferior borders of the nucleus. 7) However, the presence of higher firing rates above 5 mm from the target may suggest that the micro-

electrode is passing through the thalamus, while the lack of neuronal activity at the target site and beyond may indicate that the microelectrode is not in the pHyp but in adjacent structures (that is, the interpeduncular cistern at the inferior border). 8) To record beyond the target might be dangerous due to the proximity of the basilar artery bifurcation.

Summary of Results

Belgian Study. Unfortunately, 1 patient who underwent implantation died of an intraparenchymal and intraventricular hemorrhage 3 days after the intervention. Implantation was not undertaken in another patient because of the occurrence of a panic attack, so that the total number of patients available for follow-up is 4 in this series.

Stimulation parameters were as follows: median voltage 3.28 V, pulse width 60 μsec in 2 patients and 90 μsec in 2 patients, and stimulation frequency 185 Hz. The median follow-up was 14.5 months.

At the last clinical examination, 2 of 4 patients were pain free, another patient had a dramatic reduction in pain attacks to fewer than 3 per month, and another patient had only transient clinical benefits.

French Multicenter Study. After surgery, the patients were randomly assigned to either an active stimulation period followed by a sham stimulation period (on-off group) or vice versa (off-on group). Both random phases lasted 1 month after a wash-out period of 1 week.

An open phase of 10 months, during which all patients were set to the on-stimulation state, followed the randomization period.

Stimulation parameters were set as follows: 3 V, pulse width 60 μsec, and 185 Hz or 80% of the threshold producing eventual side effects in the randomized period. The parameters could be changed in the open phase. During the randomized phase, no significant change in the frequency or intensity of attacks in the "on" group occurred. In addition, there were no differences in the number of attacks during the last week of each period or the number of times that sumatriptan was administered. On the contrary, in the open-phase period, the mean frequency of weekly attacks decreased by 48.4%, and 6 of 11 patients were considered responders (that is, a decrease of at least 50% in the frequency of weekly attacks). No predictive factor for the efficacy of DBS was found.

German Study. Patients were stimulated with a current amplitude ranging from 1.5 to 5.5 V, a pulse width of 60 μsec, and a frequency ranging from 130 to 180 Hz. Three of the 6 patients were almost completely attack free (mean number of pain attacks per month 1) after a follow-up period ranging from 9 to 17 months. One patient benefited from the procedure for only 6 months after intervention, whereas 2 patients reported only a transient and mild benefit after the first weeks following the operation, followed by a return to the baseline frequency of pain attacks.

British Series. Both patients were stimulated with a frequency of 180 Hz. One patient was stimulated with 4.5

V at a pulse width of 60 μsec; the other with 4.0 V and a pulse width of 90 μsec. Both patients benefited from the procedure: the first patient reported only infrequent pain attacks (7 injections of sumatriptan) at the 11-month follow-up, and the second patient reported a decrease in attack frequency, from daily to weekly with "massive reduced severity."

American Study. Stimulation parameters were as follows: 1–3 V, pulse width 60 μsec, and stimulation frequency 185 Hz. The duration of the follow-up was 12 months for the first 4 patients and 6 months for a fifth patient. Three of these 5 patients could be considered responders because of a "> 50% reduction in headache frequency, intensity, or both."[47]

Italian Study. The parameters used for chronic electrical stimulation were as follows: frequency 185 Hz, pulse width 60–90 μsec, amplitude 1–3 V in unipolar configuration (case as anode). The IPG was turned on a few days after the intervention in all of the patients, and the current amplitude was progressively increased but remained below the threshold for adverse effects.

In the entire series, 71% of the postoperative days were pain free, and the intensity and duration of pain bouts was significantly reduced. The overall drug dosage was reduced to < 20% of the preoperative levels. The mean time to pain freedom or reduction was 42 days (1–86 days); the mean amplitude of stimulation used was 2.4 V (0.6–3.3 V).

The mean follow-up was 4 years; after the first 2 years of clinical follow-up, major improvements in pain or pain disappearance was observed in 15 (94%) of 16 patients. After a mean of 4 years of follow-up, a state of persistent freedom from painful attacks was still present in 10 patients (62%). Four patients (25%) still required prophylactic drugs to prevent pain attacks. In the last 2 years of follow-up 3 patients no longer benefited from stimulation despite several changes in the parameters. In these 3 patients, the disease turned from the chronic form to the episodic form (that is, periods of complete remission lasting several months alternating with periods of attacks).

With the above-reported series taken as a whole, the percentage of patients considered to be responders to DBS surgery is 63%.

Adverse Events and Side Effects

Among our surgically treated patients, a small and asymptomatic intraventricular (third ventricle) hemorrhage was disclosed on postoperative CT.[27]

The main limiting postoperative and stimulation-related side effect was visual disturbance. We have noticed that it occurs only when the amplitude is increased too much or too rapidly after implantation, subsiding after a few minutes or a few days after increasing the voltage of the electric field. Such observations have been reported by other authors as well.[3,36,45,47]

Weight loss occurred after 6 postoperative months (mean 3.0 kg), but it can be attributed to steroid withdrawal. One patient had ceased menstruating 4 months before the intervention as a result of excessive drug intake, but her cycles returned to normal after 1 month.[27]

Posterior Hypothalamus DBS for SUNCT

General Considerations

Short, unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) are a rare and highly disabling form of TAC characterized by very frequent episodes (3–200 per day) of short-lasting (5–240 seconds) pain unilaterally localized in the orbital, supraorbital, or supratemporal region, which can be of pulsatile or stabbing type. The pain bouts are usually accompanied by reddening of the ipsilateral conjunctiva, tearing, and a runny nostril. The course and severity of this pathological condition are quite variable, ranging from long periods of pain relief to a severe chronic modality of presentation devoid of pain-free periods. Unfortunately, the condition in a majority of patients is resistant to conventional pharmacological treatment.[22,48]

The scientific literature addressing the potential role of DBS of the posterior hypothalamic region in the treatment of drug-refractory SUNCT is, to date, limited to 2 patients treated in such a manner.

Case Reports

Case 1. We first reported on this patient in 2005.[19] This 66-year-old woman suffering from a 14-year history of SUNCT localized in the left orbital region and upper corner of the mouth (episodically radiating to the ear, jaw, and suboccipital region) was referred to our institute. The pain bouts, which were evoked by talking, chewing, tactile facial stimuli, and tooth brushing, were accompanied by homolateral eyelid edema, eye reddening, obstruction of the ipsilateral nostril, and tearing. The frequency of pain bouts ranged from 70 to 300 per day. Neuroradiological studies were all negative for intracranial intraaxial signal alterations, and a neurological examination was nondiagnostic. The patient's condition was resistant to multiple drug treatments, including carbamazepine, gabapentin, sodium valproate, lamotrigine, indomethacin, topiramate, steroids, and tramadol.

After obtaining written informed consent from the patient and ethics committee approval, we performed ipsilateral positioning of a DBS electrode (3389, Medtronic, Inc.) into the posterior hypothalamic region in this patient in July 2003. The surgical technique and planning are the same as those described above. Coordinates of the planned target were as follows: 2 mm lateral to the midline, 3 mm posterior to the MCP, and 5 mm below the AC-PC plane.

The postoperative course was uneventful, and control CT scans revealed correct positioning of the electrode. Initial stimulation parameters were set at the bipolar mode with a frequency of 30 Hz and a pulse width of 60 μsec. These settings did not lead to any clinical improvement, so we tried unipolar stimulation with 180 Hz from the 1st postoperative day. The main limiting side effect was the ipsilateral third nerve's related disturbances as manifested by increasing the voltage.

After several clinical follow-up examinations and after taking into account the balance between clinical benefits and adverse effects, the final stimulation param-

eters were set to 1.8 V, 60-μsec pulse width, and 180-Hz frequency in the unipolar mode. The adjunct treatment of lamotrigine (100 mg/day) led to the complete and definitive remission of symptoms, which was confirmed at the last clinical examination at the 5-year follow-up.

Case 2. The second patient with drug-refractory SUNCT treated with hypothalamic DBS was described in 2009 by Lyons and coworkers.[32] This 44-year-old woman initially presented with left-sided painful attacks at the age of 8 years. Symptoms gradually worsened over time until her current presentation, when she had 120 attacks per day lasting 60–120 seconds. The attacks also included lacrimation, conjunctival injection, rhinorrhea and episodic vomiting, blurred vision, and photophobia, all resistant to multiple pharmacological treatments with antiepilepsy drugs, beta-blockers, GABAergics, tricyclic and serotoninergic antidepressants, dihydroergotamine, steroids, and botulinum toxin Type A injections. Neurological examination disclosed only left trigeminal hypesthesia, and neuroradiological examinations were nondiagnostic. The surgical procedure was similar to that described for the patient in Case 1. Definitive stimulation parameters were as follows: monopolar configuration with Contact 0 as cathode, 1.4 V, 90 μsec, and 160 Hz. The immediate improvement of symptoms consisted of a 63% reduction in the mean number of daily attacks (133 attacks/day preoperatively vs 45/day during the 1st postoperative month). At the 12-month follow-up further improvement was observed, with an 80% reduction in the frequency of pain attacks (25 attacks/day).

Posterior Hypothalamus DBS for CPH

Chronic paroxysmal hemicrania is a pathological condition consisting of pain attacks with characteristics and associated symptoms and signs similar to those for CCH, but with shorter, more frequent bouts occurring more commonly in females and responding absolutely to indomethacin.[22] The duration of pain attacks lasts from 2 to 30 minutes; localization is at the level of the unilateral orbital, supraorbital, or temporal regions; and attacks are usually accompanied by ipsilateral conjunctival injection and/or lacrimation, nasal congestion and/or rhinorrhea, eyelid edema, forehead and facial sweating, and miosis and/or ptosis.

Attacks are described with a frequency of at least 5 per day for more than half of the time, although periods with lower frequency can occur. Probable pathophysiological analogies exist between CPH and CCH given that a recent study by Matharu and coworkers[37] showed activation of the posterior hypothalamic region during acute CPH attacks, whereas the administration of indomethacin resulted in deactivation of the same area.

Walcott and coworkers[53] reported on the clinical case of a patient affected by CPH who was treated with ipsilateral pHyp stimulation in 2009. This 43-year-old woman had a 19-month history of unilateral lancinating right headache attacks at the level of the eye and retroorbital space accompanied by nasal congestion, conjunctival injection, tearing, and ptosis. The attacks occurred 10–20 times per day. During the neurological examination peri-

od at their institute, she experienced 4 headache episodes in 50 minutes.

Pharmacological therapy undertaken without benefit consisted of ergotamine, antiepileptics, triptans, GABA agonists, melatonin, verapamil, amitriptyline, zonisamide, lithium, and tramadol; however, the administration of indomethacin was effective in alleviating symptoms. Unfortunately, this drug was later discontinued because of a diagnosis of iatrogenic gastritis superimposed on a preexisting Barrett's esophagus. The patient was then referred for implantation of a DBS system at the level of the ipsilateral pHyp. The surgical technique was similar to the one described above. Final coordinates of the target were 2 mm lateral, 3 mm posterior, and 5 mm inferior to the MCP. Initial stimulation parameters were 1.5 V, 80 μsec, and 140 Hz, which were changed to 1.5 V, 60 μsec, and 185 Hz during the 27-month follow-up period. She underwent several deactivations of the IPG, with subsequent recurrence of pain attacks. Turning on the device resulted in major improvement of symptoms in all cases. At the last clinical examination, the patient was reported to be free from "signs and symptoms of CPH."

Posterior Hypothalamus DBS for Secondary Neuropathic Trigeminal Pain

Four patients with neuropathic trigeminal pain at our institute underwent implantation procedures for pHyp DBS. One patient was a 47-year-old man with an expanding right posterior mandibular carcinoma who had undergone radical transmandibular tumor resection in 2002. After surgery he started to experience hypesthesia and burning pain in the second and third right trigeminal branches, which progressively worsened with time. A second patient was a 52-year-old woman with a 3-year history of facial pain. Symptoms appeared after a minor dental procedure and were described as continuous and disabling burning pain to the area innervated by the second and third right trigeminal branches. The third patient was a 55-year-old man with a nasopharyngeal carcinoma who had undergone radiotherapy. A few months after radiotherapy, continuous and severe burning right facial pain developed more intensely in the area innervated by the first and second divisions of the trigeminal nerve. For all of these patients, pharmacological therapy with any kind of analgesic drug (including opioids) was ineffective.

All of the patients underwent brain CT and MR imaging studies that did not disclose any intracerebral pathology.

Unfortunately, none of the 3 patients had a reduction in painful symptoms. The stimulation target's coordinates as well as the stimulation parameters were the same as for TACs (180 Hz, 60 μsec, and 1.3 V mean voltage). After 4 months of continuous stimulation, the continuous pain was the same as preoperatively, and repeated changes in the stimulation parameters did not modify the picture. Amplitudes beyond 3 V induced dizziness and oculomotor symptoms in all cases. When the IPG was switched off in 2 of the 3 patients without their awareness of it, the episodes of paroxysmal pain were described as being even slightly more intense than with active stimulation.

The fourth patient is not described because of the short follow-up.

Posterior Hypothalamus DBS for MS-Related TN

From 20 to 80% of patients affected by MS suffer from neuropathic pain, with appendicular central pain and TN being the most common forms.

Trigeminal neuralgia is a pathological condition characterized by short, shock-like pain episodes, referred to as "electric bouts" by patients, that are limited to one or more of the territories innervated by the divisions of cranial nerve V. It usually begins in the second or third division of the trigeminal nerve and involves about 5% of patients with MS, usually beginning many years after the occurrence of nontrigeminal pain. The clinical characteristics of TN in patients with MS are similar to those in patients without MS, although they tend to appear at a younger age and more commonly involve the first branch of the trigeminal nerve. Signal alterations on brain MR imaging in these patients can disclose vascular compression by an artery at the level of the root entry zone, demyelinating lesions affecting trigeminal pathways across the pons, or enlargement of the trigeminal nerve at the root entry zone. Conventional antiepileptic treatment in patients with MS could cause an elevated incidence of adverse effects at low dosages, resembling clinical worsening of MS relapse. Microvascular decompression results in these patients are usually poor with a high probability of late recurrence of paroxysmal pain, whereas ablative procedures (such as radiofrequency lesioning) harbor a high risk of nerve damage with subsequent hypesthesia/hyperesthesia, secondary deafferentation and corneal reflex impairment, corneal anesthesia, neuropathic keratitis, hearing loss, and transitory masticatory weakness.

Evidence that drug-refractory TN in some patients involves the first trigeminal division and that TACs share the same painful territories (that is, orbital region, eye, and forehead), along with the reversible nature of the DBS procedure, led us to postulate that stimulation could represent an effective treatment in appropriately selected MS patients with refractory TN involving the first trigeminal branch, without the previously noticed side effects. At our institution, 5 MS patients affected by refractory TN submitted to pHyp DBS intervention after providing written informed consent. These patients were 3 males and 2 females with a mean age of 56, a mean primary disease duration of 23 years, and a mean TN duration of 12 years. Two patients reported pain in all 3 trigeminal branches, and the remaining 3 described pain in the first and second branch. In all of these patients preoperative brain MR imaging used for target planning showed multiple demyelinating lesions at the level of the cerebral white matter, the internal capsule, and the pontomesencephalic region.

Trigeminal neuralgia in all of the patients was refractory to high-level dosages of carbamazepine, phenytoin, gabapentin, and lamotrigine. All of the patients had undergone several surgical procedures—microvascular decompressions, radiofrequency lesioning, and percutaneous balloon compressions—without benefit or with only temporary relief of pain.

After pHyp electrodes were positioned ipsilateral to the pain, 3 patients had beneficial effects within 24 hours of the procedure. All patients reported a reduction in paroxysmal pain attacks within the ophthalmic branch after surgery. Three patients reported recurrent pain in the second and third branches—although not in the first—and underwent further radiofrequency thermorhizotomies. The relapse occurred at varying time intervals (mean 23 months). Note that this time interval is longer than the interval observed after neurosurgical procedures used before DBS (mean 6 months).

The other 2 patients reported pain relief in all 3 trigeminal branches through a combination of stimulation with analgesics without the need for further surgical procedures.

The data point to procedural efficacy in controlling TN's paroxysmal pain when it is localized in the first branch.

Posterior Hypothalamus DBS for Aggressive Behavior

Several data led our group to pioneer pHyp DBS for aggressive and impulsive behavior refractory to any conservative treatment: 1) Previous experiences reported by Sano and Mayanagi,[42] Arjona,[2] Schvarcz et al.,[46] and Ramamurthi[39] in the "lesional era"; 2) the report regarding disruptive behavior induced by electrical stimulation in the so-called triangle of Sano in a Parkinsonian patient;[4] 3) the well-known occasional onset of self-aggressive and violent behavior in patients with CH during pain bouts, suggesting a common anatomofunctional involvement of the pHyp in the etiopathogenesis of both symptomatologies;[42,46,51] 4) experimental evidence about functional connections between the pHyp, amygdala, and the Papez circuit.[49]

Taking into account these data, we decided to consider for aggressive and impulsively behaved patients the option of a more conservative, reversible, and nondestructive procedure that could replace the lesional procedures previously performed, as an extreme alternative to major restraining measures (forced hospitalization or use of straightjacket) and complete social isolation. Even though our clinical experience is only based on a small series of patients, it is the only neuromodulatory procedure available to treat these patients.

Since 2002 we have treated 6 patients, including 1 female, with ages ranging from 21 to 68 years. All of them had below-average IQ scores. Two patients also had comorbid refractory and generalized multifocal epilepsy. Disease etiology was posttraumatic in 1 case with subsequent permanent damage of the temporomesial structures; congenital or unknown origin in 3 cases with normal brain MR imaging; and heart arrest in 1 case with diffuse damage of the bilateral frontal cortex. All of the patients needed major restraint measures, and 2 were chronically hospitalized.

After informed consent was obtained from relatives, the patients underwent stereotactic placement of DBS electrodes in the pHyp region and subsequent subcutaneous positioning of IPGs (Kinetra or Soletra, Medtronic, Inc.).

Deep brain stimulation of the posteromedial hypothalamus

Summary of Results

Stimulation parameters were as follows: frequency 185 Hz, pulse width 60–90 μsec, and stimulation amplitude in monopolar mode with case positive 1–3 V.

The patient in Case 1 showed quick improvement, with prompt disappearance of self-aggression. Bursts of uncontrolled violence gradually became less frequent and completely disappeared within 3 weeks. The patient returned to live with his family and started to attend a therapeutic community facility specializing in the care of mentally impaired patients. Generalized epileptic seizures disappeared, and partial seizures and absences were reduced by 50%. The antiepileptic drug therapy was consistently reconsidered and reduced to 30% of the original dosage.

Violent outbursts immediately disappeared in the patient in Case 2, and bed restraints were withdrawn. He was discharged from the hospital within 3 months of surgery and was admitted to a therapeutic community facility for mentally disabled patients. Three years later, after the IPG was temporarily turned off for knee surgery, the violent behavior–related symptoms returned, and when chronic stimulation was restored the therapeutic effect was considerably reduced despite an increase in the current amplitude, which could not be set higher than 2 V due to the appearance of side effects. Psychiatrists who had been following the patient suggested a possible evolution of the original disease to explain the loss of the therapeutic effect. Note, however, that with the IPG turned on the outbursts of violence were still less frequent and less intense than in the absence of stimulation.

The patient in Case 3 revealed a marked reduction in the frequency and duration of violent attacks only when the amplitude of stimulation was set to 1.8 V a few months after surgery. This patient is still calm, and her social activities have steadily improved. She is now able to participate in a specialized community facility, and her family integration is good. Violent outbursts appear occasionally, but only if the patient is provoked by adverse events.

The patient in Case 4 demonstrated an improvement only in his sleep pattern: before surgery he slept only 2 hours per night, and after surgery he sleeps more than 6 hours per night. Unfortunately, his behavior was not affected by the stimulation despite an increase in the electrical current to 2 V in amplitude. Two years after surgery the stimulator was turned off, but his sleep pattern did not return to the preoperative condition; by the 3-year follow-up he continued to sleep more than 6 hours per night. The same patient had a stable decrease in arterial pressure, and all antihypertensive drugs could be withdrawn. This effect is still present despite the fact that the IPG was turned off.

The patient in Case 5 had a prompt and marked improvement in behavior, and the family care became consistently easier. The therapeutic effect was stable at the 1-year follow-up, but when both IPGs were turned off the violent behavior reappeared within a few hours. The left IPG has recently been removed due to skin erosion, and the therapeutic effects seem to be sustained by right pHyp stimulation alone.

The patient in Case 6 demonstrated an impressive decrease in the frequency of epileptic seizures to 50% of the preoperative condition just a few weeks after surgery. The insertion of a second electrode at the target was immediately followed by the disappearance of interictal epileptic activity from scalp electroencephalography. This patient has undergone frequent follow-up examinations due to the onset of frequent states of somnolence after the surgical intervention. The aggressive behavior showed a progressive but significant decrease over time. Disruptive bouts have been abolished by stimulation, and the actual current amplitude is 2 V.

Hernando et al.[23] reported on the clinical case of a 22-year-old man with drug-resistant aggressiveness and mental retardation. Stereotactic bilateral electrodes were implanted in the medial portion of the pHyp; the authors used intraoperative microrecording and electroencephalographic responses for target localization. Interestingly, at the 18-month follow-up sustained clinical improvement was demonstrated using low-frequency stimulation.

Kuhn et al.[26] reported on the case of a 22-year-old woman with repetitive self-mutilating behavior in the mouth area following severe traumatic brain injury. After bilateral pHyp deep brain stimulation, complete resolution of the self-mutilation behavior was noticed at the 4-month follow-up.

Studies on Surgically Treated Patients

Schoenen and coworkers[45] studied 2 kinds of nociceptive reflexes in their surgically treated patients: the nociceptive blink reflex and the biceps femoris flexion reflex. The former was obtained with supraorbital stimulation and the latter with stimulation of the sural nerve at the ankle. Perception and pain threshold were determined bilaterally and at each site by using ascending and descending sequences of 0.2-mA intensity steps, with stimulus intensity set at 1.5 times the individual pain threshold. Responses were measured by quantifying the area of electromyography responses, assessed preoperatively and at 1 week and 1 month after surgery. The thresholds for pressure pain were determined using an algometer bilaterally positioned over the temple, the extensor muscles of the upper forearm, and the lateral aspect of the heel.

After surgery the supraorbital electrical pain threshold decreased after 1 week but not after 1 month on the side of the CCH bouts. Pain thresholds at the level of the sural nerve were higher after 1 month of DBS as compared with baseline, but only contralateral to the side of the CCH attacks.

Preoperative pressure pain thresholds were lower over the temple than over the extracephalic sites. During neurostimulation, thresholds at such sites increased, whereas at cephalic levels the thresholds did not significantly change. The level of significance was reached only after 1 month of stimulation: at the forearm ipsilateral to the CCH attacks and at the heel contralateral to the attacks. No significant change in response areas of nociceptive blink and biceps femoris flexion reflexes were noted, except for a significant increase in the ipsilateral nociceptive blink reflex response area following supraorbital stimulation ipsilateral to CCH bouts after 1 month compared with the preoperative assessment.

Endocrine tests were also performed.[45] Urinary excretion of melatonin was measured at different time epochs preoperatively. Twenty-four hour urinary excretion of cortisol was also determined, as were plasma levels of oxytocin and vasopressin. No significant hormonal changes were found postoperatively with respect to baseline.

The same group of authors also evaluated the response to sublingual nitroglycerin administration (1.2 mg) in 4 of 6 surgically treated patients. Nitroglycerin provoked CCH attacks in 3 patients preoperatively, in 2 after 1 week, and in none of 3 patients after 1 month of stimulation.

Cardiovascular effects of pHyp stimulation were studied by Cortelli et al.[10] in 8 patients who were surgically treated at our institute. Given that the pHyp, defined as the region above the mammillary bodies beside the third ventricle, is known to be involved in cardiovascular regulation[35] (and was defined as the "ergotropic area" in older literature), the authors decided to evaluate the role of the pHyp as an important component of the central autonomic nervous system. They monitored systolic and diastolic blood pressure, cardiac output, total peripheral resistance, heart rate, and breathing. Such parameters were measured during supine rest and during the head-up tilt test, Valsalva maneuver, deep breathing, cold face test, and isometric handgrip, both before and after surgery. They found that diastolic blood pressure, total peripheral resistance, and heart rate variability significantly increased during the head-up tilt test in the postoperative period with respect to baseline, and thus they concluded that DBS of the pHyp in patients with CCH could be associated with an enhancement of excitatory sympathetic drive on the cardiovascular system, resulting in mild orthostatic arterial hypotension at subclinical values.

Effects on sleep were evaluated by Vetrugno et al.[52] in 3 patients affected by refractory CCH who were surgically treated at our institute. Vetrugno and colleagues took into account the occurrence of several sleep disorders in patients with CCH (increased incidence of obstructive sleep apnea as compared with that in healthy volunteers) and the role of the pHyp region in the control of behavioral states of the sleep-wake cycle and arousal.[1] The 3 patients underwent 48-hour (consecutive) polysomnographic study and body core temperature monitoring before and after 4 months of DBS. Before implantation, all patients experienced at least 2 daytime and 1–2 nighttime CCH attacks. The baseline polysomnography showed a sleep structure characterized by prevalent light non-REM sleep Stages 1–2, normal REM sleep, and reduced sleep efficiency (ratio between total sleep time and time in bed). The total sleep time was 394.8 minutes, and wakefulness after sleep onset was 70.5 minutes. The mean arousal index and periodic limb movements (while asleep) index were increased.

Body core temperature rhythm was normal before and during stimulation of the pHyp, whereas DBS improved sleep architecture and sleep quality as compared with baseline: postoperative polysomnography showed a more continuous sleep pattern, with increased sleep time, sleep efficiency, and amount of slow-wave sleep stages. Polysomnographic indices of fragmented sleep (arousal and periodic limb movements while asleep) also decreased. All 3 patients presented with the disappearance of CCH nocturnal attacks at the 4-month follow-up.

The effects of hypothalamic stimulation on thermal sensitivity were assessed by Jürgens et al.[24] in 2009. These authors examined thermal thresholds for warm and cold sensations and for heat and cold pain in 3 groups: the DBS group (11 CCH patients with pHyp stimulation who were surgically treated at our institute), the medically treated CCH group (15 patients with unilateral CCH), and a control group (29 healthy controls with no history of primary or secondary headaches). These physiological responses were evaluated bilaterally at the forehead (first trigeminal branch), at the ventral forearm, and at the lateral lower leg and were then compared in the 3 groups. In the DBS group, the tests were performed with the stimulator switched on and again after 30 minutes off stimulation.

In the control group, thermal detection and pain thresholds did not differ significantly between the right and left side, so median values for thresholds of the right side were used for comparison with those of the stimulated side in the DBS group and with those of the painful side in the medically treated CCH group; the left side thresholds in healthy controls were compared with thresholds of the nonstimulated side in the DBS group and with thresholds of the healthy side in the medically treated CCH group.

No significant individual difference between the conditions of "on" versus "off" stimulation was found for any variable in the DBS group. Thresholds of simple detection of cold stimuli were significantly increased at all the tested locations bilaterally in the DBS group as compared with the control group; warm stimulus detection thresholds were higher bilaterally at V1 in the DBS group compared with the control group. At any rate, the thresholds for cold pain detection were only increased at the ipsilateral V1 in the DBS group.

The DBS group also showed higher thresholds for simple cold detection compared with nonimplanted patients with CCHs.

Note that in this study the difference in thresholds of cold pain detection was found after long-term stimulation, but evaluation in the "off" period was performed only after short-term cessation of the stimulus; it was not possible to examine the patients after a longer interruption of the stimulation because a recurrence in pain attacks would have been likely. For this reason, a carryover effect accounting for this lack of difference between the 2 states in the DBS group cannot be excluded.

In this study it is noted how direct reciprocal connections between the pHyp and trigeminal nuclei could justify these results.[5,33] To explain the differences found between simple and pain cold thresholds the authors suggested that the thermal perception and thermal pain perception are conveyed through different pathways and receptors, but they also stated that because of crossing fibers a central integration of the 2 systems cannot be ruled out.

Discussion

Chronic electrical stimulation of the posteromedial hypothalamus, originally introduced to treat patients with

CCHs refractory to conservative treatments, demonstrates positive results in neurological diseases other than CCH. They include facial pain involving the orbital region such as SUNCT, CPH, and first-branch TN in patients with MS. Moreover, pHyp DBS also improves other severe neurological conditions such as multifocal epilepsy[21] and disruptive behavior.[19]

Other functions modified during neurostimulation include thermal sensitivity,[24] sleep regulation,[52] and blood pressure regulation.[10] Susceptibility to nitroglycerin in patients with CCHs was also modified by chronic hypothalamic stimulation.[45]

Data suggest that the pHyp interacts with different neural networks that have a link or a common path in this small volume of brain. In particular, to understand the possibly involved neurophysiological circuits we must note the following phenomena involved in pHyp DBS: the neurovegetative responses linked to the pain threshold of the ipsilateral orbital region (CCH, SUNCT, and blood pressure regulation); the effect on cortical excitability and reticular system (multifocal epilepsy, psychomotor agitation, and sleep); the behavior responses (rage, aggressiveness, and disruptive behavior).

From these data we can argue that the pHyp modulates different neurological functions, and its dysregulation can result in a consistent variety of neurological symptoms. Unfortunately, our data are still not sufficient to build up a specific theory that could define the precise role of the pHyp, although we can hypothesize that it controls relationships between the neurophysiological circuits involved in pain behavior and the neurovegetative system. Note also that during pHyp DBS no endocrine changes have been demonstrated,[45] and so we must consider that the functions of this area are independent from the classic hormonal mechanisms controlled by the more anterior hypothalamic nuclei. Another relevant point is related to the latency periods that elapse between the beginning of stimulation and the appearance of therapeutic effects. This phenomenon has been highlighted by the French multicenter study. In fact, in the French study, turning the stimulator on and off at 1-month intervals resulted in an ineffectiveness in the control of pain in patients with CCHs; after 1 year of continuous stimulation in the same group of patients the therapeutic effect developed as in other reported series in the literature.[14]

The latency between the start of stimulation and the beginning of therapeutic effects is still much more variable and unpredictable in SUNCT,[32] although the long-term results in this syndrome appear to be good. Moreover, patients subjected to pHyp DBS for refractory aggressive behavior showed a certain delay between implantation and the full therapeutic effect. We hypothesize that pHyp DBS acts through the remodeling of neural circuits and so it requires a certain amount of time conditioned by individual neural plasticity. Similar mechanisms may be called upon to explain the time-related effects of pallidal DBS in dystonia or the latency between the start of stimulation and the therapeutic effects in depressed patients treated with CG25 area chronic stimulation or even in patients treated with vagal nerve stimulation for depression or epilepsy.

From a practical view the most relevant point in the discussion of pHyp DBS is the incidence of nonresponders, which may realistically be estimated at about 50% of all reported cases.

This percentage is not very low if we consider that, worldwide, surgically treated patients were refractory to any other treatment. Nevertheless, it is true that we cannot predict the outcome of DBS in new patients. In the future, the selection criteria will include the loss of response to greater occipital nerve stimulation, contributing to narrowing down the pool of patients selected for DBS.[47] In the future, functional neuroimaging, including PET and MR imaging, may help to disclose individual hypothalamic involvement in patients affected by CCHs. Furthermore, MR imaging spectrography in steady-state conditions has been used to search for a hypothalamic notch in patients with CCHs. In other words, patient selection based on imaging modality will improve the clinical selection based on the International Headache Society criteria.

Another ongoing problem is the place that pHyp DBS has held in the hierarchy of available surgical treatments for CCH. In our opinion, lesioning procedures such as trigeminal thermorhizotomy or surgical removal of the trigeminal nerve should be abandoned given the irreversibility of the facial sensory deficits, which may worsen patients' conditions when dysesthesias or painful anesthesias develop. The only promising lesioning technique is radiosurgical lesioning of the sphenopalatine ganglion, which should be attempted in patients who obtain significant benefits from a sphenopalatine ganglion lidocaine injection test.

Microvascular decompression of cranial nerve V has been attempted in selected cases, but the results of such a procedure are still unpredictable. Greater occipital nerve stimulation is the most promising neuromodulation procedure and will, like vagal nerve stimulation or sphenopalatine ganglion stimulation, act through peripheral electrical stimulation to modulate the CNS structures alleged to be primarily involved in the origin of pain bouts. In our opinion, DBS should be considered in highly selected cases after all of these less invasive procedures have been tried. Of the 75 pHyp DBS cases reported in the literature, a severe complication occurred in only 1 case. The safety of pHyp DBS has been confirmed by different authors.

Conclusions

In summary, we think that pHyp DBS is a powerful tool in the hands of functional neurosurgeons in treating extremely severe and rare conditions such as CCH, SUNCT, and disruptive behavior in patients with below average IQs. While the mechanisms of action are still unknown, they do seem to be mediated by a remodeling of network circuits through neural plasticity. New applications of pHyp DBS may be expected in the field of sleep disorders, epilepsy, and perhaps some other diseases involving the autonomic nervous system.

rials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Franzini, Messina. Analysis and interpretation of data: Cordella. Critically revising the article: Marras, Broggi.

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