Hypothalamic deep brain stimulation in the treatment of chronic cluster headache

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***Abstract*:** Cluster headache (CH) is a short-lasting unilateral headache associated with ipsilateral craniofacial autonomic manifestations. A positron emission tomography (PET) study has shown that the posterior hypothalamus is activated during CH attacks, suggesting that hypothalamic hyperactivity plays a key role in CH pathophysiology. On this basis, stimulation of the ipsilateral posterior hypothalamus was hypothesized to counteract such hyperactivity to prevent intractable CH. Ten years after its introduction, hypothalamic stimulation has been proved to successfully prevent attacks in more than 60% of 58 hypothalamic implanted drug-resistant chronic CH patients. The implantation procedure has generally been proved to be safe, although it carries a small risk of brain haemorrhage. Long-term stimulation is safe, and nonsymptomatic impairment of orthostatic adaptation is the only noteworthy change. Microrecording studies will make it possible to better identify the target site. Neuroimaging investigations have shown that hypothalamic stimulation activates ipsilateral trigeminal complex, but with no immediate perceived sensation within the trigeminal distribution. Other studies on the pain threshold in chronically stimulated patients showed increased threshold for cold pain in the distribution of the first trigeminal branch ipsilateral to stimulation. These studies suggest that activation of the hypothalamus and of the trigeminal system are both necessary, but not sufficient to generate CH attacks. In addition to the hypothalamus, other unknown brain areas are likely to play a role in the pathophysiology of this illness. Hypothalamus implantation is associated with a small risk of intracerebral haemorrhage and must be performed by an expert neurosurgical team, in selected patients.

***Keywords*:** chronic cluster headache, deep brain stimulation, drug-resistant, hypothalamus, neuromodulation, neurostimulation, trigeminal autonomic cephalgias

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Introduction

Cluster headache (CH) is a primary headache in which unilateral short-lasting head pain is associated with ipsilateral craniofacial autonomic manifestations and grouped at code number 3 of the International Headache Society (IHS) classification [International Headache Society, 2004]. According to the IHS diagnostic criteria, CH attacks are severe or very severe, unilateral, in the orbital, supraorbital and/or temporal regions, and last untreated for 15–180 min. The headache is accompanied by at least one of the following symptoms ipsilateral to the pain: conjunctival injection or lacrimation, nasal congestion and/or rhinorrhoea, eyelid oedema, forehead and facial sweating, miosis and/or ptosis, a sense of restlessness, and agitation. The attacks have a frequency from one every other day to eight per day and history or physical and neurological examination do not suggest any other disorder and/or they are ruled out by appropriate investigations. The two main forms are episodic and chronic CH. In the episodic form at least two cluster periods lasting 7 days to 1 year occur separated by pain-free periods lasting $\geq$1 month. In chronic CH, attacks occur for more than 1 year without remission or with remission $<$1 month [International Headache Society, 2004].

Neuroimaging findings, both during and outside CH attacks have provided the rationale for hypothalamic deep brain stimulation (DBS) in headache, as

well as important information on attack-related events and clues to pathophysiological mechanisms [May, 2009]. During CH, positron emission tomography (PET) revealed activation of areas associated with pain modulation and perception (anterior cingulate cortex, insulae and contralateral thalamus), but also activation of the posterior inferior hypothalamic grey matter ipsilateral to the pain [May *et al.* 1998]. This latter area was initially thought to be activated only in CH, and was proposed as the cluster generator [May *et al.* 1998]. Subsequently it was shown that this hypothalamic area is also activated during short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) [May *et al.* 1999a], paroxysmal emicrania (PH) [Matharu *et al.* 2006] and hemicrania continua [Matharu *et al.* 2004]. It is of interest to note that all of these headache forms are characterized by strictly unilateral headache attacks accompanied by craniofacial autonomic phenomena and are distinguished by the duration of the single attack classification [International Headache Society, 2004].

Furthermore, a voxel-based morphometry study has shown increased neuronal density in the inferior posterior hypothalamus ipsilateral to the pain, and this was the first-ever identification of a lesion apparently associated with a primary headache [May *et al.* 1999b]. Studies conducted with proton magnetic resonance spectroscopy have shown decreased N-acetylaspartate/creatine-phosphocreatine and choline/creatine-phosphocreatine ratios in the hypothalamus of CH patients compared with migraine patients and healthy subjects [Lodi *et al.* 2006; Wang *et al.* 2006].

These neuroimaging data therefore confirmed the previous hypothesis of the hypothalamic involvement in CH [Kudrow, 1980].

The observation that the posterior hypothalamus is activated during a CH attack prompted a new rational approach to CH treatment: it was supposed that high-frequency hypothalamic stimulation would inhibit apparent hyperactivity of this brain area [Leone *et al.* 2001]. Stereotactic coordinates of the target area were based on the results of the voxel-based morphometry study [May *et al.* 1999b]. New therapeutic approaches were needed as 15–20% of CH patients experience chronic CH and some of these do not respond to drugs [Kudrow, 1980]. Such patients are a major clinical problem because of the severity and frequency (several times a day) of their headache attacks. Destructive surgery that interrupts the trigeminal sensory or autonomic (cranial parasympathetic) pathway was sometimes used to treat these patients, but lasting benefit was reported in only a few cases and complications could be severe, including diplopia, hyperacusia, jaw deviation, corneal ulcers, corneal anaesthesia, and anaesthesia dolorosa [Donnet *et al.* 2005; Jarrar *et al.* 2003; O'Brien *et al.* 1999].

Patient selection for hypothalamic deep brain stimulation

The International Classification of Headache Disorders defines CH as chronic when attacks occur for more than a year without remission or with remissions of less than a month [International Headache Society, 2004]. However, the criteria allow a diagnosis of chronic CH when the patient has only three or four attacks per month over the preceding year. It does not appear prudent to select patients for an invasive surgical procedure such as DBS when they only suffer three or four attacks a month. We proposed that only CH patients suffering from daily or almost daily attacks for least 1 or 2 years be considered for posterior hypothalamic stimulation [Leone *et al.* 2004a].

Clinical experience is that drug treatments are able to control or prevent attacks in more than 80% of patients with chronic CH [Kudrow, 1980]. In some cases drugs show no efficacy and the term drug-resistant has been used to refer to these patients. The term drug-resistant has been used in different contexts, both in patients who do not respond to one or more types of drug [Magis *et al.* 2007] as well as to those who do not respond to all known medications [Leone *et al.* 2008a, 2004a]. In order to avoid confusion and to have homogeneous populations to be compared in different studies, we have proposed that patients unresponsive to one or more types of drug should be designated partially drug resistant, with the term completely drug resistant confined to patients who show no improvement from any medication [Leone *et al.* 2008a]. It is obvious that the condition of complete drug resistance is likely to be much more serious than that of partial resistance and this is a parameter to be considered when comparing the efficacy of different procedures. We propose that only when reasonable trials of drugs indicated in the guidelines or wider literature have been tried [Leone *et al.* 2004a] (unless contraindicated) at adequate dose and for a sufficient period, and shown to be ineffective or associated with

intolerable side effects, should patients be designated as completely drug-resistant patients and considered for DBS [Leone *et al.* 2008a].

The IHS guidelines propose that a reduction in the number of daily attacks should be the main aim of prophylactic treatment [International Headache Society, 1995]. Other important endpoints are pain intensity and duration of attack [International Headache Society, 1995]. A patient's expressed satisfaction with the overall treatment should also be considered, even though some studies have shown that this parameter can lead to misleading conclusions regarding treatment efficacy. In a pilot study on occipital nerve stimulation for CH, attack frequency was unchanged in patients who nevertheless said they were satisfied with the treatment and would recommend it to other patients with CH [Burns *et al.* 2007]. This finding suggested that factors other than pain have a role in patients' assessments of the treatments they are given; it further suggests that patient satisfaction should not be a primary endpoint for studies assessing the efficacy of hypothalamic or occipital nerve stimulation in CH [Leone *et al.* 2007].

Results of hypothalamic stimulation

Acute pain

Based on the observation that the posterior hypothalamus is activated during a CH attack, neuronal hyperactivity was supposed to take place in that brain area. Hence, the hypothesis that high-frequency hypothalamic stimulation would inhibit hyperactivity there [Leone *et al.* 2001]. To evaluate a possible acute inhibitory effect on the supposed hypothalamic neuronal hyperactivity, acute hypothalamic stimulation was tested to abort ongoing CH attacks [Leone *et al.* 2006a]. One hundred and thirty six attacks were acutely treated in 16 patients who had received hypothalamic implants to prevent chronic CH [Leone *et al.* 2006a]. The maximum stimulation amplitude tolerated was usually 4–5 V. Blood pressure, heart rate, sweating, and other vital and neurological signs were monitored. Pain intensity was reduced by more than 50% in 23% of patients; only 16% of pain attacks disappeared completely during acute stimulation. From these data it is evident that acute hypothalamic stimulation is ineffective as a treatment for CH [Leone *et al.* 2006a]. This is consistent with experience in the prevention of chronic CH, where typically several weeks of continuous stimulation are required before the attacks are markedly reduced or eliminated [Fontaine *et al.* 2010; Bartsch *et al.* 2008; Mateos *et al.* 2007; Starr *et al.* 2007; Owen *et al.* 2007; Benabid *et al.* 2006; D'Andrea *et al.* 2006; Leone *et al.* 2006b, 2004b, 2001; Schoenen *et al.* 2005; Franzini *et al.* 2004, 2003].

Chronic pain

Long-term hypothalamic stimulation was first tried in a patient in whom further lesional surgery was contraindicated [Leone *et al.* 2001]. Exceptional benefit was achieved with no major side effects [Leone *et al.* 2001]. The same group subsequently reported on 16 drug-resistant chronic CH patients who received hypothalamic implants after a mean follow up of over 4 years (Table 1) [Leone *et al.* 2006b]. After the first 2 years, pain abolition or major pain reduction was obtained in 13 patients (15/18 implants or 83.3%). After 4 years a persistent pain-free state was still present in 10 patients (62%) although four of these also required medical prophylaxis as an add on to control the attacks. Subsequently hypothalamic stimulation became ineffective in three despite many changes in the stimulation settings. However, the illness also changed from chronic to episodic in the same three patients, and they now experience months of complete remission punctuated by periods of brief but typical attacks [Leone *et al.* 2008b].

Similar improvements have been reported by other studies (Table 1). Overall about 62% of patients have obtained improvement (reported as 'pain free' or 'marked improvement' in Table 1).

In a double-blind, prospective, crossover study, 11 patients from centres throughout France were recruited to assess the efficacy and safety of unilateral hypothalamic stimulation for severe chronic drug-resistant CH [Fontaine *et al.* 2010]. The randomized phase compared active with sham stimulation over 1-month periods, and was followed by a 1-year open phase. The primary outcome was weekly attack frequency. Other outcomes were pain intensity, number of sumatriptan injections, and changes in emotional impact and quality of life, as assessed by the Hospital Anxiety and Depression Scale and the SF-12 Health Survey, respectively. Tolerance was assessed by active surveillance of behaviour and hormone levels. During the randomized phase, there was no significant difference in primary or secondary outcome measures between active and sham stimulation. At the end of the

Table 1. Summary of results of hypothalamic stimulation for drug-resistant chronic cluster headache patients from various centers.

Study	No. of implanted patients	Mean follow up (years)	No. of patients improved^	Percentage improved
Leone *et al.* (2006b)	16	4	10	62
Fontaine *et al.* (2010)	11	>1	6	55
Starr *et al.* (2007), Sillay *et al.* (2009)	8	1	5	62
Bartsch *et al.* (2008)	6	1.4	3	50
Schoenen *et al.* (2005)	4	4	2	50
Owen *et al.* (2007) and Brittain *et al.* (2009)	3	1	3	100
D'Andrea *et al.* (2006) (abstr)	3	2.5	2	66
Black *et al.* (2007) (abstr)	2	2.6	2	100
Mateos *et al.* (2007) (abstr)	2	1	2	100
Benabid *et al.* (2006) (abstr)	1	1	1	100
Nikka *et al.* (2006)*	2	2	0	0
Totals	58		36	62

^ Improvement: pain free or almost pain free. See text for details.
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open phase, chronic stimulation had reduced weekly attack frequency by over 50% in 6/11 patients, three of whom were pain free. There were three serious adverse events: subcutaneous infection, transient loss of consciousness and micturition syncope. There were no significant changes in hormonal function or electrolytic balance. Although the randomized phase showed no efficacy of hypothalamic stimulation, the open-phase indicated long-term efficacy in over 50% of patients without high morbidity.

Of eight CH patients implanted in California [Sillay *et al.* 2009; Starr *et al.* 2007], five had obtained >50% reduction in headache intensity or frequency after at least a year, although none were completely pain free.

A multicentre study on six CH patients implanted in Germany reported that three patients were almost pain free with treatment failure in the other three [Bartsch *et al.* 2008].

A Belgian centre reported that of four successfully implanted patients, two were pain free and one had improved substantially [Schoenen *et al.* 2005]. All three patients implanted in Oxford, UK, were reported as pain free with no side effects after a follow up of 6 months to 2 years [Brittain *et al.* 2009; Owen *et al.* 2007]. Outcomes in unpublished cases and those presented in abstracts are given in Table 1.

Tolerability and adverse events

Like all cerebral electrode implantation procedures, implantation to the hypothalamus is associated with a small risk of intracerebral haemorrhage and must be performed by an expert neurosurgical team, in patients without specific risk factors for cerebral haemorrhage [Leone *et al.* 2006b]. The centre with the largest experience (16 patients given 18 implants) reported a small transient nonsymptomatic haemorrhage into the third ventricle in one case, identified on postoperative computed tomography (CT). Follow-up CT showed complete resolution [Leone *et al.* 2006b]. Untoward intraoperative modifications in electroencephalography (EEG), blood pressure, temperature, breathing, affective state or state of consciousness were not observed [Leone *et al.* 2006b].

In one study, one of the six patients implanted died soon after the operation due to implantation-induced intracerebral haemorrhage [Schoenen *et al.* 2005]; in another patient the implantation was stopped because of a panic attack [Schoenen *et al.* 2005]. It is possible that this patient had anxiety disorder; alternatively the electrode may have missed the target: panic attacks have not been reported in other studies during hypothalamic implantation/stimulation [Fontaine *et al.* 2010; Bartsch *et al.* 2008; Mateos *et al.* 2007; Owen *et al.* 2007; Starr *et al.* 2007; Benabid *et al.* 2006; D'Andrea *et al.* 2006; Leone *et al.* 2006b, 2004b, 2001; Franzini *et al.* 2004, 2003].

Visual disturbances, mainly diplopia, are the main limiting side effects induced by hypothalamic stimulation [Fontaine *et al.* 2010; Bartsch *et al.* 2008; Mateos *et al.* 2007; Owen *et al.* 2007;

Starr *et al.* 2007; D'Andrea *et al.* 2006; Benabid *et al.* 2006; Leone *et al.* 2006b, 2004b, 2001; Franzini *et al.* 2004, 2003]. Diplopia occurs in most patients when the amplitude is increased too rapidly; it subsides within a few minutes, although a few days may be required for complete disappearance [Fontaine *et al.* 2010; Bartsch *et al.* 2008; Mateos *et al.* 2007; Owen *et al.* 2007; Starr *et al.* 2007; Benabid *et al.* 2006; D'Andrea *et al.* 2006; Leone *et al.* 2006b, 2004b; 2001; Franzini *et al.* 2004, 2003]. No changes in electrolyte balance, body temperature, blood pressure, sleep–waking cycle, appetite, thirst or EEG have been observed on prolonged hypothalamic stimulation; levels of cortisol, prolactin, thyroid hormones, thyroid-stimulating hormone and testosterone also remain unchanged [Fontaine *et al.* 2010; Bartsch *et al.* 2008; Mateos *et al.* 2007; Owen *et al.* 2007; Starr *et al.* 2007; Benabid *et al.* 2006; D'Andrea *et al.* 2006; Leone *et al.* 2006b, 2004b, 2001; Franzini *et al.* 2004, 2003]. Weight loss of around 3 kg generally occurs in the first 3–6 months postoperatively and may be due to steroid withdrawal, although a central effect of neurostimulation cannot be ruled out completely [Leone *et al.* 2006b].

One patient ceased menstruating 4 months before implantation as a result of excessive drug use; her cycles returned to normal a month after implantation [Leone *et al.* 2006b]. During long-term stimulation, depressive or dysphoric symptoms, or changes in character or behaviour, have not been observed [Fontaine *et al.* 2010; Bartsch *et al.* 2008; Mateos *et al.* 2007; Owen *et al.* 2007; Starr *et al.* 2007; Benabid *et al.* 2006; D'Andrea *et al.* 2006; Leone *et al.* 2006b, 2004b, 2001; Franzini *et al.* 2003, 2004]. In the double-blind, multicentre study involving 11 patients, no significant changes in hormone levels or electrolytic balance were observed, but subcutaneous infection, transient loss of consciousness and micturition syncope were major side effects [Fontaine *et al.* 2010].

The autonomic nervous system and sleep during hypothalamic stimulation

Hypothalamic stimulation has meant that the human hypothalamus has for the first time received long-term stimulation [Leone *et al.* 2001], providing an opportunity to study this brain area. Cortelli and colleagues investigated aspects of autonomic nervous system function in eight patients with chronic drug-resistant CH, before and after implantation of an electrode for unipolar stimulation of the posterior hypothalamus [Cortelli *et al.* 2007]. Systolic and diastolic blood pressure, cardiac output, total peripheral resistance, heart rate and oronasal and abdominal breathing were monitored continuously at supine rest, during the head-up tilt test (HUTT), Valsalva manoeuvre, deep breathing, the cold face test and isometric handgrip. The results before and after surgery were compared. It was found that continuous long-term unipolar stimulation was associated with an enhanced sympathoexcitatory effect on the cardiovascular system during HUTT, whereas the Valsalva manoeuvre, deep breathing, cold face test, isometric handgrip and baroreflex sensitivity were unaffected. These findings suggest that chronic stimulation of the posterior hypothalamus can alter the modulation of orthostatic adaptation without affecting the baroreflex, cardiorespiratory interactions or efferent sympathetic and vagal functions [Cortelli *et al.* 2007]. Thus, in the supine resting position, the cardiovascular system is not influenced by posterior hypothalamic stimulation, providing important evidence that long-term stimulation is safe. Body core temperature (BCT) rhythm was also normal in hypothalamic-stimulated patients [Vetrugno *et al.* 2007].

The hypothalamus, especially its posterior part, is involved in control of the sleep–wake cycle and regulation of arousal [Swaab, 2004]. Thus, the structure and quality of sleep were investigated in three chronic drug-resistant CH patients before and during chronic lasting stimulation of the posterior hypothalamus [Vetrugno *et al.* 2007]. The patients underwent 48 h consecutive polysomnography (PSG) using the Vitaport system [Vetrugno *et al.* 2007]. In these patients nocturnal CHs disappeared during hypothalamic stimulation, although in two patients occasional daytime attacks were occurring 4 months after implantation when PSG was applied. PSG during stimulation revealed more continuous sleep with increased total sleep time and sleep efficiency with slow-wave sleep stages becoming more prominent. No daytime sleepiness or sleep-related breathing disorders were observed in posterior hypothalamic stimulation providing further evidence that hypothalamic stimulation is safe [Vetrugno *et al.* 2007].

Microrecordings

The brain area targeted in CH does not correspond to a specific anatomical entity, and there is

no consensus as to whether it is part of the posterior hypothalamus or anterior periventricular grey matter [Talairach and Tournoux, 1988]. Microrecording techniques to investigate the characteristics of the neurons at that level could be of great help in identifying main neurophysiological characteristics of neurons located there.

Several studies have obtained single unit microrecordings from this hypothalamic area in stimulated CH patients [Sillay *et al*. 2009; Bartsch *et al*. 2008; Cordella *et al*. 2007; Starr *et al*. 2007; Schoenen *et al*. 2005; Franzini *et al*. 2003] but it has to be underlined that two sets of stereotactic coordinates have been used to identify this target [Franzini *et al*. 2003].

The first microrecording was performed in a single unit using a Medtronic Lead Point system, but the authors provided no quantitative data [Franzini *et al*. 2003]. In another study, in two patients bursts of action potentials synchronous with heart beats were recorded using a Medtronic 9013-SD-08411 microelectrode and Medtronic Lead Point system, starting 10 mm above the target and continuing at 1-mm intervals down to the target [Schoenen *et al*. 2005].

Quantitative microrecording data were obtained in another study with the Medtronic Lead Point system from awake CH and SUNCT patients [Cordella *et al*. 2007]. Recording was done at the hypothalamic target. Signals from a single cell in each patient were collected for sufficient time to permit off-line analysis with the Spike2 package (CED, Cambridge, UK). The average firing rate was 24 per second. Most recordings showed isolated action potentials, with most interstimulus intervals in the range 10–15 ms. Autocorrelograms of two of the cells showed no periodicity of discharge rate, but a 1-Hz oscillatory pattern was identified in the SUNCT patient, possibly a pulse artefact [Cordella *et al*. 2007].

In another study, single microelectrode penetration toward the posterior hypothalamus was performed beginning 10 mm above the anatomic target, without systemic sedation. Twenty four units were evaluated in 6 CH patients. The neurons investigated showed slow, regular spontaneous discharge with wide, low-amplitude action potentials. The mean discharge rate was 13 Hz (mean), with no oscillatory activity. There was no morbidity [Sani *et al*. 2009; Cordella *et al*. 2007; Starr *et al*. 2007].

Bartsch and colleagues reported on four patients who received posterior hypothalamic implant for drug-resistant CH [Bartsch *et al*. 2004]. Microrecordings were obtained at 1 mm around the target and were obtained using high-impedance microelectrodes, making it possible to pick up discharges from a single neuron. Units had a tonic nonrhythmic firing pattern; the average discharge rate was 17 Hz (range 13–35 Hz). None of the applied stimuli (sensory stimulation of the trigeminal and spinal dermatomes, motor stimulation, counting backwards under stress, cold pack and bladder filling, and affective stimulation—pictures with emotional content) produced an obvious response.

Brittain and colleagues recorded local field potentials during a CH attack that occurred while surgical implantation of a hypothalamic electrode was ongoing [Brittain *et al*. 2009]. Local field potentials were characterized by a significant increase in power during the attack. This appears to be the first report of neuronal activity during a CH and lends strong support to the data (mainly indirect haemodynamic neuroimaging techniques) implicating hypothalamic activation in CH generation.

Putative mechanism of action of hypothalamic stimulation

A direct connection between the posterior hypothalamus and the trigeminal nucleus caudalis (TNC) through the trigeminohypothalamic tract (THT) has been shown in rats [Malick *et al*. 2000]. Information from trigeminal territory and including meninges, cranial skin and intracranial blood vessels are conveyed to the hypothalamus via the THT [Malick *et al*. 2000]. Other studies showed that stimulation of the posterior hypothalamus also modulates the activity of TNC neurons. Injection into the posterior hypothalamus of different neuropeptides including orexin A and B and the $GABA_A$ receptor antagonist bicuculline affect spontaneous and trigeminally evoked TNC activity in the TNC [Bartsch *et al*. 2004]. These observations indicate that the posterior hypothalamus is a physiological modulator of TNC activity [Bartsch *et al*. 2004]. These animal experiments could give an account of the observed efficacy of posteromedial hypothalamotomy to treat intractable facial pain

[Sano *et al.* 1975]; it is of interest to note that to be effective the hypothalamic lesion had to be performed on the pain side [Sano *et al.* 1975].

The relationship between the hypothalamus and the trigeminal system in humans has been elucidated in a recent study. In a H_2 ^{15}O PET study performed in CH patients successfully treated with hypothalamic DBS, hypothalamic stimulation provoked increased blood flow (activation) in both the ipsilateral posterior inferior hypothalamic grey at the site of the stimulator tip and the ipsilateral trigeminal system [May *et al.* 2006]. A functional connection between the hypothalamus and the trigeminal system in humans *in vivo* has been documented for the first time. In this study, activation of the trigeminal system was not followed by headache attacks, trigeminal pain or autonomic craniofacial phenomena [May *et al.* 2006]. Based on these observations, it has been suggested that trigeminal system activation is necessary for a CH attack to occur, but it is not sufficient on its own to explain the attacks [May *et al.* 2006].

The latency of chronic stimulation and inefficacy of acute stimulation suggest that the mechanism of hypothalamic stimulation is complex and not the result of simple inhibition of hypothalamic neurons, as supposed initially [Leone and Bussone, 2009]. At least part of the effect exerted by hypothalamic stimulation could be due to modulation of the antinociceptive system, as suggested by the finding of increased threshold for cold pain at the site of the first trigeminal branch ipsilateral to the stimulated side in chronically stimulated patients [Jürgens *et al.* 2009].

As well as causing increased blood flow in the ipsilateral trigeminal system (noted previously), hypothalamic stimulation also increases blood flow in brain areas involved in the pain matrix [May *et al.* 2006]. In particular, activation has been observed in the thalamus, somatosensory cortex, precuneus, and anterior cingulate cortex; while deactivation occurs in the middle temporal gyrus, posterior cingulate cortex, and insula [May *et al.* 2006]. The fact that hypothalamic stimulation has the potential to interfere with major pain matrix components suggests that it could act by gradually restoring normal function and metabolism in hypometabolic areas in CH patients, eventually restoring deficient top–down modulation [Sprenger *et al.* 2007].

In the original neuroimaging study which documented hypothalamic activation in CH, the authors gave prominence to the idea that the hypothalamus had a permissive or triggering role in CH, rather than hypothalamic activation simply being a pain-induced epiphenomenon [May *et al.* 1998]. The idea that the hypothalamus is the trigger or generator of CH is attractive, but the more recent neuroimaging findings examined above, and accumulated experience with hypothalamic stimulation, suggest other interpretations [Leone and Bussone, 2009]. If the hypothalamus were the trigger site, one would expect hypothalamic stimulation to trigger CH pain attacks, but this is not the case [Fontaine *et al.* 2010; Bartsch *et al.* 2008; Mateos *et al.* 2007; Owen *et al.* 2007; Starr *et al.* 2007; Benabid *et al.* 2006; D'Andrea *et al.* 2006; Leone *et al.* 2006b, 2004b, 2001; Franzini *et al.* 2004, 2003]. One would also expect that certain stimulation settings should block an ongoing attack, but again this does not occur [Leone *et al.* 2006a]. One possible explanation of the role of the hypothalamus in CH and TACs, consistent with the accumulated data on hypothalamic activations, is that this brain area plays a major role in terminating rather than triggering attacks [Leone and Bussone, 2009]. This idea envisages the hypothalamus as regulating the duration of an attack, and the extent to which it does so would give rise to the different phenotypic expressions of the TACs which are principally distinguished by attack duration.

It seems that the autonomic nervous system has little or no role in the mechanism of action of hypothalamic stimulation since prolonged hypothalamic stimulation does not affect parasympathetic activity [Cortelli *et al.* 2007] and only a mild (nonsymptomatic) sympathetic deficit develops (impaired orthostatic tolerance) [Cortelli *et al.* 2007].

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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