HHS Public Access

Author manuscript

Neurosurg Clin N Am. Author manuscript; available in PMC 2015 November 25.

Published in final edited form as:

Neurosurg Clin N Am. 2014 October ; 25(4): 671–692. doi:10.1016/j.nec.2014.07.009.

Deep Brain Stimulation for Chronic Pain:

Intracranial Targets, Clinical Outcomes, and Trial Design Considerations

Orion Paul Keifer Jr, PhD[a], **Jonathan P. Riley, MD, MS**[b], and **Nicholas M. Boulis, MD**[b,*]

[a] MD/PhD Program, School of Medicine, Emory University, Suite 375-B, 1648 Pierce Drive, Atlanta, GA 30322, USA

[b] Department of Neurosurgery, Emory University, 1365-B Clifton Road Northeast, Suite 2200, Atlanta, GA 30322, USA

Keywords

Deep brain stimulation; Surgery; Chronic pain; Clinical trial design; Sensory thalamus; Intracranial stimulation; Anterior cingulate cortex; Periventricular and periaqueductal gray

INTRODUCTION

The use of electrical stimulation as a neurosurgical tool is rooted firmly in the history of treating hypokinetic and hyperkinetic disorders. Its emergence was directly related to the use of neurosurgical interventions that included lesions to the thalamus and fibers projecting to and from the thalamus as a treatment of motor signs like rigidity, bradykinesia, and tremor.[1–6] Although promising, these results were overshadowed by the introduction of L-Dopa as a method for treating Parkinson disease.[7] The use of chronic intracranial stimulation for the treatment of neurologic disorders would remain nearly quiescent for nearly 2 decades until 1987, when Benabid and colleagues[8] reintroduced thalamic stimulation for Parkinson patients who had emerging symptoms after a unilateral thalamotomy. The renaissance of intracranial chronic stimulation further flourished after Parkinson patients on chronic L-Dopa developed adverse side effects.[9,10] From there, the 1990s through the present would see a strong reemergence of the use of chronic stimulation in hyperkinetic and hypokinetic disorders with targets including the subthalamic nucleus, globus pallidus internus, and ventral intermediate thalamus (Vim).[11–14]

Embedded within the success story of deep brain stimulation (DBS) for movement disorders is the use of chronic intracranial stimulation as an intervention for pain. The work of Heath and Mickle in the 1950s is often thought of as the birth of intracranial stimulation for pain control. Their observation that septal stimulation acutely alleviated intractable pain would lead to the birth of the field. From there, DBS targets for pain control would expand to include the internal capsule (IC), the ventral posterolateral nucleus (VPLP) and the ventral posteromedial nucleus (VPM) of the sensory thalamus (STH), the centro-median

* Corresponding author. nboulis@emory.edu.

Conflict of Interest: No related conflicts of interest.

parafasicular region (CM-Pf) of the thalamus, the periaqueductal/paraventricular gray (PAG/PVG), the posterior hypothalamus (PH), the motor cortex, the nucleus accumbens (NAcc), and the anterior cingulate cortex. The following sections highlight the past, present, and future DBS targets used to treat various types of pain.

INTRACRANIAL TARGETS

Within each target section is a brief review of the history behind stimulating the area for pain, the current literature surrounding its use as a target, and the current clinical standing of that area. Tables present a summarized account for the literature on each region. Each entry is based on the information reported in the article with no attempts to standardize terminology across studies. In other words, independent criteria for "successful treatment" (most reports will define this as >50% improvement of their outcome measure), "side effects" (listed side effects only pertain to stimulation, not due to the surgery or postoperative care), or "pain type" (details of patients conditions and source of pain) have not been defined. Several reports included stimulation to multiple targets for pain (eg, a patient will have electrodes placed in the VPLP/VPM and PVG/PAG). These articles are listed once in the table corresponding to the target used for most patients but are noted in the charts for the other brain areas. The notes section of the table contains an abbreviated accounting of other areas stimulated and any additional aspects of the article that should be considered.

Septal Interventions

The stimulation of the septal region of the human brain (**Table 1**) was first initiated by Heath and Mickle[15] likely based on the rewarding (or "pleasurable") effects seen in rats.[20] In their work, Heath and Mickle noted that most patients with septal stimulation were more alert and spoke more rapidly. In addition, a few patients were also acutely relieved of their chronic pain (pain due to either rheumatoid arthritis or advanced carcinoma). Later work stimulating the medial forebrain bundle in patients with terminal carcinoma also echoed these results.[16] In particular, Ervin and colleagues[16] stimulated the medial forebrain bundle, among many other areas, and noted an amelioration of the pain reported in their patients with cancer. Because the medial forebrain bundle is part of the mesolimbic pathway, including ventral tegmentum, and NAcc, and also connects to septal nuclei, it is not clear what part of the "pleasure system" could be generating these results. More directly, Gol[17] attempted to study the effects of septal stimulation on pain further and showed some success in a few patients but not the majority (2 of 6 patients). Given these early challenges and only moderate success, it appears that the septum has fallen out of favor. However, it should be noted that 2 works have been published by Schvarcz[18,19] that suggest a nearly 60% success rate of intractable pain relief with septal stimulation. Currently, septal targeting is not common and there is not a double-blind, randomized, placebo-controlled trial to evaluate it efficacy.

IC Interventions

The idea of stimulating the internal capsule as a therapeutic option for treating intractable pain (**Table 2**) started in 1974 when Fields and Adams reported efficacy in a case report.[21]

Their results would later expand to a case series.[22] These results would be further bolstered by other groups in the late 1970s to mid-1980s.[23,28,29] Interestingly, the notion of stimulating the IC for pain would remain dormant for more than 2 decades until Franzini and colleagues[32] reported a case study in 2008. As of late, Plow and colleagues[33] have published their clinical trial design for stimulation of the ventral striatum and anterior limb of the internal capsule. Although the proposal by Plow and colleagues[33] is not the first clinical trial for the treatment of pain with DBS, it does hold a great deal of promise because it improves several limitations of older clinical trials (discussed later in the Consideration for Trial Design Section).

STH, VPM/Lateral Nucleus Interventions

Primary literature focusing on the treatment of intractable pain with STH stimulation (**Table 3**) dates to the early 1970s. Inspired by the results of VPM lesions,[73] the gate control theory of pain,[74] and the paresthesias noted by Ervin,[16] the often cited paper by Hosobuchi and colleagues[34] would involve the treatment of facial anesthesia dolorosa with stimulation of the VPM nucleus of the thalamus. They noted success in 4 of 5 patients. That year and a year later, Mazars and colleagues[35,36] published their work (started in the early 1960s) on treating intractable pain with thalamic stimulation with 13 of 17 patients showing benefit. Expanding more broadly to chronic neuropathic pain in general, Turnbull and colleagues[39] showed complete or partial success in 14 of 18 patients (including cases of complex regional pain syndrome, lumbar arachnoiditis, phantom limb pain, and plexus avulsion) when stimulating the ventral posterior portion of the thalamus. During these early studies, it was noted that some patients showed an acute relief of pain with VPM/VPLP stimulation, but that the pain would recur gradually. Several attempts would be made to prevent stimulation tolerance. In the peri(aqueductal)ventricular gray (PV[A]G) literature, Hosobuchi[75] would propose the use of L-tryptophan, and Meyerson and colleagues[76] would propose the use L-Dopa to prevent the reduction of the DBS effect. Tsubokawa[26,27] would pay particular attention to this phenomenon as he further explored VPLP stimulation over several studies. He would introduce the use of L-Dopa and L-Tryptophan supplements in thalamic stimulation to help mitigate the appearance of “stimulation tolerance,” although this practice would not continue because of the lack of evidence for efficacy. Interestingly, stimulation tolerance is still a very real concern and is only further compounded with current work that has suggested that there is also an insertional effect (benefit with electrode insertion but no stimulation, as opposed to a developing tolerance to stimulation[66]).

The late 1980s and early 1990s would show the first attempts by neurosurgeons to summarize their cases with DBS of the VPLP/VPM and PVG/PAG.[47,50] These results would, for the first time, cast some doubt on the efficacy of DBS for pain (eg, previous reports had success rates in the 60%–80% range, and reports in this era would document long-term success in the 30%–40% range). They would also come at a time when the US Food and Drug Administration (FDA) ruled that DBS devices must be undergo evaluation for safety and efficacy with chronic pain.[77] To add further complication, this ruling would come out at nearly the same time as the retirement of older-generation Medtronic 4 contact platinum electrodes (3380); hence, the appearance of a newer model (thinner diameter and more narrowly spaced contacts) in the literature (3387). Therefore, 2 clinical trials were

conducted to evaluate the use of DBS electrodes for the treatment of chronic, intractable pain (1993 was the final report on model 3380, 1999 for 3387). Summarized years later in 2001, Coffey and colleagues[77] would evaluate the new and older electrodes (3380 and 3387) across 2 centers with 246 patients in a prospective clinical trial. The results for VPLP/VPM and PVG/PAG stimulation were disappointing. In the case of the model 3380 electrode trial, only 46.1% of patients showed greater than 50% improvement at 12 months, which dropped to 17.8% at 24 months. The 3387 numbers were even more disheartening with only 16.2% showing greater than 50% pain relief at 12 months and only 13.5% at 24 months (note that withdrawals were counted as failures with these calculations).

Fortunately, despite Medtronic not pursuing FDA approval for DBS electrode use for intractable pain patients, several studies have been published in the interim showing some efficacy of STH stimulation in specific situations.[61,65,78] Currently, the STH is often co-targeted with the PVG/PAG areas as first studied by Hosobuchi.[44] The most recent work for DBS stimulation of the STH for pain control suggests that the VPLP/VPM should be considered a second-line treatment target if PAG/PVG stimulation should fail.[71] A well-powered, double-blind, randomized, placebo-controlled trial has yet to occur.

CM-Pf Interventions

The CM-Pf intralaminar complex of the thalamus has a small history of stimulation for the control of pain (**Table 4**). A comprehensive review of the potential for the CM-Pf is provided by Weigel and Krauss,[83] while the evidence in patients was mostly driven by Andy,[79,80] with a more recent interest by Krauss and colleagues.[82] Given the recent resurgence of exploring different neurosurgical targets for intractable, chronic pain control, this area may be of future interest.

P(A)VG Interventions

Boethius and colleagues[24] and Richardson and Akil[84–86] used previous work in animals[87–89] as evidence to target the PAG and PVG (**Table 5**) for alleviation of chronic and acute pain.[99] For Richardson and Akil, of the 6 patients they tested, 5 patients had the electrode traversing the PVG alongside the medial aspect of the nucleus parafascicularis. Of these 5 patients, 3 patients (phantom limb pain, carcinoma-related pain, and thalamic pain syndrome) showed good-to-excellent reduction in pain.[84] In the course of their study, they noted that stimulation of the PAG also resulted in pain reduction, albeit at the cost of increased side effects, including nystagmus, vertigo, and nausea. Their follow-up work included chronic implantation of electrodes targeting the PVG for patients with chronic intractable pain. Of these 8 patients, 7 patients (lumber disc disease, carcinoma, brachial plexus avulsion, spine/back/hip injury, pancoast tumor) showed fair to good results (the eighth patient was addicted to narcotics and did not complete the study).[85] In complementary work, Hosobuchi and colleagues[90] showed that PAG stimulation was effective in 6 patients (3 carcinoma pains, 1 diabetic neuropathy, 1 sacral chordoma, and 1 facial anesthesia dolorosa, albeit the latter had more relief with fifth VPM stimulation).

Working toward a mechanism and building on the work of others,[76] Hosobuchi and colleagues[25] would show higher levels of β-endorphins during PAG stimulation. These

results, in combination with studies, noted that the benefits of DBS for pain could be reversed by the opioid antagonist[76,90,100] naloxone, and an opioid-mediated mechanism was put forth. However, ultimately, further studies would not replicate the effect, changes in β-endorphin levels were attributed to contrast agents casting doubt on this as a mechanism.[27,51,101,102] Despite that lack of a cogent mechanism, PV(A)G stimulation use as a therapeutic tool for intractable chronic pain would continue to increase. As noted in the STH section, PV(A)G stimulation was often combined or compared with stimulation in other areas. This stimulation has led to the assertion that stimulation of the PAG/PVG is preferred in cases of somatogenic pain, and the STH is preferred in cases of neurogenic pain.[44] As a review of the PAG/PVG and STH charts clearly shows, this assertion is only partially consistent with the evidence.

Like the STH stimulation, PAG/PVG was evaluated in the clinical trials reported by Coffey,[77] although the data were not parsed by stimulation site, limiting any definitive conclusions. Importantly, since that time, many studies have attempted to address the efficacy of PAG/PVG stimulation better.[62,70,71,96–98] These studies include a randomized, placebo-controlled, N-of-1 series by Green and colleagues[96] and a meta-analysis by Bittar and colleagues,[97] both having favorable conclusions on the use of DBS for chronic intractable pain. A well-powered, double-blind, randomized, placebo-controlled trial has yet to be done.

PH Interventions

In the following section, reports on stimulation of the PH and surrounding area for the treatment of cluster headaches are briefly reviewed (**Table 6**; for a more comprehensive review of the specific topic, see Magis and Schoenen, 2012[116]). In expanding on the conventional targets of DBS for pain, Leone and colleagues[103,104] and Franzini and colleagues[105] reported that stimulation of the PH (targeted based on the circadian and hormonal findings with cluster headaches[117]) helped ameliorate cluster headache–related pain. Of the 5 patients reported, 2 were able to receive stimulation only and 3 were on lower doses of analgesic medication. They further expanded their findings a year later to 8 patients: 3 requiring no medication and 5 requiring low doses of methysergide and verapamil.[106] They would provide further evidence of the success of the treatment of a rare disorder known as short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing, which would be corroborated by another case report.[118] **Table 6** documents their growing cohort of patients,[109] including attempts to treat atypical facial pain, where stimulation of the PH was unsuccessful in 3 patients.[110] In addition, other groups would publish their results for stimulating the posterior thalamus for cluster headaches, mostly showing positive results,[107,111,112] although there were also notable failures.[113]

Given the calls for a larger, well-controlled, double-blind clinical trials, Fontaine and colleagues[114] would report on 11 patients in a prospective crossover, double-blind, multicenter study assessing the efficacy and safety of unilateral hypothalamic DBS in cluster headaches. Interestingly, during the 1-month randomization phase, there were no differences in primary or secondary outcomes between those with and without stimulation. In the

following open phase of the trial over the course of 10 months, however, there was notable success in 60% of the patients (in keeping with previous reports). Although the reasons for the discrepancy are not clear, the authors postulate that the rather short period (1 month) of randomization at the start of the trial may have been too brief because the effect is thought to take weeks to over a month. Second, the report stated that default stimulation parameters were used, whereas efficiency was only higher after highly individualized and exhaustive measures were taken to tune the stimulation parameters. Third, they noted higher variability than expected in their primary outcome measures, suggesting their study was underpowered. In an interesting follow-up using the same patients, Fontaine and colleagues[119] determined the anatomic localization of their placed electrodes using computed tomography and magnetic resonance imaging, determining that effective placements (using coordinates of studies listed in the chart) tended to be more posterior than the hypothalamus. In the 5 responders of the cohort of 10, structures located less than 2 mm from the centers of effective contacts were as follows: the mesencephalic gray substance, the red nucleus, the fascicle retroflexus, the fascicle longitudinal dorsal, the nucleus of ansa lenticularis, the fascicle longitudinal medial, and the thalamus superficialis medial. Revising their coordinates, Seijo and colleagues[115] modified their targeting to include the PH (additionally the stimulation area included the fasciculus mammillotegmentalis, the fasciculus mammillotegmentalis, and the fasciculus medialis telencephali). Using this targeting with 5 patients, an average of 54 days were used to optimize parameters, resulting in 2 patients becoming completely pain free, 2 having a reduction of more than 90%, and 1 having a reduction of attacks to half of the original value. In terms of long-term follow-up, Piacentino and colleagues[120] recently reported on 4 patients who had greater than a 50% decrease in pain intensity perception for more than 5 years. Clearly, the results are optimistic, although a better powered clinical trial is necessary to be conclusive.

Motor Cortex Interventions

Expanding beyond “deep brain” structures, Tsubokawa and colleagues[121] noted particular difficulty with VPLP and IC stimulation in thalamic syndrome patients and therefore pursued the stimulation of the cortex, particularly precentral and postcentral, to evaluate their potential for treatment of chronic pain. In a study of 11 patients with thalamic syndrome, they were able to show an improvement in the pain acutely in 8 of these patients, with 3 of those patients losing efficacy by 2 years. Since that time, research into motor cortex stimulation (MCS) has expanded drastically. This is addressed in the article by Ostergard and colleagues, “Motor Cortex Stimulation for Chronic pain” in this issue.

Other Areas

Along the course of DBS for chronic pain, a few other areas have been targeted for stimulation. In the mid-1980s, Katayama and colleagues[122] presented work on the successful stimulation of the pontomesencephalic parabrachial region for the alleviation of pain in 2 patients with cancer pain. Also, in the parabrachial region, in 1992, Young and colleagues[123] would stimulate the Kolliker Fuse nucleus, showing relief of pain in 3 of the 6 patients. However, there is no clear follow-up work on targeting the parabrachial region for DBS to alleviate chronic pain. More recently, Mallory and colleagues[124] targeted the NAcc ventral striatum in a case report of central poststroke pain, noting success when combining

NAcc stimulation with commiserate PV(A)G stimulation (although they report stimulating the NAcc alone helps alleviate pain). Finally, targeting the affective components of pain, Boccard and colleagues[125] recently reported success when stimulating the anterior cingulate cortex of a patient with neuropathic pain.

CONSIDERATIONS FOR PATIENT SELECTION AND TRIAL DESIGN

Given that the evidence for the use of chronic intracranial stimulation for the control of pain is still controversial, there is a clear need for well-designed and executed clinical trials. The aforementioned studies have highlighted a large number of points about researching pain in general and the role of intracranial stimulation specifically.

General Consideration of Pain Research

- There is no well-validated classification scheme for pain; the current use of somatogenic and neurogenic or nociceptive versus neuropathic is helpful, but not necessarily divided along the lines of therapeutic options.
- There is no well-validated and objective method of evaluating pain; current methods rely heavily on subjective reports (see the Visual Analog Scale [VAS] and McGill Pain Questionnaire [MPQ]).

Specific Considerations to Chronic Stimulation for the Treatment of Pain

- The patients used for chronic intracranial stimulation research are already biased because they have failed nearly all other pain-control methods.
- There is no easy way to optimize DBS parameters while also keeping double-blind and placebo-controlled requirements, especially if the stimulation results in a perceivable entity (paresthesias).
- Patients require adjustment of their parameters for optimal effect both in the operating room and during the long-term follow-up.
- Based on a limited pain classification scheme and lack of objective measures, it is hard to understand why patients have successful interventions while others fail.

Importantly, Plow and colleagues[33] have proposed an exciting clinical trial design (NCT01072656) for the use of intracranial stimulation, which includes a much needed control arm that has been absent in many past studies.

SUMMARY

The use of DBS for the control of intractable, chronic pain has a history stretching more than half a century. Within this literature, targets have varied from major white matter tracts like the internal capsule to a specific gray matter island, like the Kolliker Fuse nucleus. Perhaps more impressive, the type and causes of the chronic pain in the patients have been even more diverse from crush injuries to poststroke pain. In lieu of all this variability, it is not surprising that the field still has inconsistent results on the efficacy of DBS for treating pain.

As noted, much of the literature is retrospective case reports that leave much to be desired in terms of blinding, controls, and pain measures.

There have been only a few clinical trials, and those have had major limitations. Nevertheless, overall, the preponderance of evidence is in favor of DBS for specific patients. Although many would point to the clinical trials sponsored by Medtronic in the 1990s as a definitive challenge to the use of DBS for pain, it should be noted that those trials were hampered by a lack of enrollment, long-term follow-up, randomization, placebo control, and the inability to address the concerns listed in the general considerations on pain research and specific considerations to chronic stimulation for the treatment of pain sections. Thus, like the studies before those clinical trials, the results are hardly definitive. A major benefit of the publication of the Medtronic trials has been an increase in more rigorous studies being published on the use of DBS with pain. Furthermore, it has encouraged scientists and neurosurgeons to expand beyond the classical brain targets and explore other options within known pain and affective circuits. Finally, and most importantly, more recent and ongoing clinical trials have the promise of being flexible, while rigorous, well-controlled, randomized, and blind, allowing for more definitive conclusions on DBS efficacy in chronic pain treatment.

Acknowledgments

Funding Sources: No related funding sources.

REFERENCES

1. Spiegel EA, Wycis HT, Szekely EG, et al. Stimulation of Forel's field during stereotaxic operations in the human brain. Electroencephalogr Clin Neurophysiol. 1964; 16:537–48. [PubMed: 14189791]
2. Hassler R, Riechert T. Indications and localization of stereotactic brain operations. Nervenarzt. 1954; 25(11):441–7. in German. [PubMed: 14356288]
3. Cooper IS. Anterior chorodial artery ligation for involuntary movements. Science. 1953; 118(3059): 193. [PubMed: 13076243]
4. Albe Fessard D, Arfel G, Guiot G, et al. Characteristic electric activities of some cerebral structures in man. Ann Chir. 1963; 17:1185–214. in French. [PubMed: 14084565]
5. Bekhtereva NP, Grachev KV, Orlova AN, et al. Utilization of multiple electrodes implanted in the subcortical structure of the human brain for the treatment of hyperkinesis. Zh Nevropatol Psikhiatr Im S S Korsakova. 1963; 63:3–8. in Russian. [PubMed: 13970358]
6. Sem-Jacobsen CW. Depth electrographic stimulation and treatment of patients with Parkinson's disease including neurosurgical technique. Acta Neurol Scand Suppl. 1965; 13(Pt 1):365–77. [PubMed: 5320070]
7. Cotzias GC, Papavasiliou PS, Gellene R. Modification of Parkinsonism–chronic treatment with L-dopa. N Engl J Med. 1969; 280(7):337–45. [PubMed: 4178641]
8. Benabid AL, Pollak P, Louveau A, et al. Combined (thalamotomy and stimulation) stereotactic surgery of the VIM thalamic nucleus for bilateral Parkinson disease. Appl Neurophysiol. 1987; 50(1–6):344–6. [PubMed: 3329873]
9. Vingerhoets FJ, Villemure JG, Temperli P, et al. Subthalamic DBS replaces levodopa in Parkinson's disease: two-year follow-up. Neurology. 2002; 58(3):396–401. [PubMed: 11839838]
10. Marsden CD. Problems with long-term levodopa therapy for Parkinson's disease. Clin Neuropharmacol. 1994; 17(Suppl 2):S32–44. [PubMed: 9358193]
11. Limousin P, Krack P, Pollak P, et al. Electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med. 1998; 339(16):1105–11. [PubMed: 9770557]

12. Benabid AL, Pollak P, Gervason C, et al. Long-term suppression of tremor by chronic stimulation of the ventral intermediate thalamic nucleus. Lancet. 1991; 337(8738):403–6. [PubMed: 1671433]
13. Siegfried J, Lippitz B. Bilateral chronic electrostimulation of ventroposterolateral pallidum: a new therapeutic approach for alleviating all parkinsonian symptoms. Neurosurgery. 1994; 35(6):1126–9. discussion: 1129–30. [PubMed: 7885558]
14. Kumar R, Lozano AM, Kim YJ, et al. Double-blind evaluation of subthalamic nucleus deep brain stimulation in advanced Parkinson's disease. Neurology. 1998; 51(3):850–5. [PubMed: 9748038]
15. Heath, RG.; Mickle, WA. Evaluation of seven years' experience with depth electrode studies in human patients.. In: Re, R.; Odd, C., editors. Electrical studies on the unanesthetized brain. Harper & Brothers; New York: 1960. p. 214-47.
16. Ervin FR, Mark VH, Stevens J. Behavioral and affective responses to brain stimulation in man. Proc Annu Meet Am Psychopathol Assoc. 1969; 58:54–65. [PubMed: 4898742]
17. Gol A. Relief of pain by electrical stimulation of the septal area. J Neurol Sci. 1967; 5(1):115–20. [PubMed: 6061755]
18. Schvarcz JR. Chronic stimulation of the septal area for the relief of intractable pain. Appl Neurophysiol. 1985; 48(1–6):191–4. [PubMed: 3915645]
19. Schvarcz JR. Long-term results of stimulation of the septal area for relief of neurogenic pain. Acta Neurochir Suppl. 1993; 58:154–5. [PubMed: 8109280]
20. Olds J, Milner P. Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. J Comp Physiol Psychol. 1954; 47(6):419–27. [PubMed: 13233369]
21. Fields HL, Adams JE. Pain after cortical injury relieved by electrical stimulation of the internal capsule. Brain. 1974; 97(1):169–78. [PubMed: 4434168]
22. Adams JE, Hosobuchi Y, Fields HL. Stimulation of internal capsule for relief of chronic pain. J Neurosurg. 1974; 41(6):740–4. [PubMed: 4609304]
23. Hosobuchi Y, Adams JE, Rutkin B. Chronic thalamic and internal capsule stimulation for the control of central pain. Surg Neurol. 1975; 4(1):91–2. [PubMed: 1080907]
24. Boethius, J.; Lindblom, V.; Meyerson, BA., et al. Sensory functions of the skin in primates, with special reference to man. Pergamon Press; Oxford (United Kingdom): 1976. Effects of multifocal stimulation on pain and somatosensory functions.; p. 531-48.
25. Hosobuchi Y, Rossier J, Bloom FE, et al. Stimulation of human periaqueductal gray for pain relief increases immunoreactive beta-endorphin in ventricular fluid. Science. 1979; 203(4377):279–81. [PubMed: 83674]
26. Tsubokawa T, Yamamoto T, Katayama Y, et al. Deep brain stimulation for relief of intractable pain. Clinical results of thalamic relay stimulation (author's transl). Neurol Med Chir (Tokyo). 1982; 22(3):211–8. in Japanese. [PubMed: 6178991]
27. Tsubokawa T, Yamamoto T, Katayama Y, et al. Thalamic relay nucleus stimulation for relief of intractable pain. Clinical results and beta-endorphin immunoreactivity in the cerebrospinal fluid. Pain. 1984; 18(2):115–26. [PubMed: 6324055]
28. Namba S, Nakao Y, Matsumoto Y, et al. Electrical stimulation of the posterior limb of the internal capsule for treatment of thalamic pain. Appl Neurophysiol. 1984; 47(3):137–48. [PubMed: 6334494]
29. Namba S, Wani T, Shimizu Y, et al. Sensory and motor responses to deep brain stimulation. Correlation with anatomical structures. J Neurosurg. 1985; 63(2):224–34. [PubMed: 3894595]
30. Young RF, Kroening R, Fulton W, et al. Electrical stimulation of the brain in treatment of chronic pain. Experience over 5 years. J Neurosurg. 1985; 62(3):389–96. [PubMed: 3871844]
31. Kumar K, Toth C, Nath RK. Deep brain stimulation for intractable pain: a 15-year experience. Neurosurgery. 1997; 40(4):736–46. discussion: 746–7. [PubMed: 9092847]
32. Franzini A, Cordella R, Nazzi V, et al. Long-term chronic stimulation of internal capsule in poststroke pain and spasticity. Case report, long-term results and review of the literature. Stereotact Funct Neurosurg. 2008; 86(3):179–83. [PubMed: 18334861]
33. Plow EB, Malone DA Jr, Machado A. Deep brain stimulation of the ventral striatum/anterior limb of the internal capsule in thalamic pain syndrome: study protocol for a pilot randomized controlled trial. Trials. 2013; 14:241. [PubMed: 23902631]

34. Hosobuchi Y, Adams JE, Rutkin B. Chronic thalamic stimulation for the control of facial anesthesia dolorosa. Arch Neurol. 1973; 29(3):158–61. [PubMed: 4591720]
35. Mazars G, Merienne L, Ciolocca C. Intermittent analgesic thalamic stimulation. Preliminary note. Rev Neurol. 1973; 128(4):273–9. in French. [PubMed: 4774913]
36. Mazars G, Merienne L, Cioloca C. Treatment of certain types of pain with implantable thalamic stimulators. Neurochirurgie. 1974; 20(2):117–24. in French. [PubMed: 4418054]
37. Mazars GJ. Intermittent stimulation of nucleus ventralis posterolateralis for intractable pain. Surg Neurol. 1975; 4(1):93–5. [PubMed: 1080908]
38. Schvarcz JR. Chronic self-stimulation of the medial posterior inferior thalamus for the alleviation of deafferentation pain. Acta Neurochir Suppl. 1980; 30:295–301. [PubMed: 6937110]
39. Turnbull IM, Shulman R, Woodhurst WB. Thalamic stimulation for neuropathic pain. J Neurosurg. 1980; 52(4):486–93. [PubMed: 6966326]
40. Plotkin R. Results in 60 cases of deep brain stimulation for chronic intractable pain. Appl Neurophysiol. 1982; 45(1–2):173–8. [PubMed: 6977318]
41. Siegfried J. Monopolar electrical stimulation of nucleus ventroposteromedialis thalami for postherpetic facialpain. Appl Neurophysiol. 1982; 45(1–2):179–84. [PubMed: 6977319]
42. Roldan P, Broseta J, Barcia-Salorio JL. Chronic VPM stimulation for anesthesia dolorosa following trigeminal surgery. Appl Neurophysiol. 1982; 45(1–2):112–3. [PubMed: 6977312]
43. Tsubokawa T, Yamamoto T, Katayama Y, et al. Clinical results and physiological basis of thalamic relay nucleus stimulation for relief of intractable pain with morphine tolerance. Appl Neurophysiol. 1982; 45(1–2):143–55. [PubMed: 6977315]
44. Hosobuchi Y. Combined electrical stimulation of the periaqueductal gray matter and sensory thalamus. Appl Neurophysiol. 1983; 46(1–4):112–5. [PubMed: 6608316]
45. Tsubokawa T, Katayama Y, Yamamoto T, et al. Deafferentation pain and stimulation of the thalamic sensory relay nucleus: clinical and experimental study. Appl Neurophysiol. 1985; 48(1–6):166–71. [PubMed: 3017207]
46. Kumar K, Wyant GM. Deep brain stimulation for alleviating chronic intractable pain. Can J Surg. 1985; 28(1):20–2. [PubMed: 3871656]
47. Hosobuchi Y. Subcortical electrical stimulation for control of intractable pain in humans. Report of 122 cases (1970-1984). J Neurosurg. 1986; 64(4):543–53. [PubMed: 3485191]
48. Young RF, Brechner T. Electrical stimulation of the brain for relief of intractable pain due to cancer. Cancer. 1986; 57(6):1266–72. [PubMed: 3484665]
49. Siegfried J. Sensory thalamic neurostimulation for chronic pain. Pacing Clin Electrophysiol. 1987; 10(1 Pt 2):209–12. [PubMed: 2436180]
50. Levy RM, Lamb S, Adams JE. Treatment of chronic pain by deep brain stimulation: long term follow-up and review of the literature. Neurosurgery. 1987; 21(6):885–93. [PubMed: 3325851]
51. Young RF, Chambi VI. Pain relief by electrical stimulation of the periaqueductal and periventricular gray matter. Evidence for a non-opioid mechanism. J Neurosurg. 1987; 66(3):364–71. [PubMed: 3493333]
52. Kumar K, Wyant GM, Nath R. Deep brain stimulation for control of intractable pain in humans, present and future: a ten-year follow-up. Neurosurgery. 1990; 26(5):774–81. discussion: 781–2. [PubMed: 2352595]
53. Gybels J, Kupers R. Deep brain stimulation in the treatment of chronic pain in man: where and why? Neurophysiol Clin. 1990; 20(5):389–98. [PubMed: 2092202]
54. Kuroda R, Nakatani J, Yamada Y, et al. Location of a DBS-electrode in lateral thalamus for deafferentation pain. An autopsy case report. Acta Neurochir Suppl. 1991; 52:140–2. [PubMed: 1792955]
55. Hariz MI, Bergenheim AT. Thalamic stereotaxis for chronic pain: ablative lesion or stimulation? Stereotact Funct Neurosurg. 1995; 64(1):47–55. [PubMed: 8751314]
56. Taira T, Kawamura H, Takakura K. Posterior occipital approach in deep brain stimulation for both pain and involuntary movement. A case report. Stereotact Funct Neurosurg. 1998; 70(1):52–6. [PubMed: 9691241]

57. Katayama Y, Yamamoto T, Kobayashi K, et al. Motor cortex stimulation for phantom limb pain: comprehensive therapy with spinal cord and thalamic stimulation. Stereotact Funct Neurosurg. 2001; 77(1–4):159–62. [PubMed: 12378068]
58. Katayama Y, Yamamoto T, Kobayashi K, et al. Motor cortex stimulation for post-stroke pain: comparison of spinal cord and thalamic stimulation. Stereotact Funct Neurosurg. 2001; 77(1–4): 183–6. [PubMed: 12378074]
59. Nandi D, Smith H, Owen S, et al. Peri-ventricular grey stimulation versus motor cortex stimulation for post stroke neuropathic pain. J Clin Neurosci. 2002; 9(5):557–61. [PubMed: 12383415]
60. Nandi D, Aziz T, Carter H, et al. Thalamic field potentials in chronic central pain treated by periventricular gray stimulation – a series of eight cases. Pain. 2003; 101(1–2):97–107. [PubMed: 12507704]
61. Marchand S, Kupers RC, Bushnell MC, et al. Analgesic and placebo effects of thalamic stimulation. Pain. 2003; 105(3):481–8. [PubMed: 14527708]
62. Green AL, Owen SL, Davies P, et al. Deep brain stimulation for neuropathic cephalalgia. Cephalalgia. 2006; 26(5):561–7. [PubMed: 16674765]
63. Romanelli P, Heit G. Patient-controlled deep brain stimulation can overcome analgesic tolerance. Stereotact Funct Neurosurg. 2004; 82(2–3):77–9. [PubMed: 15305078]
64. Bittar RG, Otero S, Carter H, et al. Deep brain stimulation for phantom limb pain. J Clin Neurosci. 2005; 12(4):399–404. [PubMed: 15925769]
65. Yamamoto T, Katayama Y, Obuchi T, et al. Thalamic sensory relay nucleus stimulation for the treatment of peripheral deafferentation pain. Stereotact Funct Neurosurg. 2006; 84(4):180–3. [PubMed: 16905881]
66. Hamani C, Schwalb JM, Rezai AR, et al. Deep brain stimulation for chronic neuropathic pain: long-term outcome and the incidence of insertional effect. Pain. 2006; 125(1–2):188–96. [PubMed: 16797842]
67. Owen SL, Green AL, Nandi D, et al. Deep brain stimulation for neuropathic pain. Neuromodulation. 2006; 9(2):100–6. [PubMed: 22151633]
68. Owen SL, Green AL, Stein JF, et al. Deep brain stimulation for the alleviation of post-stroke neuropathic pain. Pain. 2006; 120(1–2):202–6. [PubMed: 16359796]
69. Rasche D, Rinaldi PC, Young RF, et al. Deep brain stimulation for the treatment of various chronic pain syndromes. Neurosurg Focus. 2006; 21(6):E8. [PubMed: 17341052]
70. Owen SL, Green AL, Nandi DD, et al. Deep brain stimulation for neuropathic pain. Acta Neurochir Suppl. 2007; 97(Pt 2):111–6. [PubMed: 17691296]
71. Boccard SG, Pereira EA, Moir L, et al. Long-term outcomes of deep brain stimulation for neuropathic pain. Neurosurgery. 2013; 72(2):221–30. discussion: 231. [PubMed: 23149975]
72. Pereira EA, Boccard SG, Linhares P, et al. Thalamic deep brain stimulation for neuropathic pain after amputation or brachial plexus avulsion. Neurosurg Focus. 2013; 35(3):E7.
73. Obrador S, Bravo G. Thalamic lesions for the treatment of facial neuralgias. J Neurol Neurosurg Psychiatry. 1960; 23:351–2.
74. Melzack R, Wall PD. Pain mechanisms: a new theory. Science. 1965; 150(3699):971–9. [PubMed: 5320816]
75. Hosobuchi Y. Tryptophan reversal of tolerance to analgesia induced by central grey stimulation. Lancet. 1978; 2(8079):47. [PubMed: 78245]
76. Meyerson BA, Boethius J, Carlsson AM. Percutaneous central gray stimulation for cancer pain. Appl Neurophysiol. 1978; 41(1–4):57–65. [PubMed: 310285]
77. Coffey RJ. Deep brain stimulation for chronic pain: results of two multicenter trials and a structured review. Pain Med. 2001; 2(3):183–92. [PubMed: 15102250]
78. Katayama Y, Yamamoto T, Kobayashi K, et al. Deep brain and motor cortex stimulation for post-stroke movement disorders and post-stroke pain. Acta Neurochir Suppl. 2003; 87:121–3. [PubMed: 14518537]
79. Andy OJ. Parafascicular-center median nuclei stimulation for intractable pain and dyskinesia (painful-dyskinesia). Appl Neurophysiol. 1980; 43(3–5):133–44. [PubMed: 6975062]

80. Andy OJ. Thalamic stimulation for chronic pain. Appl Neurophysiol. 1983; 46(1–4):116–23. [PubMed: 6367639]
81. Krauss JK, Pohle T, Weigel R, et al. Somatosensory thalamic stimulation versus center median-parafasicular complex stimulation in 11 patients with neuropathic pain. Stereotact Funct Neurosurg. 2001; 77:194.
82. Krauss JK, Pohle T, Weigel R, et al. Deep brain stimulation of the centre median-parafascicular complex in patients with movement disorders. J Neurol Neurosurg Psychiatry. 2002; 72(4):546–8. [PubMed: 11909924]
83. Weigel R, Krauss JK. Center median-parafascicular complex and pain control. Review from a neurosurgical perspective. Stereotact Funct Neurosurg. 2004; 82(2–3):115–26. [PubMed: 15305084]
84. Richardson DE, Akil H. Pain reduction by electrical brain stimulation in man. Part 1: acute administration in periaqueductal and periventricular sites. J Neurosurg. 1977; 47(2):178–83. [PubMed: 327030]
85. Richardson DE, Akil H. Pain reduction by electrical brain stimulation in man. Part 2: chronic self-administration in the periventricular gray matter. J Neurosurg. 1977; 47(2):184–94. [PubMed: 301558]
86. Richardson, DE.; Akil, H. Chronic Self-Administered brain stimulation for the relief of intractable pain.. Paper presented at: 7th Annual Meeting of Neuro Electric. Soc. 1974.; Louisiana. November 21, 1974;
87. Reynolds DV. Surgery in the rat during electrical analgesia induced by focal brain stimulation. Science. 1969; 164(3878):444–5. [PubMed: 4887743]
88. Mayer DJ, Wolfle TL, Akil H, et al. Analgesia from electrical stimulation in the brainstem of the rat. Science. 1971; 174(4016):1351–4. [PubMed: 5167502]
89. Cox VC, Valenstein ES. Attenuation of aversive properties of peripheral shock by hypothalamic stimulation. Science. 1965; 149(3681):323–5. [PubMed: 17838112]
90. Hosobuchi Y, Adams JE, Linchitz R. Pain relief by electrical stimulation of the central gray matter in humans and its reversal by naloxone. Science. 1977; 197(4299):183–6. [PubMed: 301658]
91. Dieckmann G, Witzmann A. Initial and long-term results of deep brain stimulation for chronic intractable pain. Appl Neurophysiol. 1982; 45(1–2):167–72. [PubMed: 6977317]
92. Boivie J, Meyerson BA. A correlative anatomical and clinical study of pain suppression by deep brain stimulation. Pain. 1982; 13(2):113–26. [PubMed: 6750509]
93. Baskin DS, Mehler WR, Hosobuchi Y, et al. Autopsy analysis of the safety, efficacy and cartography of electrical stimulation of the central gray in humans. Brain Res. 1986; 371(2):231–6. [PubMed: 3486027]
94. Hosobuchi Y. Dorsal periaqueductal gray-matter stimulation in humans. Pacing Clin Electrophysiol. 1987; 10(1 Pt 2):213–6. [PubMed: 2436181]
95. Tasker RR, Vilela Filho O. Deep brain stimulation for neuropathic pain. Stereotact Funct Neurosurg. 1995; 65(1–4):122–4. [PubMed: 8916340]
96. Green AL, Shad A, Watson R, et al. N-of-1 trials for assessing the efficacy of deep brain stimulation in neuropathic pain. Neuromodulation. 2004; 7(2):76–81. [PubMed: 22151187]
97. Bittar RG, Kar-Purkayastha I, Owen SL, et al. Deep brain stimulation for pain relief: a meta-analysis. J Clin Neurosci. 2005; 12(5):515–9. [PubMed: 15993077]
98. Owen SL, Heath J, Kringelbach M, et al. Pre-operative DTI and probabilistic tractography in four patients with deep brain stimulation for chronic pain. J Clin Neurosci. 2008; 15(7):801–5. [PubMed: 18495481]
99. Akil H, Liebeskind JC. Monoaminergic mechanisms of stimulation-produced analgesia. Brain Res. 1975; 94(2):279–96. [PubMed: 125141]
100. Adams JE. Naloxone reversal of analgesia produced by brain stimulation in the human. Pain. 1976; 2(2):161–6. [PubMed: 800249]
101. Dionne RA, Mueller GP, Young RF, et al. Contrast medium causes the apparent increase in beta-endorphin levels in human cerebrospinal fluid following brain stimulation. Pain. 1984; 20(4): 313–21. [PubMed: 6097857]

102. Fessler RG, Brown FD, Rachlin JR, et al. Elevated beta-endorphin in cerebrospinal fluid after electrical brain stimulation: artifact of contrast infusion? Science. 1984; 224(4652):1017–9. [PubMed: 6326266]
103. Leone M, Franzini A, Bussone G. Stereotactic stimulation of posterior hypothalamic gray matter in a patient with intractable cluster headache. N Engl J Med. 2001; 345(19):1428–9. [PubMed: 11794190]
104. Leone M, Franzini A, Broggi G, et al. Long-term follow-up of bilateral hypothalamic stimulation for intractable cluster headache. Brain. 2004; 127(Pt 10):2259–64. [PubMed: 15329350]
105. Franzini A, Ferroli P, Leone M, et al. Stimulation of the posterior hypothalamus for treatment of chronic intractable cluster headaches: first reported series. Neurosurgery. 2003; 52(5):1095–9. discussion: 1099–101. [PubMed: 12699552]
106. Franzini A, Ferroli P, Leone M, et al. Hypothalamic deep brain stimulation for the treatment of chronic cluster headaches: a series report. Neuromodulation. 2004; 7(1):1–8. [PubMed: 22151120]
107. Schoenen J, Di Clemente L, Vandenheede M, et al. Hypothalamic stimulation in chronic cluster headache: a pilot study of efficacy and mode of action. Brain. 2005; 128(Pt 4):940–7. [PubMed: 15689358]
108. Leone M, Franzini A, D'Andrea G, et al. Deep brain stimulation to relieve drug-resistant SUNCT. Ann Neurol. 2005; 57(6):924–7. [PubMed: 15929061]
109. Leone M, Franzini A, Broggi G, et al. Hypothalamic stimulation for intractable cluster headache: long-term experience. Neurology. 2006; 67(1):150–2. [PubMed: 16832097]
110. Broggi G, Franzini A, Leone M, et al. Update on neurosurgical treatment of chronic trigeminal autonomic cephalalgias and atypical facial pain with deep brain stimulation of posterior hypothalamus: results and comments. Neurol Sci. 2007; 28(Suppl 2):S138–45. [PubMed: 17508161]
111. Starr PA, Barbaro NM, Raskin NH, et al. Chronic stimulation of the posterior hypothalamic region for cluster headache: technique and 1-year results in four patients. J Neurosurg. 2007; 106(6):999–1005. [PubMed: 17564171]
112. Bartsch T, Pinsker MO, Rasche D, et al. Hypothalamic deep brain stimulation for cluster headache: experience from a new multicase series. Cephalalgia. 2008; 28(3):285–95. [PubMed: 18254897]
113. Pinsker MO, Bartsch T, Falk D, et al. Failure of deep brain stimulation of the posterior inferior hypothalamus in chronic cluster headache - report of two cases and review of the literature. Zentralbl Neurochir. 2008; 69(2):76–9. [PubMed: 18444218]
114. Fontaine D, Lazorthes Y, Mertens P, et al. Safety and efficacy of deep brain stimulation in refractory cluster headache: a randomized placebo-controlled double-blind trial followed by a 1-year open extension. J Headache Pain. 2010; 11(1):23–31. [PubMed: 19936616]
115. Seijo F, Saiz A, Lozano B, et al. Neuromodulation of the posterolateral hypothalamus for the treatment of chronic refractory cluster headache: experience in five patients with a modified anatomical target. Cephalalgia. 2011; 31(16):1634–41. [PubMed: 22116943]
116. Magis D, Schoenen J. Advances and challenges in neurostimulation for headaches. Lancet Neurol. 2012; 11(8):708–19. [PubMed: 22814542]
117. Leone M, Bussone G. A review of hormonal findings in cluster headache. Evidence for hypothalamic involvement. Cephalalgia. 1993; 13(5):309–17. [PubMed: 8242722]
118. Bartsch T, Falk D, Knudsen K, et al. Deep brain stimulation of the posterior hypothalamic area in intractable short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT). Cephalalgia. 2011; 31(13):1405–8. [PubMed: 21628443]
119. Fontaine D, Lanteri-Minet M, Ouchchane L, et al. Anatomical location of effective deep brain stimulation electrodes in chronic cluster headache. Brain. 2010; 133(Pt 4):1214–23. [PubMed: 20237130]
120. Piacentino M, D'Andrea G, Perini F, et al. Drug-resistant cluster headache: long-term evaluation of pain control by posterior hypothalamic deep-brain stimulation. World Neurosurg. 2014; 81442(2):e11–5. [PubMed: 23416782]

121. Tsubokawa T, Katayama Y, Yamamoto T, et al. Treatment of thalamic pain by chronic motor cortex stimulation. Pacing Clin Electrophysiol. 1991; 14(1):131–4. [PubMed: 1705329]

122. Katayama Y, Tsubokawa T, Hirayama T, et al. Pain relief following stimulation of the pontomesencephalic parabrachial region in humans: brain sites for nonopiate-mediated pain control. Appl Neurophysiol. 1985; 48(1–6):195–200. [PubMed: 3879789]

123. Young RF, Tronnier V, Rinaldi PC. Chronic stimulation of the Kolliker-Fuse nucleus region for relief of intractable pain in humans. J Neurosurg. 1992; 76(6):979–85. [PubMed: 1588433]

124. Mallory GW, Abulseoud O, Hwang SC, et al. The nucleus accumbens as a potential target for central poststroke pain. Mayo Clin Proc. 2012; 87(10):1025–31. [PubMed: 22980165]

125. Boccard SG, Pereira EA, Moir L, et al. Deep brain stimulation of the anterior cingulate cortex: targeting the affective component of chronic pain. Neuro-report. 2014; 25(2):83–8.

126. Ray CD, Burton CV. Deep brain stimulation for severe, chronic pain. Acta Neurochir Suppl (Wien). 1980; 30:289–93. [PubMed: 7008523]

KEY POINTS

- For more than half a century, neurosurgeons have attempted to treat pain from a diversity of causes using acute and chronic intracranial stimulation.
- Targets of stimulation have included the sensory thalamus, periventricular and periaqueductal gray, the septum, the internal capsule, the motor cortex, posterior hypothalamus, and more recently, the anterior cingulate cortex.
- The current work focuses on presenting and evaluating the evidence for the efficacy of these targets in a historical context while also highlighting the major challenges to having a double-blind placebo-controlled clinical trial.
- Considerations for pain research in general and use of intracranial targets specifically are included.

Table 1

Review of the studies investigating the clinical role for septal stimulation for the treatment of pain

Study, Year	Study Type	Pain Type	Total-(Implanted)-Success	Electrode and Stimulation Parameters	Side Effects
Heath & Mickle,[15] 1960	CS	RA/CP	6-NFS	4 Strand, silver-plated copper wire, plastic insulation, silver ball tip	Rapid speech, alert, acute relief of pain
Ervin et al,[16] 1969	CS	CP	NFS	NFS	Mild euphoria, acute relief of pain
Gol,[17] 1967	CS	CP/BP	6-1	Heavy, single-lead electrode, 6 terminal, silver ball tip, 2000–5000 c/s, 0–12 V	More cheerful, alert
Schvarcz,[18] 1985	CS	CP/DP	10-10-6	Standard DBS electrode	Feeling of warmth, well-being, relaxation
Schvarcz,[19] 1993	CS	CP/DP	19-19-12	Bipolar or tetrapolar electrode	Feeling of warmth, well-being

Abbreviations: BP, back pain; CP, cancer pain; CS, case series; NFS, not further specified; RA, rheumatoid arthritis; V, volts.

Table 2

Review of the studies investigating the clinical role for internal capsule stimulation for the treatment of pain

Study, Year	Study Type	Pain Type	Total-(Implanted)-Success	Electrode and Stimulation Parameters	Side Effects	Notes
Fields & Adams,[21] 1974	CR	SH	1-1-1	Medtronic, 30–150 Hz, 0.25–0.45 ms, 0.7 mA	Paresthesias	F-U: 12 mo
Adams et al,[22] 1974	CS	SH, PSP, SCI	6-5-5	Medtronic, 30–150 Hz, 0.25–0.45 ms, 0.7 mA	Paresthesias	STH electrodes; bilateral pain, patient shifted electrode position = lost unilateral therapeutic effect. VPLP stimulation led to worse pain
Hosobuchi et al,[23] 1975	Please see entry in the STH Section					
Boethius et al,[24] 1976	CS	AD, TPS, PI, PLP	5-5-4	Medtronic, 10–100 Hz, 0.1–0.3 ms, 0.15–7 mA	Motor responses, visual phenomena	Pulvinar, CM-Pf, STH, PAG electrodes; Pulvinar, STH, IC successful
Hosobuchi et al,[25] 1979	Please see entry in the PV(A)G Section					
Tsubokawa et al,[26] 1982	Please see entry in the STH Section					
Tsubokawa et al,[27] 1984	Please see entry in the STH Section					
Namba et al,[28] 1984	CS	PSP, TPS	7-6-5	Medtronic, 50 Hz, 0.2–1.0 ms, 2–8 V	Feeling of warmth	F-U: 9–31 mo
Namba et al,[29] 1985	CS	PSP, TPS, MS	11-11-8	Medtronic, 50 Hz, 0.6 ms, 2–3 V	Paresthesias; muscle contraction (putamen involvement)	STH electrodes; most medial/posterior IC past the posterior commissure level
Young et al,[30] 1985	Please see entry in the PV(A)G Section					
Kumar et al,[31] 1997	Please see entry in the PV(A)G Section					
Famzini et al,[32] 2008	CR	TS	1-1-1	Medtronic, 3389, 100 Hz, 60 ms, 1 V	Paresthesias, contralateral motor responses	Pain/spasticity reduction; F-U 60+ mo
Plow et al,[33] 2013	Write up of design of clinical trial NCT01072656					

Abbreviations: AD, anesthesia dolorosa; CR, case report; CS, case series; F-U, follow-up; Hz, Hertz; mA, milliampere; ms, millisecond; PI, plexus injury; PLP, phantom limb pain; PSP, poststroke pain; SCI, spinal cord injury; SH, subdural hematoma; TPS, thalamic pain syndrome; V, volts.

Table 3

Review of the studies investigating the clinical role for STH stimulation for the treatment of pain

Study, Year	Study Type	Pain Type	Total-(Implanted)-Success	Electrode and Stimulation (F, PW, V)	Side Effects	Notes
Hosobuchi et al,[34] 1973	CS	AD	5-4	7 Intertwined, insulated, platinum wires. 0–4.5 V, 0.4-ms pulse, 60–125 Hz	Paresthesias	F-U: 3–24 mo
Mazars et al,[35] 1973	CS	PLP, PHP, AD, DP	14-13	Monopolar or bipolar gold/copper electrodes, 0.6–1.8 V, 20–50 Hz, 2-ms pulse	NFS	NFS
Mazars et al,[36] 1974	CS	PLP, AD, TPS, PHP	25-18	Monopolar or bipolar gold/copper electrodes, 0.6–1.8 V, 20–50 Hz, 2-ms pulse	NFS	First cohort of 17 patients: external stimulators; second cohort of 8 patients: implantable stimulators
Adams et al,[22] 1974	Please see entry in the IC Section					
Hosobuchi et al,[23] 1975	CS	AD, TPS, PP	11-9	7 Intertwined, insulated, platinum wires. 0–4.5 V, 0.4-ms pulse, 60–125 Hz	NFS	IC electrodes; 2 patients who failed, medullary syndrome
Mazars,[37] 1975	CS	PLP, AD, TPS, PHP, PP, PI, CP	44-29	Monopolar or bipolar gold/copper electrodes, 0.6–1.8 V, 20–50 Hz, 2 ms	NFS	NFS
Boethius et al,[24] 1976	Please see entry in the IC Section					
Schvarcz,[38] 1980	CS	TPS, PCD, SCI	6-6-4	Medtronic, 20 Hz, 0.25 ms, 0.5 mA	Sensation of well-being and relaxation	Medial posterior inferior thalamic stimulation, F-U: 6–42 mo
Turnbull et al,[39] 1980	CS	LA, PI, CRPS	18-14-12	Medtronic, 75–100 Hz, NFS	Paresthesias	PV(A)G electrodes
Plotkin,[40] 1982	Please see entry in the PV(A)G Section					
Siegfried,[41] 1982	CS	PHP	10-8	Platinum electrode, monopolar, 33–195 Hz, NFS	NFS	F-U: 8–17 mo
Roldan et al,[42] 1982	CS	AD	2-2-2	Medtronic, 80–120 Hz, NFS	NFS	F-U: 5–11 mo
Tsubokawa et al,[26] 1982	CS	CP, TPS, PP	5-5-4	Medtronic, 50 Hz, 200 μs, 0.1–2.0 V	Stimulation tolerance	PV(A)G, IC electrodes; L-Dopa supplement
Tsubokawa et al,[43] 1982	CS	SCI, STP, PLP	6-6-5	Medtronic, 25–100 Hz, NFS	Rapid stimulation tolerance noted	Used L-Dopa and L-Tryptophan for stimulation tolerance, F-U: 12 mo
Hosobuchi,[44] 1983	Please see entry in the PV(A)G Section					

Study, Year	Study Type	Pain Type	Total-(Implanted)-Success	Electrode and Stimulation (F, PW, V)	Side Effects	Notes
Tsubokawa et al,[27] 1984	CS	CP, PLP	14-14-13	Platinum electrode, NFS	Stimulation tolerance noted	PV(A)G, IC electrodes; no clear relationship between STH stimulation and β-Endorphin/pain levels
Tsubokawa et al,[45] 1985	CS	PLP, PHP, CP	24-24-24	Medtronic, NFS		PV(A)G electrodes
Namba et al,[29] 1985	Please see entry in the IC Section					
Schvarcz,[18] 1985	Please see entry in Septal Section					
Young et al,[30] 1985	Please see entry in the PV(A)G Section					
Kumar & Wyant,[46] 1985	Please see entry in the PV(A)G Section					
Hosobuchi,[47] 1986	Please see entry in the PV(A)G Section					
Young & Brechner,[48] 1986	Please see entry in the PV(A)G Section					
Siegfried,[49] 1987	CS	PHP, AD, TSP, PI, PLP, STP, PP, DP	112-112-89	Medtronic, 33–100 Hz, 0.5–2 ms, 0.5–3 V	Paresthesias	F-U: 6–72 mo
Levy et al,[50] 1987	CS	TPS, PN, AD, PP, PCD, PLP, CP, BP	141-141-84I, 42LT	Medtronic, STH, 20–100 Hz, 3–8 V; PV(A)G, 5–15 Hz, 1–5 V	PV(A)G: diplopia, nausea, vertical gaze palsies, blurred vision, horizontal nystagmus, persistent oscillopsia; STH, paresthesias, local pain	PV(A)G electrodes; review of literature, differentiated deafferentation and nociceptive pain, F-U: 24–169 mo
Young & Chambi,[51] 1987	Please see entry in the PV(A)G Section					
Kumar et al,[52] 1990	Please see entry in the PV(A)G Section					
Gybels & Kupers,[53] 1990	CS	PHP, TPS, PLP, FBS, PI, AD, SCI	36-36-22I, 11LT	NFS	NFS	F-U: up to 120 mo, 48 mo avg
Kuroda et al,[54] 1991	CR	CM	1-1-1	Medtronic, NFS	NFS	Histologic analysis of placement medial lemniscus and VIM
Schvarcz,[19] 1993	Please see entry in the Septal Section					
Hariz & Bergenheim,[55] 1995	CS	PLP, DP, TPS, CP	14-9	Monopolar ISSAL, NFS	Paresthesias	Comparison to ablative procedures, F-U: 1–72 mo
Taira et al,[56] 1998	CR	FP	1-1-1	Medtronic 3387, 200 Hz, 100 μs, NFS	NFS	Patient cotreated for pain/movement disorder, F-U: 10 mo

Study, Year	Study Type	Pain Type	Total-(Implanted)-Success	Electrode and Stimulation (F, PW, V)	Side Effects	Notes
Katayama et al,[57] 2001	CS	PLP	19-10-6	Medtronic, NFS	NFS	10 STH electrodes after spinal cord stimulation failed
Katayama et al,[58] 2001	CS	PSP	45-12-7	Medtronic, NFS	NFS	12 STH electrodes after spinal cord stimulation failed
Coffey,[77] 2001	CT MC P	LBP, LP, TPS, PI, PHP, TMJ, AD, MS, FBS	194-169-90I, 30LT for the 3380 trial; 50-37-8I, 5LT for the 3387 trial	Medtronic, 3380/3387, NFS	NFS	Data not parsed for analysis of target location
Nandi et al,[59] 2002	Please see entry in the PV(A)G Section					
Nandi et al,[60] 2003	Please see entry in the PV(A)G Section					
Marchand et al,[61] 2003	CS PC Pseudo-DB	TN, FP, LP, PI	6-6-6	NFS	NFS	Small, significant effect of stimulation vs control
Green et al,[62] 2004	Please see entry in the PV(A)G Section					
Romanelli & Heit,[63] 2004	CR	PSP	1-1-1	Medtronic 3387, 31–130 Hz, 60 μs, 0–3.0 V	Stimulation tolerance	Patient tolerance at 29 mo, autonomous control of stimulation mitigated tolerance
Bittar et al,[64] 2005	Please see entry in the PV(A)G Section					
Yamamoto et al,[65] 2006	CS	PLP, STP	18-18-14	Medtronic 3387, 20–135 Hz, 0.15–0.21 ms, NFS	NFS	NFS
Hamani et al,[66] 2006	CS R	PSP, FP, PLP, MS, SCI	21-13-5	Medtronic 3387, 25–125 Hz, 60–250 μs, 0–10 V	Insertional effect of 45%	PV(A)G electrodes
Owen et al,[67] 2006	Please see entry in the PV(A)G Section					
Owen et al,[68] 2006	Please see entry in the PV(A)G Section					
Green et al,[62] 2006	Please see entry in the PV(A)G Section					
Rasche et al,[69] 2006	Please see entry in the PV(A)G Section					
Owen et al,[70] 2007	Please see entry in the PV(A)G Section					
Boccard et al,[71] 2013	Please see entry in the PV(A)G Section					
Pereira et al,[72] 2013	CS P	PLP, PI	12-11-11	Medtronic 3387, 5–50 Hz, 200–450 μs, 0.5–5 V	Unremarkable	F-U at 1, 3, 6, and 12 mo

Abbreviations: AD, anesthesia dolorosa; CP, cancer pain; CR, case report; CRPS, complex regional pain syndrome; CS, case series; CT, clinical trial; DB, double blind; F-U, follow-up; FBS, failed back syndrome; FP, facial pain; Hz, Hertz; LBP, lower back pain; LP, leg pain; mA, milliampere; MS, multiple sclerosis; ms, millisecond; NFS, not further specified; P, prospective; PHP, postherpetic pain; PI, plexus injury; PLP, phantom limb pain; PP, paraplegia pain; PSP, poststroke pain; R, retrospective; SCI, spinal cord injury; STP, stump pain; TMJ, temporo-mandibular joint; TN, trigeminal neuralgia; TPS, thalamic pain syndrome; V, volts.

Table 4

Review of the studies investigating the clinical role for centro-median parafascicular complex stimulation for the treatment of pain

Study, Year	Type of Study	Type of Patient	Total-(Implanted)-Success	Electrode and Stimulation Parameters	Side Effects	Notes
Boethius et al,[24] 1976	Please see the IC Section					
Ray & Burton,[126] 1980	CS	FBS, CP, SCI, PSP, TSP, PLP	28-26-23	Medtronic, NFS	Feeling of warmth, visual effects	F-U: 1–33 mo
Andy,[79] 1980	CS	PAD	4-4-4	Bipolar platinum electrode. 25–125 Hz, 0.1–0.5 ms, 6–20 V	NFS	4 Patients with dyskinesia, 1 without pain but stimulation treated dyskinesia
Andy,[80] 1983	CS	TPS, HA	5-5-5	Electrode NFS, 50 Hz, 200 ms, 0.1–5.0 V	NFS	Stimulation of the CM-Pf with concurrent EEG recordings
Krauss et al,[81] 2001	CS P	NFS	11-10-10	Quadripolar electrodes, NFS	NFS	CM-Pf was compared with STH stimulation and was found more efficacious
Krauss et al,[82] 2002	CS P	—	3-2-2	Medtronic 3387, NFS	NFS	Part of a larger case series, this paper focused on movement disorders

Abbreviations: CP, cancer pain; CS, case series; EEG, electroencephalogram; F-U, follow-up; FBS, failed back syndrome; HA, headache; Hz, Hertz; ms, millisecond; NFS, not further specified; P, prospective; PAD, pain associated with dyskinesia; PLP, phantom limb pain; PSP, poststroke pain; SCI, spinal cord injury; TPS, thalamic pain syndrome; V, volts.

Table 5

Review of the studies investigating the clinical role for PVG/PAG stimulation for the treatment of pain

Study, Year	Study Type	Pain Type	Total-(Implanted)-Success	Electrode and Stimulation Parameters	Side Effects	Notes
Boethius et al,[24] 1976	Please see entry in the IC Section					
Richardsen & Akil,[84] 1977	CS	PLP, CP, TPS	6-3	Radionics, Monopolar, stainless steel electrode, 25–75 Hz, 0.5–5 V	Nystagmus, vertigo, nausea	Five patients had an electrode over the PVG
Richardsen & Akil,[85] 1977	CS	SCI, CP, PI, BP	8-7-7	Medtronic, 0–250 Hz, 0.250 ms, 0–4 V	Paresthesias, relaxation, dizziness, anxiety	F-U: 2–18 mo
Hosobuchi et al,[90] 1977	CS PC	CP, PN, AD	6-6-5	Medtronic, 10–20 Hz, 0.2–1.2 ms, 3–4 V	Oscillopsia, ocular fluttering, nausea, hot feeling, stimulation tolerance	Patient developed tolerance, stopped stimulation, and tolerance decreased, F-U: 3–18 mo
Meyerson et al,[76] 1978	CS	CP	9-7	Custom, platinum-iridium, 4–6 contacts, NFS	Transient diplopia, pleasant warmth spreading to body	Used L-Dopa, F-U: average 3 mo
Hosobuchi et al,[25] 1979	CS	PCD, TPS, LA, CP	6-6	Medtronic, PV(A)G, 5–20 Hz, 3–10 V; IC, 50–75 Hz, 3–5 V		IC electrodes
Turnbull et al,[39] 1980	Please see entry in the STH Section					
Dieckmann & Witzmann,[91] 1982	CS	PI, PLP, AD, TPS, PP, PHP, PCD	52: 23 PVG/PAG & 23 STH-32	Multiple platinum electrode types, NFS		F-U: 6–30 mo
Plotkin,[40] 1982	CS	FBS, CP, PP, STP, BP	48-38	Medtronic, NFS	NFS	STH electrodes (12 reported, NFS); F-U: 6–42 mo
Boivie & Meyerson,[92] 1982	CS	CP	5-5-4	6-Pole, platinum iridium, 30 Hz, 0.2 ms, 0.2–0.4 mA	Pleasant feeling of warmth	Confirmed anatomic location; F-U 1–17 mo
Hosobuchi,[44] 1983	CS	BP, LP, CIP	11-11-11	Medtronic, 2–60 Hz, 0–10 V, 0.1–0.5 ms	Paresthesia with VPLP/VPM, headache with dual stimulation	Dual implant of PAG and STH, F-U: 12–36 mo
Tsubowkawa et al,[27] 1984	Please see entry in the STH Section					
Schvarcz,[18] 1985	Please see entry in Septal Section					
Young et al,[30] 1985	CS	FBS, CP, SCI, PHP, PI	48-43-38	Medtronic, NFS	Eye movement disorders, motor responses	IC, STH electrodes; F-U: 2–60 mo, 20 avg
Kumar & Wyant,[46] 1985	CS	BP, CP	18-18-14	Medtronic, 50–100 Hz, 0.5 ms, 3–4 V	Transient blurred vision	Subthalamic nucleus electrodes; F-U: 6–48 mo

Study, Year	Study Type	Pain Type	Total-(Implanted)-Success	Electrode and Stimulation Parameters	Side Effects	Notes
Tsubokawa et al,[45] 1985	Please see entry in the STH Section					
Young & Brechner,[48] 1986	CS	CP	17-16-15	NFS	NFS	STH electrodes; F-U: 1–21 mo 5.8 avg
Hosobuchi,[47] 1986	CS	TP, AD, PHP, PI, PP, PLP, PCD, BP, LP	65 PV(A)G, 76 STH: 64 PV(A)G, 252STH, 50 PV(A)G, 44 STH	Medtronic, PAG, 30–30 Hz, 0.2–0.3 ms, 2–4 V; VPLP/VPM, 50–100 Hz, 0.2–0.3 ms, 2–6 V	Dysconjugate vertical eye movements	Use of L-Dopa, L-Tryptophan, F-U: 24–168 mo
Baskins et al,[93] 1986	CS MC	CP, PN	7-7-7I, 6LT	Medtronic, 20 Hz, 1–4 V, NFS	Stimulation tolerance	Confirmed anatomic location; F-U: 1–7 mo
Hosobuchi,[94] 1987	CS	CP	7-2-2	Monopolar electrode, Pulse width 0.5 ms, 0.5–1.5 Amps, 30 Hz	5 Reported feelings of nausea, fright, piloerection, cold sensation	Stimulation of dorsal PAG
Young & Chambi,[51] 1987	CS	NFS	52-45-45I, 29LT	Medtronic, 60 Hz, 0.1–1 ms, NFS	High levels of stimulation tolerance, feeling of warmth, diplopia, oscillopsia	STH electrodes in separate cohort, no Naloxone reversal
Levy et al,[50] 1987	Please see entry in the STH Section					
Kumar et al,[52] 1990	CS R	BP, LP, TPS, PN, CP	48-39-30	Medtronic, PVG, 25–50 Hz, 0.1–0.5 ms, 1–5 V; VPM/VPLP, 50–100 Hz, 0.2–0.8 ms, 3–8 V	Blurred vision, stimulation tolerance	STH electrodes; F-U: 6–120 mo
Gybels & Kupers,[53] 1993	CS	TPS, PI, PLP, SCI, FBS	36-36-22I, 211LT	NFS		
Schvarcz,[19] 1993	Please see entry in the Septal Section					
Tasker & Vilela Filho,[95] 1995	CS	NFS	54-25-15	NFS	Warmth, pleasure	Ventrocaudal nucleus electrodes; compare PAG vs PVG
Kumar et al,[31] 1997	CS R	FBS, PHP, TPS, TN, CP, PLP	68-53-42	Medtronic 3280 & 3387, PV(A)G, 25–50 Hz, 0.1–0.5 ms, 1–5 V; STH, 50–100 Hz, 0.2–0.8 ms, 2–8 V	Stimulation tolerance	IC and STH electrodes; F-U: 78 mo avg
Nandi et al,[59] 2002	CS	PSP	4-2-2	Medtronic 3387, 3389, 15 Hz, 0.45 ms, 5 V	Motor response	STH and MC electrodes; failure of MCS in 5/6
Nandi et al,[60] 2003	CS	PSP, TN, MS	8-6-6	Medtronic 3389, 3387, 5-35 Hz, 210 μs, 1.5–2.5 V	PV(A)AG >50 Hz elicited pain, STH elicited paresthesias	STH electrodes; noted a correlation of thalamic electrical activity and chronic pain, F-U: 3–30 mo, 9 mo avg
Green et al,[96] 2004	CT P PC RA	TPS, PLP, PHP	7-7-4	Medtronic 3387, NFS	Feeling of warmth	STH electrodes; F-U at 6mo

Study, Year	Study Type	Pain Type	Total-(Implanted)-Success	Electrode and Stimulation Parameters	Side Effects	Notes
Bittar et al,[64] 2005	CS	PLP	3-3-3	Medtronic 3387, NFS		STH electrodes; F-U: 8–20 mo
Bittar et al,[97] 2005	Meta-analysis: “DBS is frequently effective when used in well-selected patients”					
Hamani et al,[66] 2006	Please see entry in the STH Section					
Owen et al,[67] 2006	CS P	PSP, PLP, AD, SCI	34-26-14	Medtroinic 3387, PVG, 5–30 Hz, 120–450 ms, 0.8–4.5 V; STH, 10–50 Hz, 60–400 ms, 0.7–4.4 V	NFS	STH electrodes
Owen et al,[68] 2006	CS R	PSP	15-12-12	Medtronic 3387, NFS	Eye bobbing	STH electrodes; F-U: 27 avg
Green et al,[62] 2006	CS P	AD, TN, POP	7-7-5	Medtronic 3387, 10–50 Hz, 120 μs, <3 V	Feeling of warmth, paresthesias, eye disorders	STH electrodes
Rasche et al,[69] 2006	CS	FBS, AD, PLP, SCI, PSP, PHP	56-32-22	Medtronic 3387, NFS	PVG: feeling of warmth, dizziness, floating, eye deviations, gaze paralysis; STH: paresthesias	STH electrodes; F-U: 12–96 mo
Owen et al,[70] 2007	CS	PSP, PLP, AD, SCI, MS, PHP, CP	47-38-32	Medtronic 3387, PV(A) G, 5–30 Hz, 120–450 ms, 0.8–4.5 V; STH, 10–50 Hz, 60–400 ms, 0.7–4.4 V	PVG: feeling of warmth; STH: paresthesias	STH electrodes; PV(A)G alone or with STH stimulation was most efficacious
Owen et al,[98] 2008	CS	PSP, PI, STP	4-3-3	Medtronic 3387, NFS	NFS	Surgical planning with diffusion tensor imaging
Boccard et al,[71] 2013	CSP	PLP, STP, PI, PSP, SCI, FP	85-74-39	Medtronic 3387, St. Jude 6143, 5–50 Hz, 200–450 μs, 0.5–5 V	NFS	STH electrodes; F-U: 28 mo avg

Abbreviations: AD, anesthesia dolorosa; BP, back pain; CP, cancer pain; CS, case series; CT, clinical trial; F-U, follow-up; FP, face pain; FBS, failed back syndrome; Hz, Hertz; LP, leg pain; mA, milliampere; MC, multicenter; MS, multiple sclerosis; ms, millisecond; NFS, not further specified; P, prospective; PHP, postherpetic pain; PI, plexus injury; PLP, phantom limb pain; POP, postoperative pain; PP, paraplegia pain; PSP, poststroke pain; R, retrospective; SCI, spinal cord injury; STP, stump pain; TN, trigeminal neuralgia; TPS, thalamic pain syndrome; V, volts.

Table 6

Review of the studies investigating the clinical role for PH stimulation for the treatment of pain

Study, Year	Study Type	Pain Type	Total-(Implanted)-Success	Electrode and Stimulation Parameters	Side Effects	Notes
Leone et al,[103] 2001 Leone et al,[104] 2004	CR	CH	1-1-1	Medtronic 3389, 180 Hz, 60 μs, 1–7 V	NFS	F-U: 42 mo
Franzini et al,[105] 2003	CS	CH	5-5-5	Medtronic 3389, 180 Hz, 60 μs, 1–7 V	>4 V: conjugated eye deviation, extreme verbal reports (eg, "near to death")	F-U: 2–22 mo
Franzini et al,[106] 2004	CS	CH	8-8-8	Medtronic 3389, 180 Hz, 60 μs, 1–3.8 V	NFS	F-U: 2–26 mo
Schoenen et al,[107] 2005	CS	CH	6-4-4	Medtronic 3389, 180 Hz, 60 μs, 1–3 V	Transient diplopia, dizziness	One patient died of intracerebral hemorrhage with ventricular inundation, F-U: 14.5 mo avg
Leone et al,[108] 2005	CR	SUNCT	1-1-1	Medtronic 3389, 180 Hz, 60 μs, 1–4 V	>4 V diplopia	Patient underwent blind stimulator deactivation and symptoms reappeared
Leone et al,[109] 2006	CS	CH	16-16-16	Medtronic 3389, 180 Hz, 60 μs, 1–7 V	Hemorrhage of the 3rd ventricle, diplopia	9 patients stimulators turned off, single blind, and recurrence of symptoms, F-U: 23 mo
Broggi et al,[110] 2007	CS	SUNCT, CH, FP	20-?-14	Medtronic 3389, 180 Hz, 60 μs, 1–7 V	NFS	4 Cases of stimulation cessation leading to attacks, F-U: 23 mo avg
Starr et al,[111] 2007	CS	CH	4-2	Medtronic 3387, 180 Hz, 60 μs, 0–3 V	NFS	—
Bartsch et al,[112] 2008	CS	CH	6-3	Medtronic 3387, 3389, 130–185 Hz, 60 μs, 0–5.5 V	Vertigo and diplopia	F-U: 17-mo avg
Pinsker et al,[113] 2008	CS	CH	2-0	Medtronic, 180–185 Hz, 60 μs, 3–5.5 V	NFS	Patients showed an initial response, by 3 mo pain returned
Fontaine et al,[114] 2010	CT PC DB MC P	CH	11-6	Medtronic 3389, 185 Hz, 60 μs, set to 3 V or 80% of side effects	Transient visual disturbances, hemiparesis, micturition syncope	Reported successes in open arm of the trial
Seijo et al,[115] 2011	CS	CH	5-5	Medtronic 3389, 130 Hz, 60–12 μs, 2–3.5 V	Myosis, euphoria, diplopia	F-U: 33 mo avg

Abbreviations: avg, average; CH, chronic headache; CR, case report; CS, case series; CT, clinical trial; DB, double blind; F-U, follow-up; FP, face pain; Hz, Hertz; NFS, not further specified; P, prospective; SUNCT, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing; V, volts.