Anatomical location of effective deep brain stimulation electrodes in chronic cluster headache

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Deep brain stimulation of the posterior hypothalamus is a therapeutic approach to the treatment of refractory chronic cluster headache, but the precise anatomical location of the electrode contacts has not been clearly assessed. Our aim was to study the location of the contacts used for chronic stimulation, projecting each contact centre on anatomic atlases. Electrodes were implanted in a series of 10 patients (prospective controlled trial) in the so-called ‘posteroinferior hypothalamus’ according to previously described coordinates, i.e. 2 mm lateral, 3 mm posterior and 5 mm below the mid-commissural point. The coordinates of the centre of each stimulating contact were measured on postoperative computed tomography or magnetic resonance imaging scans, taking into account the artefact of the electrode. Each contact centre (n = 10; left and right hemispheres pooled) was displayed on the Schaltenbrand atlas and a stereotactic three dimensional magnetic resonance imaging atlas (4.7 tesla) of the diencephalon–mesencephalic junction for accurate anatomical location. Of the 10 patients with 1-year follow-up, 5 responded to deep brain stimulation (weekly frequency of attacks decrease >50%). In responders, the mean (standard deviation) coordinates of the contacts were 2.98 (1.16) mm lateral, 3.53 (1.97) mm posterior and 3.31 (1.97) mm below the mid-commissural point. All the effective contacts were located posterior to the hypothalamus. In responders, structures located <2 mm from the centres of effective contacts were: the mesencephalic grey substance (5/5), the red nucleus (4/5), the fascicle retroflexus (4/5), the fascicle longitudinal dorsal (3/5), the nucleus of ansa lenticularis (3/5), the fascicle longitudinal medial (1/5) and the thalamus superficialis medial (1/5). The contact coordinates (Wilcoxon test) and the structures (Fisher’s exact test) were not significantly different between responders and non-responders. These findings suggest that failure of deep brain stimulation treatment in cluster headache may be due to factors unrelated to electrode misplacement. They also suggest that the therapeutic effect is probably not related to direct hypothalamic stimulation. Deep brain stimulation might modulate either a local cluster headache generator, located in the hypothalamus or in the mesencephalic grey substance, or non-specific anti-nocioceptive systems.

Keywords: cluster headache; deep brain stimulation; hypothalamus; headache
Introduction

Deep brain stimulation (DBS) of the posteroinferior hypothalamus has been proposed as a treatment for refractory chronic cluster headache (Leone et al., 2001; Franzini et al., 2003; Schoenen et al., 2005) on the basis of arguments that highlight the hypothalamus as the central generator of the disease (Goadsby, 2002). Functional imaging studies showed brain activation during cluster headache attacks at the diencephalo-mesencephalic region, next to the posterior region of the third ventricle (May et al., 1998). Based on the Talairach atlas (Talairach and Tournoux, 1988), this region matched to the hypothalamic grey matter. Structural change in this area, i.e. an increase in grey matter density, has also been suggested by voxel-based morphometry in patients with chronic cluster headache (May et al., 1999). These arguments led Leone et al. (2001) to treat refractory chronic cluster headache by high-frequency DBS targeting this region. To date, 41 patients with chronic cluster headache treated by DBS have been reported, and ~60% of these cases showed marked improvement (Schoenen et al., 2005; Leone et al., 2006a; Owen et al., 2007; Starr et al., 2007; Bartsch et al., 2008). However, the mechanism of action, specifically the anatomic structures inducing the therapeutic effect in response to high-frequency stimulation, is still unknown. Our aim was to identify the structures potentially stimulated and consequently involved in the therapeutic effect, using stereotactic localization of the stimulating contacts projected on stereotactic anatomic atlases.

Methods

Patients

Eleven patients with severe and therapy-resistant chronic cluster headache were enrolled in a prospective controlled trial (clinicaltrials.gov number NCT00662935) conducted in four centres associating neurological and neurosurgical teams highly qualified in DBS and pain management. In this study, a randomized phase compared active and sham stimulation during 1 month periods, and was followed by a 1 year open phase. The randomized phase was negative, probably due to methodological bias directly related to the study design (Fontaine et al., 2010). For the present study, only outcome and stimulation parameters of the open phase were considered. Inclusion criteria were: chronic cluster headache according to the International Classification of Headache Disorders-II criteria (Headache Classification Committee of the International Headache Society, 2004); disease duration over 3 years; resistance to prophylactic pharmacological treatment with adequate trials (verapamil up to 960 mg/day, lithium with plasma level from 0.6 to 1 mEq/l, association of both; absence of adverse events); daily attacks; absence of substance abuse or dependence; age 18-65 years old; normal findings on MRI; and no contraindications for surgery or anaesthesia. Patient assessments were carried out by a neurologist repeatedly over 1 year. Primary endpoint was the weekly frequency of cluster headache attacks. One year after surgery, patients with at least a 50% decrease in weekly attack frequency were considered as responders.

Surgery and stimulation parameters

The intended theoretical target was the posterior hypothalamus according to published coordinates, i.e. 2 mm lateral to the midline, 3 mm posterior and 5 mm below the mid-commissural point (Franzini et al., 2003). The four-contact electrode (model 3389 DBS, Medtronic, Minneapolis) was implanted stereotactically according to classical stereotactic landmarks, anterior white commissure (AC) and posterior white commissure (PC) and the AC–PC line travelling through their centres. The deepest contact (numbered 0) was positioned on the target and was used for the early chronic stimulation. The electrode was placed ipsilaterally to the pain side, and then connected to the pulse generator (Kinetra, Medtronic). Postoperative imaging has been performed in 10 of the 11 patients (eight MRI and two CT scans) to localize the electrodes. Only these 10 patients were considered for further analysis. The frequency of chronic stimulation was set to 185 Hz with a pulse duration of 60 μs in monopolar mode (Leone et al., 2001; Franzini et al., 2003; Schoenen et al., 2005). For each patient, voltage was set at 80% of the voltage threshold leading to side-effects, up to a maximum of 3 V. During the follow-up period, stimulation parameters and contacts were eventually adjusted to improve clinical benefit. For further analysis, we only considered the stimulating contacts leading to the best improvement after optimization of electric parameters, 1 year after the surgery.

Stereotactic location of stimulating contacts

The coordinates of the centre of each stimulating contact were measured on postoperative imaging (MRI or CT scan). The centre of the stimulating contact was determined within the artefact generated by the electrode contacts (Pollo et al., 2004; Hemm et al., 2009) using reconstructed images along the electrode axis (Iplan, BrainLab) (Fig. 1). Postoperative imaging was co-registered with preoperative MRI (Mutual Information algorithm; Wells et al., 1996). The coordinates of the centre of stimulating contact were calculated classically. AC–PC line and related plans were used as reference to calculate x (laterality), y (anteroposterior) and z (above or below the AC–PC horizontal plan) values. The locations (x, y, z) of centres of stimulating contacts were projected within atlases using the same anatomic landmarks, i.e. AC–PC line and related plans. Coordinates were expressed in millimetres, relative to the mid-commissural point. When chronic bipolar stimulation was used, we considered the coordinates of the mid-point between the two contacts.

Anatomic structures neighbouring stimulating contacts

The 10 centres of stimulating contacts (pooling left plus right hemispheres) were projected into the 2D-slice Schaltenbrand and Bailey atlas (1959) and into a 3D-voxel MRI-based 4.7 tesla (T)
atlas (Lemaire et al., 2007a, b) of the diencephalon–mesencephalic junction. To identify structures potentially involved in the therapeutic effect, we hypothesized that the volume of tissue excited by the current around the electrode contact should not extend laterally more than 3 mm. This hypothesis was based on empirical clinical observations that different clinical effects (chronic monopolar stimulation) are provoked by two different and adjacent contacts of the same electrode and by two different contacts of two parallel semi-micro-electrodes separated by 2 mm (intraoperative assessment: Lemaire et al., 2007b); and on theoretical considerations on macroscopic current diffusion in isotropic environment (Volkmann et al., 2006). The structures within the spherical theoretical volume of excited tissue around the centre of each contact were identified using reconstructed coronal, axial and sagittal slices along the AC–PC line. They were segregated into four membership volumes according to distance (d, radius of the sphere) from the centre of contact: (i) close, \( d \leq 1 \text{ mm} \); (ii) intermediate, \( 1 \text{ mm} < d \leq 2 \text{ mm} \); (iii) distant, \( 2 \text{ mm} < d \leq 3 \text{ mm} \); and (iv) outside the volume of excitation.

Analysis of structures within the theoretical volume of excited tissue was carried out using only the 3D-voxel MRI-based 4.7T atlas. Discrepancy between the three planes (three different anatomic specimens; axial plane not aligned along the AC–PC axis) and the discrete location of sections in each plane made 3D analysis with the Schaltenbrand and Bailey atlas (1959) impossible. The anatomic structures were labelled according to classical anatomical knowledge (Riley, 1943; Schaltenbrand and Bailey, 1959; Laget, 1973; Dejerine, 1980; Nieuwenhuys et al., 1988; Talairach and Tournoux, 1988; Carpenter, 1991; Paxinos and Huang, 1995) derived from Riley’s book (Riley, 1943).

Figure 1  Location of stimulating contacts. Top row: postoperative 3D T1-weighted MRI on sagittal (A), coronal (B) and axial (C) slices. The black artefact generated by electrode contacts is visible within the diencephalon–mesencephalic region; centre of the stimulating contact (green), projections (dotted line) of the electrode axis (purple) and the four-contact group (represented by a segment, yellow). White bar = 10 mm. Bottom row: projection of the centre of the stimulating contact (green circle) on coronal (D), and axial (E) sections of the Schaltenbrand and Bailey atlas (linear registration; atlas overlay on T1-weighted MRI) and on coronal (F) and axial (G) sections of the 4.7 T 3D MRI-based atlas. Each anatomic structure is outlined using a colour code (see Figs 2 and 3). The white circle around the centre of the stimulating contact has a radius of 1 mm.
Data analysis

We searched for differences between (i) the stereotactic coordinates, \( x \) (lateral), \( y \) (anteroposterior along the AC–PC) and \( z \) (below or above the AC–PC line; absolute, mm and proportional, percentage of AC–PC) of stimulating contacts; and (ii) the anatomic structures according to the four membership volumes (1 = close; 2 = intermediate; 3 = distant; 4 = outside the volume of excitation), across all 10 patients, responders versus non-responders.

A Wilcoxon rank-sum test was used to compare the stereotactic coordinates \((x, y, z)\) independently. Fisher’s exact test was used to test independence according to the four membership volumes (ordinal variable: 1, 2, 3, 4), and when possible, we estimated the crude odds ratio and its 95% confidence interval. Adjusted odds ratio and confidence interval were also estimated by fitting a multiple logistic regression model to the binary outcome (responder versus non-responder), and a final model was assessed using a stepwise forward selection method.

We tested for rejection of the null hypothesis (no difference), setting type I error to 0.05. Analyses were performed on SAS software (SAS v9.1, SAS institute inc., Cary, NC, USA).

Results

Table 1 summarizes the results of all-10 patients, giving optimal stimulation parameters and stereotactic coordinates of the stimulating contacts. Detailed clinical and biological results of our study have been previously reported (Fontaine et al., 2010). The global distribution of the centre of the stimulating contacts is displayed in Figs 2 and 3. The mean (standard deviation—SD) coordinates of all stimulating contacts \((n = 10)\) were \(x = 2.36 \pm 1.16 \text{ mm lateral,} \ 3.24 \pm 1.72 \text{ mm posterior and} \ 3.66 \pm 1.61 \text{ mm below the mid-commissural point,} \) distributed around the target point corresponding to Franzini's target (Franzini et al., 2003). The mean (SD) coordinates \((/\text{mid-commissural point})\) of the stimulating contacts in responders \((n = 5)\) were \(x = 2.98 \pm 1.16 \text{ mm,} \ y = -3.53 \pm 1.97 \text{ mm and} \ z = -3.31 \pm 1.97 \text{. The mean (SD) coordinates of the best stimulating contacts (inducing the best improvement, even if <50%) in non-responders \((n = 5)\) were \(x = 1.73 \pm 0.85 \text{ mm lateral,} \ y = -2.95 \pm 1.60 \text{ mm posterior and} \ z = -4.01 \pm 1.28 \text{ mm below the mid-commissural point.} \) The mean stereotactic location of stimulating contacts was not significantly different between responders and non-responders (absolute coordinates: \(x, y, z\) for responders: \(0.1777, 0.5464, 0.5454\); relative coordinates: \(0.1290, 0.4250, 0.0546\)).

Globally speaking, all the stimulating contacts were embedded in the posterior and ventral wall of the third ventricle. All of them were posterior to the mamillary body and the mammillo-thalamic tract. All anatomic structures related to the stimulating contacts are listed in Table 2. In the five responders, neural structures located <2 mm from effective contacts (and consequently strong candidates to drive the therapeutic effect) were (occurrences over five responders): the grey mesencephalic substance (5/5), the red nucleus (4/5, superficial; 3/5, core), the fascicle retroflexus (4/5), the fascicle longitudinal dorsal (3/5), the nucleus of ansa lenticularis (3/5), the fascicle longitudinal medial (1/5) and the thalamus superficial medial (1/5). None of the structures of interest was significantly more often close to the contacts in responders than in non-responders: grey mesencephalic substance, \(P = 1\); red nucleus shell, \(P = 0.0682\), and core, \(P = 0.7143\); fascicle retroflexus, \(P = 0.3810\); fascicle longitudinal medial, \(P = 0.3691\); fascicle longitudinal dorsal, \(P = 1\); fascicle mammillo-tegmental, \(P = 0.4444\); nucleus of the ansa lenticularis, \(P = 0.5238\); medial superficial thalamus, \(P = 0.4444\); fascicle mammillo-thalamic, \(P = 1\); nucleus entopeduncularis, \(P = 0.7143\); brachium conjunctivum, \(P = 0.5238\); substantia nigra, \(P = 1\).

Discussion

In our series of refractory patients with chronic cluster headache treated by DBS, the stereotactic and anatomical locations of the stimulating contacts did not significantly differ between responders and non-responders. These findings suggest that DBS treatment failures in chronic cluster headache may not be solely due to electrode misplacement. Other factors, related to the pathophysiology of the disease or the patient's individual structural or functional

Table 1 Overall outcome, optimal stimulation parameters and stereotactic coordinates of stimulating contacts for the 10 patients with chronic refractory cluster headache treated by DBS

<table>
<thead>
<tr>
<th>Patient</th>
<th>Hemisphere</th>
<th>Voltage (V)</th>
<th>Contact</th>
<th>Outcome</th>
<th>AC–PC length</th>
<th>Stereotactic coordinates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(x)</td>
</tr>
<tr>
<td>C1P1</td>
<td>L</td>
<td>2.5</td>
<td>1–</td>
<td>Responder</td>
<td>29.76</td>
<td>1.81</td>
</tr>
<tr>
<td>C2P1</td>
<td>R</td>
<td>2.8</td>
<td>0–</td>
<td>Responder</td>
<td>26.28</td>
<td>3.45</td>
</tr>
<tr>
<td>C1P2</td>
<td>R</td>
<td>2.5</td>
<td>0–1+</td>
<td>Non-responder</td>
<td>26.51</td>
<td>2.34</td>
</tr>
<tr>
<td>C3P1</td>
<td>R</td>
<td>2.5</td>
<td>0–</td>
<td>Responder</td>
<td>25.65</td>
<td>2.36</td>
</tr>
<tr>
<td>C1P3</td>
<td>L</td>
<td>2.5</td>
<td>1–</td>
<td>Non-responder</td>
<td>25.36</td>
<td>2.02</td>
</tr>
<tr>
<td>C1P4</td>
<td>L</td>
<td>2.5</td>
<td>0–1+</td>
<td>Responder</td>
<td>26.06</td>
<td>4.77</td>
</tr>
<tr>
<td>C1P5</td>
<td>R</td>
<td>2.8</td>
<td>0–</td>
<td>Non-responder</td>
<td>27.58</td>
<td>0.54</td>
</tr>
<tr>
<td>C3P2</td>
<td>L</td>
<td>2.5</td>
<td>0–</td>
<td>Non-responder</td>
<td>28.06</td>
<td>2.59</td>
</tr>
<tr>
<td>C4P2</td>
<td>R</td>
<td>2.5</td>
<td>0–</td>
<td>Non-responder</td>
<td>26.31</td>
<td>1.18</td>
</tr>
<tr>
<td>C2P2</td>
<td>L</td>
<td>1.5</td>
<td>1–</td>
<td>Responder</td>
<td>26.23</td>
<td>2.52</td>
</tr>
<tr>
<td>Mean (±SD)</td>
<td></td>
<td>2.26 (0.42)</td>
<td></td>
<td></td>
<td>26.78 (1.32)</td>
<td>2.36 (1.16)</td>
</tr>
</tbody>
</table>

L = left; R = right; MCP = mid-commissural point. Stereotactic coordinates and AC–PC length are expressed in millimetres. Patients are referenced by centre (C1, C2, C3 and C4) and chronological order of inclusion (P1, P2, etc).
anatomy, could explain the absence of improvement despite correct electrode placement. As ~40% of treated patients do not respond to this therapy (Leone et al., 2008), factors predictive of poor outcome should be identified to avoid operating on patients who will receive little or no benefit.

We confirmed that all the stimulating contacts in both responders and non-responders were located posterior to the mamillary body and the mamillo-thalamic fasciculus. This finding, already pointed out by Starr (2008), was concordant with electrode locations on postoperative imaging in previously published series (Franzini et al., 2003; Owen et al., 2007; Starr et al., 2007; Bartsch et al., 2008). Medially, within the wall of the third ventricle, there is a continuity between the grey mesencephalic substance and the posterior nucleus of the hypothalamus (Nauta, 1969; Carpenter, 1991). Consequently, the determination of a well-defined boundary of the posterior hypothalamus is somewhat artificial. However, most of the anatomical data define the mamillary region (the posterior limit of the mamillary body and mamillo-thalamic fasciculus) (Riley, 1943; Morgane, 1979; Dejerine, 1980; Nieuwenhuys et al., 1988; Carpenter, 1991;
Figure 3 Location of the centres of all the stimulating contacts on 3D rendering of relevant anatomic structures from medial (A) and superior (B) views. Medial (left) and superior (right) 3D views along the AC–PC axis (yellow line). Ant = anterior; Inf = inferior; Lat = lateral. White bar = 5 mm. Contacts of responders are in green and non-responders in red. Same colour-coding as Fig. 2. The region of interest is centered by the red nucleus (Rn, transparent, orange). Medially, the mesencephalic grey substance (Sg, transparent, purple) belongs to the wall of the third ventricle and is in continuity with the posterior hypothalamus anteriorly and with the peri-acqueductal grey substance posteriorly. The mamillary body (Mb, light blue), with the mamillo–thalamic fascicle (Fmt, light green) and the mamillo–tegmental fascicle (Fmtg, transparent, dark green), constitute the macroscopic posterior border of the hypothalamus. The ventral tegmental area, which contains the nucleus entopeduncularis (Nep, beige), is located immediately posterior to the mamillary bodies. The nucleus of ansa lenticularis (Nal, brown) laterally contours the mamillary complex when entering the subthalamus, placed above the nucleus entopeduncularis. Several bundles cross this area. The fascicle retroflexus of Meynert (FrF, green, transparent) makes a notch in the medial region of the red nucleus and links the habenula with the interpeduncular nucleus. The fascicle longitudinal medial (Flm, red) connects the hypothalamus with autonomic centres in both brain stem and spinal cord. The fascicle longitudinal dorsal (Fld, transparent, purple; only thin portions are individualized at this level) connects the paraventricular nucleus of the hypothalamus with the peri-acqueductal grey matter, the locus coeruleus and autonomic centres of the brain stem. Several structures have been erased for simplification.

Table 2 Anatomical structures covered by the stimulating contacts according to the radius of the hypothetical volume of tissue excited by the current

<table>
<thead>
<tr>
<th>Patient</th>
<th>Improvement</th>
<th>SG</th>
<th>Rn (s)</th>
<th>Rn (c)</th>
<th>FrF</th>
<th>Flm</th>
<th>Fld</th>
<th>Fmtg</th>
<th>Nal</th>
<th>Thal</th>
<th>Fmt</th>
<th>Nent</th>
<th>Bc</th>
<th>Sn</th>
</tr>
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<tbody>
<tr>
<td>C1P1</td>
<td>&gt;75%</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>4</td>
<td>2</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>C2P1</td>
<td>&gt;75%</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>C1P2</td>
<td>&lt;25%</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>4</td>
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<td>4</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>C3P1</td>
<td>50–75%</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>4</td>
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<tr>
<td>C1P3</td>
<td>25–50%</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>1</td>
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<tr>
<td>C1P4</td>
<td>&gt;75%</td>
<td>2</td>
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<td>1</td>
<td>1</td>
<td>4</td>
<td>3</td>
<td>3</td>
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</tr>
<tr>
<td>C1P5</td>
<td>&lt;25%</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td>3</td>
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<td>C3P2</td>
<td>Worse</td>
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<td>4</td>
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<td>3</td>
</tr>
<tr>
<td>C4P2</td>
<td>Worse</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>2</td>
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<td>2</td>
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<td>1</td>
<td>2</td>
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<td>3</td>
<td>2</td>
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<td>4</td>
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</tr>
</tbody>
</table>

Membership volume

| Close (1) | 5  | 6  | 1  | 4  | 2  | 4  | 0  | 1  | 0  | 0  | 0  |
| Intermediate (2) | 5  | 2  | 3  | 3  | 1  | 3  | 0  | 3  | 1  | 0  | 1  |
| Distal (3) | 0  | 2  | 4  | 2  | 1  | 2  | 2  | 1  | 4  | 3  | 0  |
| Outside (4) | 0  | 0  | 2  | 1  | 5  | 2  | 8  | 4  | 9  | 4  | 6  |
| Total       | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Distribution of anatomic structures belonging to three hypothetical spherical volumes of tissue around the stimulating contact, i.e. close (radius < 1 mm), intermediate (between 1 and 2 mm) and distal (between 2 and 3 mm), across all 10 patients. SG = diencephalon–mesencephalic grey matter; Rn = red nucleus shell (s = superficial and c = core); FrF = fascicle retroflexus; Flm = fascicle longitudinal medial; Fld = fascicle longitudinal dorsal; Fmtg = mamillo–tegmental fascicle; Nal = nucleus of the ansa lenticularis; Thal = medial superficial thalamus; Fmt = mamillo–thalamic fascicle; Nent = nucleus entopeduncularis; Bc = brachium conjunctivum; Sn = substantia nigra.
Braak and Braak, 1992) or the posterior nucleus (Nauta, 1969) as the posterior limit of the hypothalamus. It is obvious that the confusing terminology governing anatomic structures within the mamillo-subthalamic area has stilled better understanding. Hassler’s human nomenclature (Schaltenbrand and Wahren, 1977) defined a retro-mamillary posterior hypothalumus which is likely to correspond with the ventral tegmental area of most species, including humans (see Nieuwenhuys et al., 1988 for references) (Fig. 4). Two structures have been described in humans within the ventral tegmental area: the area densa and the nucleus of ansa lenticularis or nucleus entopeduncularis (Riley, 1943) (Fig. 4).

Posterior hypothalamic lesions performed in the past to treat severe aggressive behaviour were located 2 mm lateral to the third ventricle wall, around the mid-commissural point (from 1 mm in front to 2 mm posterior) and 3 mm below the AC–PC axis (Sano et al., 1970; Schwarz et al., 1972); hence ~3 mm anterior to our contact location. The so-called ‘triangle of Sano’ was defined by the stereotactic locations (on ventriculography) of autonomic responses obtained during intraoperative electrical stimulation (10–20V) on patients under general anaesthesia slightly reduced during the stimulation phase. This triangle extended posteriorly to the mamillary body, and Sano hypothesized that this stimulated area might correspond to the dorsal longitudinal fascicle or the posterior portion of the posterior hypothalamic nucleus (Sano et al., 1970). According to anatomic topography relative to the mid-commissural point, it seems likely that the triangle of Sano involved the posterior medial hypothalamus and possibly the anterior ventral tegmental area, where some of our effective contacts are located.

If, like most authors, we consider that the posterior border of the hypothalamus contains the mamillary body and mamillo-thalamic fasciculus, none of our stimulating contacts was located in the hypothalamus, as was likely in most of the previously published cases. Consequently, we suggest that the term ‘hypothalamic stimulation’ initially used for this procedure (Franzini et al., 2003; Schoenen et al., 2005; Bartsch et al., 2008) should be replaced by ‘DBS of the posterior hypothalamic region’, as proposed by Starr (2008), or by ‘DBS of the retro-hypothalamic region’.

Beyond the anatomic structures previously described and available in human atlases, several other structures potentially present in this region were not considered in our study, notably the medial forebrain bundle. The medial forebrain bundle, connecting the preoptic region with the tegmentum, has been widely described in rodents, cats and monkeys, but is poorly documented and not precisely localized in humans (Peel, 1954; Nauta, 1969). However, given its theoretical location bridging the hypothalamus and the tegmentum, it may also be stimulated. A recent tractography study showed that the region where electrodes were implanted in chronic cluster headache was connected with the basal forebrain, probably via the medial forebrain bundle (Owen et al., 2007). Moreover, fibres belonging to the orexinergic system, a system involved in pain modulation and whose centres are located in the posterior hypothalamus in rats (Holland and Goadsby, 2007), are likely to be located in our region of interest in humans.

We identified several anatomical structures close to the stimulating contacts and thus potentially involved in the therapeutic effect of DBS in chronic cluster headache. However, there were several methodological limits to localizing these structures, including the poor definition of this region in classical human atlases (Talairach et al., 1957; Schaltenbrand and Bailey, 1959; Nauta, 1969; Schaltenbrand and Wahren, 1977; Nieuwenhuys et al., 1988; Talairach and Tournoux, 1988; Carpenter, 1991; Paxinos and Huang, 1995) and the small patient population included in this study. Chronic cluster headache is an orphan disease and only 41 refractory cases treated by DBS have been reported so far in the literature (Franzini et al., 2003; Schoenen et al., 2005; Starr et al., 2007; Bartsch et al., 2008; Leone et al., 2008). Another limit stems from the method used to localize the contacts, i.e. projection of AC–PC coordinates (absolute and proportional) on atlases. We consider that the technique of contact location, AC–PC-based position, the volumes of anatomic structures and the contact size (1.5 mm height and 1.27 mm diameter) do not allow a more precise anatomic analysis.

Nevertheless, all the effective contacts were located close to or within the mesencephalic grey substance. This is part of the central grey substance, a nuclear material which forms the wall of the third ventricle, the annulus of the aqueduct (periaqueductal grey) and the floor of the fourth ventricle. The mesencephalic grey substance, defined according to Riley (1943) was distinct from the periaqueductal grey matter, which is more posterior, and overlapped the so-called periventricular grey matter. However, the periventricular grey matter target used to alleviate chronic pain is located ~8–10 mm posterior from the cluster headache target (Richardson and Akl, 1977; Levy et al., 1987; Kumar et al., 1997). Most of our effective contacts were located close to the red nucleus and the fascicle retroflexus. This fascicle links the habenula and the interpeduncular nucleus and is classically thought to belong to the limbic system. The red nucleus might be involved in the physiopathology of migraine (Cao et al., 2002; Kruit et al., 2009), but not in cluster headache (Goadsby, 2002).

The fascicle longitudinal medial and the fascicle longitudinal dorsal (of Schultz) link hypothalamic nuclei with autonomic centres of the brain stem (Riley, 1943; Nieuwenhuys et al., 1988; Carpenter, 1991). The frequency of their proximity with the effective contacts might have been underestimated, since they become thin and scattered as they cross our area of interest, and consequently they were only partially individualized on our 4.7T MRI-based 3D atlas.

These findings suggest that the therapeutic effect of DBS in chronic cluster headache is probably not related to direct high-frequency stimulation of the hypothalamus. DBS might act...
Figure 4 The retro hypothalamic region. (A) Pseudo-axial section going through the posterior commissure and the mamillary body according to Nieuwenhuys et al. (1988) (right) and the equivalent section with the 3D MRI-based 4.7 T atlas (left). (B) Pseudo-axial section going approximately through the posterior commissure and the mamillary body according to Riley (1943) (right) and the equivalent section with the 3D MRI-based 4.7 T atlas (left). (C) Sagittal section 2 mm lateral to the midline according to Schaltenbrand and Bailey (1959) (left) and the equivalent section with the 3D MRI-based 4.7 T atlas (right). (D) Sagittal section going through the fornix according to Riley (1943) (left) and the equivalent section with the 3D MRI-based 4.7 T atlas (right). Sn = Substantia nigra; Nep = nucleus entopeduncularis;Fmt = mamillo–thalamic fascicle; T = thalamus; Nal = nucleus of the ansa lenticularis; Frf = fascicle retroflexus; Rn = red nucleus; Sg = substantia grisea of the diencephalon–mesencephalic junction; III = third cranial nerve; Ad = area densa; At = area tegmental; Hp = hypothalamus; Vf = ventricular foramen; Zi = zona incerta; Ppn = nucleus peripeduncular; Ot = optic tract; Ac = anterior commissure; V3 = third ventricle; Vta = ventral tegmental area.
either on a local cluster headache generator, or non-specifically through anti-nociceptive systems. A cluster headache generator, suggested by neuroimaging studies (May et al., 1998, 1999), could be located either in the hypothalamus or in the mesencephalic grey substance, as the activation observed during attacks and structural changes overlapped both these structures. However, the latency of chronic stimulation and inefficacy of acute stimulation (Leone et al., 2006b) suggest that high frequency DBS does not act through a lesion-like mechanism but more likely involves neuroplastic mechanisms. Ipsilateral increase of trigeminal pain thresholds (Schoenen et al., 2005) and activation of the pain matrix (May et al., 2006) suggest that retro-hypothalamic DBS acts also through modulation of the anti-nociceptive system. Considering our anatomical data, mesencephalic grey substance and fibres linking hypothalamus and brain stem might be stimulated in responders. Consequently DBS-induced modulation might involve the mesencephalic grey substance or periventricular grey matter (activated in PET studies e.g. May et al., 2006), the orexinergic system, or other descending anti-nociceptive projections to caudal trigeminal nucleus (Bartsch et al., 2009). Additional studies will be necessary to determine precisely the mechanisms of action of DBS in cluster headache.

To conclude, in this prospective study, DBS electrodes implanted to treat refractory chronic cluster headache were not located in the hypothalamus but posterior to the mamillary bodies, at the diencephalo-mesencephalic junction. We identified several structures close to the electrodes whose stimulation could drive the therapeutic effect. These findings suggest that the therapeutic effect of DBS in chronic cluster headache is not related to direct stimulation of the hypothalamus. DBS might modulate either a local cluster headache generator, located in the hypothalamus or in the mesencephalic grey substance, or non-specific anti-nociceptive systems. Moreover, the optimal stimulating contact location did not differ between responders and non-responders, suggesting that other factors not related to electrode misplacement may be responsible for failure of DBS treatment in cluster headache.

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