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REVIEW

Neuropathic Pain and Deep Brain Stimulation

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Abstract Deep brain stimulation (DBS) is a neurosurgical intervention the efficacy, safety, and utility of which are established in the treatment of Parkinson's disease. For the treatment of chronic, neuropathic pain refractory to medical therapies, many prospective case series have been reported, but few have published findings from patients treated with current standards of neuroimaging and stimulator technology over the last decade . We summarize the history, science, selection, assessment, surgery, programming, and personal clinical experience of DBS of the ventral posterior thalamus, periventricular/periaqueductal gray matter, and latterly rostral anterior cingulate cortex (Cg24) in 113 patients treated at 2 centers (John Radcliffe, Oxford, UK, and Hospital de São João, Porto, Portugal) over 13 years. Several experienced centers continue DBS for chronic pain, with success in selected patients, in particular those with pain after amputation, brachial plexus injury, stroke, and cephalalgias including anesthesia dolorosa. Other successes include pain after multiple sclerosis and spine injury. Somatotopic coverage during awake surgery is important in our technique, with cingulate DBS under general anesthesia considered for whole or hemibody pain, or after unsuccessful DBS of other targets. Findings discussed from neuroimaging modalities, invasive neurophysiological insights from local field potential recording, and autonomic assessments may translate into improved patient selection and enhanced efficacy, encouraging larger clinical trials.

Key Words Deep brain stimulation · chronic pain · sensory thalamus · periaqueductal gray · cingulate

Introduction

"When one sets out to make a historical survey of surgical attempts to relieve the tremor and rigor in Parkinson's disease, one cannot help feeling that it would have been a far easier task to list those nervous structures which have not been attacked", remarked the pioneer neurosurgeon Lauri Laitinen [1, 2]. Neurosurgical attempts to relieve intractable pain echo his sentiment—all structures from peripheral nerve, through dorsal root, spinal cord, midbrain, and thalamus to cingulate cortex having been first lesioned and later electrically stimulated or perfused with analgesics or anesthetics (Fig. 1). Yet chronic pain continues to present a considerable burden to society, transcending many debilitating medical diseases, including cancer, stroke, trauma, and failed surgery [3]. Its prevalence may be >20 % [4]. Neuropathic pain was recently redefined as pain caused by a lesion or disease of the somatosensory system [5]. Its symptom severity and duration are often greater than for other types of chronic pain [6], with 5 % of adults debilitated despite analgesic medication [7]. For such patients, neurosurgery offers several treatments.

Impetus for deep brain stimulation (DBS) was provided in the mid-1960s by the theoretical paradigm shift initiated by Melzack and Wall's gate theory [8], and advances in stimulator technology. Gate theory was first translated into implantable peripheral nerve stimulators [9] and then into spinal cord stimulation (SCS) [10], developed by Medtronic

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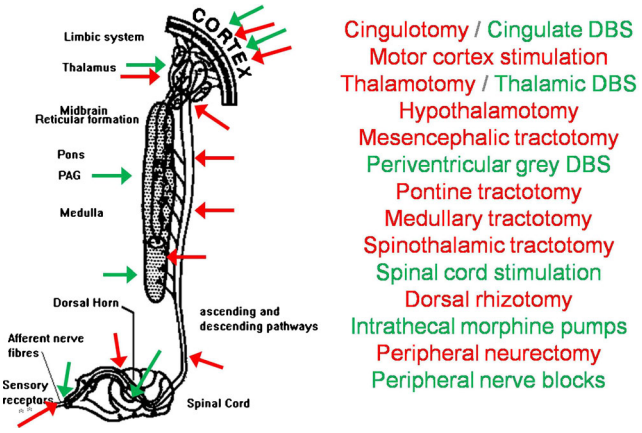

Fig. 1 Structures in the pain neuromatrix targeted by ablative neurosurgery (in red) and electrical stimulation or neuromodulation (in green). DBS = deep brain stimulation; PAG = periaqueductal gray

(Minneapolis, MN, USA) into a commercially available, permanently implantable device [11, 12].

Identification of the periventricular and periaqueductal gray (PAG) regions as a target for DBS has its origins in animal research. Reynolds and others were able to perform major surgery in awake rodents using analgesia induced by PAG stimulation alone [13, 14]. Pain relief by PAG DBS was first reported in patients by Richardson and Akil, and then Hosobuchi [15–18]. Evidence supporting ventral posterior lateral and medial (VPL/VPM) thalamic nuclei and adjacent structures as putative targets for DBS came from ablative surgery [19–22], leading Hosobuchi to treat anesthesia dolorosa with VPM thalamic DBS [23]. Several others pioneered thalamic DBS, including Mazars [24–27] and Adams who, along with Hosobuchi, also targeted the internal capsule [28–30]. Observations from inadvertent localization errors and investigations into current spread from the PAG led others to target more medial thalamic nuclei, including the centromedian-parafascicular complex (Cm-Pf) [31–34]. The rostral anterior cingulate cortex (Cg24) was recently targeted for DBS on the basis of functional neuroimaging demonstrating its activation and half a century of its lesioning by cingulotomy in cancer pain [35–38].

The US Medical Device Amendments of 1976 compelled the US Food and Drugs Administration (FDA) to request DBS manufacturers to conduct further studies to show the benefits of DBS for pain; an additional ruling in 1989 required clinical trials to demonstrate safety and efficacy. Two multicenter trials were conducted: the first in 1976 using the Medtronic Model 3380 electrode (196 patients) and the second in 1990 with Medtronic Model 3387 (50 patients) that superseded it [39]. The two studies were an amalgam of prospective case series from participating neurosurgical centers, neither randomized nor case controlled, and both suffered from poor enrollment and high attrition. Other shortcomings included heterogeneous case mixes with underspecified patient selection criteria, and subjective and unblinded assessment of patient outcomes. Confounds arose from inconsistencies in the deep brain sites stimulated, the numbers of electrodes used per patient, andthe stimulation parameters chosen. Improvements made to the later Model 3387 trial included limiting deep brain sites stimulated to 2 per patient and using visual analog scores (VAS) to rate pain intensity, but the number of cases included per center was tiny, with a mean of 5 and median of 3 patients treated.

Neither trial satisfied study criteria for efficacy of at least half of patients reporting at least 50 % pain relief 1 year after surgery. US FDA approval for analgesic DBS was therefore not sought by the device manufacturer. However, intriguingly, the large numbers of patients lost to follow-up resulted in a steady increase with time in the proportion of patients with at least 50 % pain relief; 2 years after implantation they comprised 18 out of the 30 remaining patients (60 %) followed-up in the Model 3380 trial and 5 out of the 10 in the Model 3387 trial (50 %). Nonetheless, the trials resulted in the US FDA giving DBS for pain "off label" status, thus precluding its approval by medical insurers [39–41]. As a consequence, few clinical investigations into DBS for pain using current technology and techniques have been reported.

In the last decade only 6 centers, to our knowledge, have published case series of >6 patients [42–50]. Only about 20 groups worldwide have reported long-term efficacy in up to 83 % of patients with follow-ups of up to 6 years (Table 1). In contrast, both other centrally implantable neurostimulation treatments for pain—SCS and motor cortex stimulation (MCS)—have continued to yield research publications, albeit mostly of uncontrolled case series [51, 52], with small randomized, controlled, clinical trials in SCS emerging [53–55].

Our experience is that DBS is superior to MCS for selected refractory pain syndromes [56]. Similarly, we have found DBS to be more appropriate than SCS for certain pain etiologies, although few published data exist that control for surgeon and patient differences. Two retrospective studies from the same group have compared all 3 modalities of central neurostimulation, but the results are obfuscated first by different treatments trialed, both between and sequentially within patients, and second by limited outcome information [57, 58]. Recent reviews attempting to compare the 3 neurostimulatory therapies have been limited by variable outcome measures and a heterogeneous case mix [59, 60].

Patient Selection

Historically, clinical approaches to DBS have sought to categorise patients first by cause of pain and second by dichotomizing the pain into such categories as nociceptive or deafferentation, "epicritic" or "protopathic", peripheral, or central. Such distinctions are largely unhelpful to our patient selection

Table 1 Summary of prospective case series of thalamic and periventricular deep brain stimulation (DBS) for pain

References	Patients implanted (*n*)	Deep brain target	% success: long-term (initially)	Follow-up time, months: (mean)	Evaluation method used
[26, 24, 164]	84 121	PVG/PAG VPL/VPM	0 69	NA	Verbal report
[15–17, 125]	30	PVG/PAG	70	1–46 (18)	Self-report; NRS
[165]	7	PVG/PAG	16	–	Nociceptive stimuli
[166]	6	PVG/PAG	33	6–42	Verbal report
[31]	28	PVG/PAG	76	1–33 (14)	NA
[70, 167]	24	VPL/VPM	67	1–47 (10)	Verbal report; HRQoL; analgesic use
[32, 168]	26 20	PVG/PAG VPL/VPM	28	6–54	3 category rating
[169]	48 12	PVG/PAG VPL/VPM	79	6–42 (36)	VAS
[170–172]	24	VPL/VPM	63	NA	3 category rating; activity; analgesic use
[173]	41	PVG/PAG VPL/VPM	41	NA	VAS; HRQoL
[18, 126, 144, 174–178]	65 77	PVG/PAG VPL/VPM	77 (82) 58 (68)	14–168	Verbal report; analgesic use
[179]	141	PVG/PAG VPL/VPM	31 (59)	24–168 (80)	Verbal report
[180]	89	VPL/VPM	67	NA	VAS; verbal report; analgesic use
[181, 186]	36	VPL/VPM	30 (61)	(48)	Nociceptive stimuli
[141, 153]	25 43 12	VPL/VPM Both Other	14 (overall)	NA	Verbal report
[101, 129, 182, 183]	178	PVG/PAG VPL/VPM	50 (80)	12–180 (90)	VAS; analgesic use; HRQoL
[184]	68	PVG/PAG VPL/VPM	62 (78)	6–180 (78)	VAS, MPQ
[151]	12	PVG/PAG	NA	NA	NA
[100]	8 3 45	PVG/PAG VPL/VPM Both	63 33 38	6–66	NA
[44]	6	VPL/VPM	83	(42)	NRS, nociceptive and placebo stimuli
[43]	21	PVG/PAG VPL/VPM	24 (62)	2–108 (24)	VAS, use of DBS
[47, 49, 56, 81, 73, 107]	33 15 37 16	PVG/PAG VPL/VPM Both Cg24	See below 46 (69) See above 73 (93)	(28) 1–32 (13)	VAS, MPQ, HRQoL
[50]	12	VPL	92 (92)	12 (12)	VAS, BPI, UWNPS, HRQoL

PVG/PAG = periventricular and periaqueductal gray and adjacent mid-line thalamic nuclei; VPL/VPM = ventroposterolateral and ventroposteromedial thalamic nuclei; NA = not applicable; NRS = numerical rating scale; HRQoL = health-related quality of life; VAS = visual analogue scale; MPQ = McGill Pain Quesionnaire; BPI = brief pain inventory; UWNPS = University of Washington Neuropathic Pain Score

as a gathering body of human functional neuroimaging and electrophysiological evidence confirms that chronic pain arises concomitantly with centrally mediated changes related to neuronal plasticity, regardless of etiology [61–66]. Thus, it can be assumed that chronic pain of organic origin following neural injury and refractory to medical treatment is largely central pain and thus neuropathic. The challenges for patient selection for DBS then become 2-fold. First, the confirmation that the patient's pain is neuropathic and neither factitious nor psychogenic.

Second, the selection of those with neuropathic pain who are likely to obtain benefit from DBS.

Essential to the patient selection process is assessment by a multidisciplinary team consisting, as a minimum, of a pain specialist, neuropsychologist, and neurosurgeon. Comprehensive neuropsychologic evaluation forms best practice in patient selection to exclude psychoses, addiction and medically refractory psychiatric disorders, and to ensure minimal cognitive impairment [67–70]. Outcomes should be scored using both pain and health-related quality of life indices preoperatively and at regular follow-up; our methods are detailed elsewhere [49, 50, 71]. The specific etiology of the chronic pain appears less important to efficacy than its symptom history, which may involve hyperalgesia, allodynia, and hyperpathia. The pain must have a definable organic origin with the patient refractory to or poorly tolerant of pharmacologic treatments. Surgical treatments may have been attempted, for example peripheral neuroablative or decompressive procedures for trigeminal neuralgia; however, failure of other neurostimulatory therapies is not a prerequisite for DBS. Patients tend to have been refractory to medications for at least 2 years. Our preference is to trial DBS rather than SCS or MCS in carefully selected patients wherever the etiologies of chronic pain are consistent with neuronal reorganization at multiple levels of the central neuromatrix.

Our experience of DBS for pain after upper limb or brachial plexus injury [72, 73] encourages us to consider DBS as a first-line treatment for complex regional pain syndromes. A recent paradigm shift towards central brain reorganization with autonomic dysfunction as the mechanism underlying complex regional pain syndromes support the treatment for brachial and lumbar plexus injuries, and stump pain after amputation, as well as phantom limb pain [74–78].

Other pain etiologies for which we and others have obtained good outcomes using DBS are stroke [48, 79]; cephalalgia, including postherpetic trigeminal neuralgia and anesthesia dolorosa [47, 80]; multiple sclerosis [43]; genital pain; and malignancy [73, 81]. We find little merit in the administration of opiates or naloxone to determine suitability for DBS, although a historical literature exists [46]. Medical contraindications to DBS include uncorrectable coagulopathy obviating neurosurgery and ventriculomegaly sufficient to preclude direct electrode passage to the surgical target.

Basic Science

Anatomy

Thalamic and midbrain DBS targets are contralateral to the painful side of the body, but the anterior cingulate is targeted bilaterally. Sites for DBS can be divided anatomically, first into somaesthetic regions of the ventrobasal thalamus (VP); second into more medial regions surrounding the third ventricle and aqueduct of Sylvius, including the gray matter (PAG) and medial thalamic Cm-Pf; and third into rostral anterior cingulate cortex area Cg 24, 20–25 mm posterior to the anterior horns of the lateral ventricles with electrode tips abutting the corpus callosum (Fig. 2) [82].

Ultimate adjustment of intracerebral electrode position is directed by awake patient reports of somaesthetic localization during intraoperative stimulation. Such subjective information may alter the final electrode site by several millimeters from preoperative target co-ordinates. A guiding principle is the established somatotopic organization of the somaesthetic thalamic and PAG regions. Human microelectrode studies reveal a mediolateral somatotopy in the contralateral ventroposterior thalamus, the head of the homunculus being medial and the feet lateral [83]. Subjective observation of a rostrocaudally inverted sensory homunculus in contralateral PAG has been confirmed objectively by our human macroelectrode recordings of somatosensory evoked potentials [84, 85]. The PAG target is found at a point 2–3 mm lateral to the third ventricle at the level of the posterior commissure, 10 mm posterior to the mid-commissural point. Its pertinent anatomical boundaries in the midbrain include the medial lemniscus laterally, superior colliculus inferoposteriorly, and the red nucleus inferoanteriorly. Sensory thalamic targets are found 10–13 mm posterior to the mid-commissural point and from 5 mm below to 2 mm above it. The VPM is targeted for facial pain only and found midway between the lateral wall of the third ventricle and the internal capsule; the arm area of VPL is 2–3 mm medial to the internal capsule and the leg area of VPL 1–2 mm medial to the internal capsule. The sensory thalamus is bordered by Cm-Pf medially; the internal capsule laterally; the thalamic fasciculus, zona incerta, and subthalamic nucleus inferiorly; the thalamic nucleus ventralis intermedius anteriorly; and the pulvinar thalamic nucleus posteriorly.

Physiology

A wealth of electrophysiological, anatomical, and radiological evidence in humans and animals, reviewed elsewhere, establishes both PAG and VP as structures important to pain perception and the pathophysiology of chronic pain syndromes [86–94]. The subtleties of hierarchical position and the behavioral function of individual brain structures, whether sensory-discriminative, attentional, motivational-affective, or hedonic, are much debated. However, the consensus is towards a pain neuromatrix also involving spinal cord, posterior hypothalamus, amygdala, and neocortical structures, including somatosensory, insular, anterior cingulate, and prefrontal cortex. Whether pain control is top-down or bottom-up in its hierarchy is unresolved and often depends upon the experimental paradigm used. Our human electrophysiological studies of neuronal coherence have

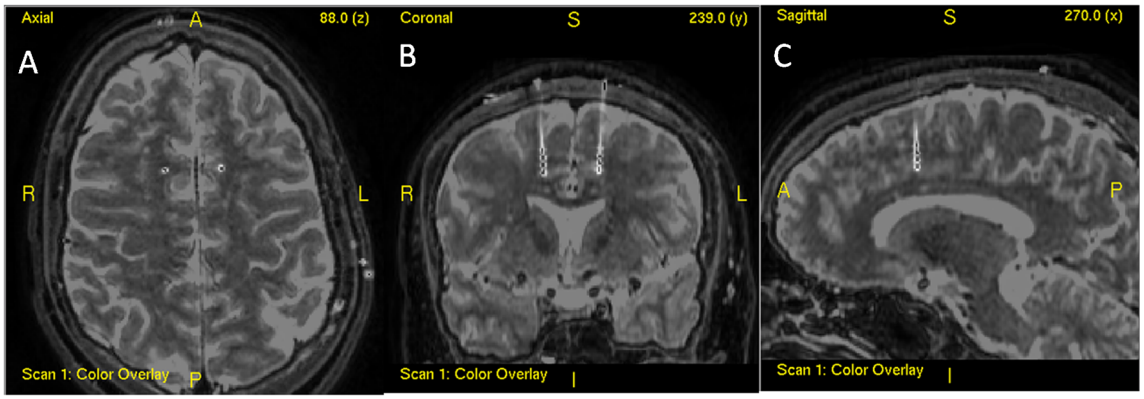

Fig. 2 Fused magnetic resonance and computed tomographic images highlighting Cg24 electrode placement: (a) axial, (b) coronal, and (c) sagittal

utilized somatosensory evoked potentials and statistical modeling to suggest that PAG exerts ascending modulation upon VP [95].

Central to the rationale for DBS is the concept of aberrant neuronal firing at the target sites concomitant with the chronic pain. Human and animal electrophysiological experiments show increased thalamic neuronal firing in pain [96]. Comprehensive reviews of electrophysiological studies conclude that the mechanisms of analgesic stimulation are not clearly delineated [46, 97–101]. From insights revealed by basal ganglia microelectrode recordings and DBS for movement disorders reviewed elsewhere [102–104], we postulate that altered rhythmic activity in VP and PAG neurons is likely to play an important role in the pathophysiology of central pain. At either target, our clinical experience is that, in general, DBS at lower frequencies (≤50 Hz) is analgesic and at higher frequencies (>70 Hz) hyperalgesic [79, 105, 106], supporting a dynamic model whereby synchronous oscillations in discrete neuronal populations centrally modulate chronic pain perception. Analgesic DBS may therefore either disrupt pathological high-frequency synchronous oscillations or, more likely, augment pathologically diminished low-frequency synchronous oscillations in the thalamic and reticular components of a reticulo-thalamo-corticofugal pain neuromatrix. We have shown a positive correlation between analgesic efficacy at either DBS site and the amplitude of slow frequency (<1 Hz) VP local field potentials [107, 108], allowing for physiologically modulated artifacts [109]. We also have early evidence that patients off DBS have characteristically enhanced low-frequency (8–14 Hz) power spectra of both PAG and VP local field potentials when in pain [110]. Further research is required to elucidate if such neuronal signatures could aid patient selection, in particular if combined with technical advances in noninvasive functional neuroimaging and electrophysiological techniques, like single photon emission computed tomography (SPECT) and magnetoencephalography (MEG), to characterize functional neuronal connectivity [111–113].

The PAG is a structure optimally sited anatomically to integrate interoceptive function, both from adjacent mesencephalic cardiovascular centers and more distal pain processing areas. Its autonomic effects have been well studied in animals [92, 114–117] and changes noted with DBS [101]. We have demonstrated a positive correlation between the degree of analgesia in patients receiving PAG DBS and the magnitude of blood pressure reduction [118], and have shown that whereas dorsal PAG stimulation can acutely elevate blood pressure, ventral stimulation reduces it [119, 120]. Such findings advance investigations for objective markers of chronic pain and also the potential selection of patients who may respond best to PAG DBS. Indeed, our investigations into heart rate variability changes and preliminary findings from ambulatory blood pressure monitoring that such blood pressure changes are sustained may provide objective somatic measures of efficacy that correlate to analgesia [121, 122].

Current thinking is that ventral PAG DBS engages analgesia commensurate with passive coping behavior, whereas dorsal PAG DBS may involve “fight or flight” analgesia with associated sympathetomimetic effects [118]. However, evidence to substantiate the conjecture that PAG DBS acts via the augmentation of endogenous opioid release is contentious. The hypothesis arose from animal experiments that revealed that stimulation produced analgesia reversed by naloxone [123, 124], and human studies that also showed elevated levels of cerebrospinal fluid enkephalins and endorphins with DBS [18, 125, 126]. However, the cerebrospinal fluid measures were artifactual [127, 128], and double blinded investigation in humans has revealed no cross-tolerance between DBS and morphine and similar reversibility between naloxone and saline placebo [129], confirming others’ findings [33, 130]. Our human naloxone studies suggest that only dorsal PAG/periventricular gray DBS may be acting via opioidergic mechanisms [131].

An obstacle yet to be overcome in the quest to understand the mechanisms of analgesic stimulation is the lack of adequate animal models of chronic pain [132, 133]. In addition to their limited homology in chronic pain paradigms, the smaller brains of rodent and murine models increase targeting inaccuracies, in particular for small brainstem structures like PAG.

Such experience emphasizes the important opportunities presented by patient-based translational research into DBS to study the mechanisms underlying its efficacious analgesia.

Clinical Assessment

Our surgical and clinical assessment techniques are detailed elsewhere [49, 71, 134]. In general, we do not decide between permanent implantation of PAG, VP, or dual site stimulation on any criteria other than demonstrable efficacy in each individual patient.

Another method favored for evaluating analgesia in single cases and small groups of patients is the N-of-1 trial [135–137]. A randomized, placebo-controlled intrapatient trial is conducted whereby the patient receives pairs of treatment periods during which each intervention—be it DBS on or off, or different stimulation targets or parameters—occurs once. The order of treatments is randomized and the effects of treatment or placebo can be compared between treatment periods. We have demonstrated the validity of N-of-1 trials using the VAS, and their concordance with overall MPQ has been demonstrated for VP, PAG, and dual-target DBS [138]. Blinding and randomization methodologies have also been adopted by others to investigate the efficacy of thalamic DBS [44]. However, the process is labor intensive for the clinician and thus not routinely practicable with limited clinical resources.

Regarding programming, bipolar 5–50-Hz stimulation is performed during awake surgery, using pulse widths from 100 to 450 μs and amplitudes 0.1–3 V. VP stimulation aims to supplant painful sensation by pleasant paraesthesia, and PAG stimulation seeks to induce a sensation of warmth or analgesia in the painful area. Adjustment is primarily somatotopic so as to evoke appropriate topographic responses, but the assessor should be alert to pyramidal signs suggesting capsular involvement with VP DBS, and with PAG DBS for oscillopia and reports of visual disturbances caused by superior collicular involvement or facial paraesthesia arising from medial lemniscus stimulation.

All electrodes are externalized for 1 week of trial stimulation. During this period, the patient records VAS scores at least twice daily and is kept blinded to DBS settings. Targets are trialed individually for 1–2 days using the stimulator parameters described above to determine which settings of quadripolar electrode contact polarities confer maximum analgesia to the optimal somatic region. Monopolar stimulation is also trialed if bipolar settings fail to give pain relief. After this period, both electrodes are trialed together for 1–2 days. If the patient is satisfied with the degree of pain relief obtained, full implantation of the efficacious electrode(s) is performed and DBS commenced at the optimized stimulation parameters. Ideally, patients leave hospital the day after implantation of the impulse generator, and we endeavor to follow their progress with clinic appointments at 1 month, 3 months, 6 months, and then every 6 months thereafter. Initially, they are given a pain diary to record their VAS and stimulator settings weekly for review at follow-up. In addition to being able to switch the DBS on and off at will, they are usually only given control over its amplitude, which is typically limited by the clinician to a maximum efficacious amplitude. In general, low-frequency stimulation at the lowest efficacious pulse widths and amplitudes attainable is set with tolerance overcome either by increasing pulse width or amplitude, trying different low frequencies or even periods of several weeks off stimulation.

Evidence

There are no recent North American guidelines for DBS for pain owing to its off-label indication in the USA. We have contributed to the European Federation of Neurological Societies' guidelines on neurostimulation therapy for neuropathic pain, which concludes that DBS should be limited to specialist centers willing to study and report their outcomes owing to the few recent case series published [139]. The UK National Institute for Health and Clinical Excellence approves the treatment on the basis of expert opinion and patient-reported outcomes [140].

Several reviews of DBS for chronic pain have been published—many expert, some commentaries, and several systematic [39, 40, 45, 46, 59, 60, 97, 98, 101, 139, 141–163].

Our systematic searches have identified a number of primary studies [15–18, 24, 26, 31, 32, 43–45, 47, 49, 50, 56, 70, 73, 81, 101, 107, 125, 126, 129, 144, 151, 153, 164–186].

Published case series of at least 6 patients using current DBS targets are listed in Table 1 and their efficacy summarized. Where the same authors reviewed their clinical data more than once, only their latest or largest patient series was considered. Pain relief scores showing≥50 % improvement or verbal ratings of "good" or "excellent" after surgery were considered successful outcomes, and patients not permanently implanted included as failed outcomes. However, not all authors reported such failures, leading to overestimation of efficacy in some reports. The literature is also obfuscated by varying and often simplistic or subjective outcome measures, and a paucity of double-blind, placebo-controlled studies. To our knowledge, only 5 groups, using current standards of target localization and currently available models of deep brain stimulators in all patients with adequate follow-up and description of outcomes, have published studies of at least 6 patients [43–45, 49, 50].

Discussion

Although not a new therapy, DBS has evolved over the last decade, concomitant with advances in both stimulator technology and neuroimaging techniques, and by corollary improvements in efficacy and reductions in complications. Few centers have published detailed studies of patients treated during the last decade. Our results suggest that DBS gives analgesia most consistently to patients with pain after amputation, either phantom or stump, cranial and facial pain, including anesthesia dolorosa, and plexopathies. Our experience of pain after stroke reveals greatest efficacy for stroke patients complaining of burning hyperaesthesia [48, 79]. Therefore, the stroke case series illustrates how important patient selection is to outcome. Consistent with the notion that chronic pain states confer specific central neuropathic changes are results showing poor DBS efficacy for spinal cord-related pain, for example from failed back surgery. Predominantly, spinal injuries, and hence spinal neuropathic changes, are unlikely to respond favorably to PAG or thalamic brain stimulation, but may be relieved by Cg24 DBS. Conversely, causes of chronic pain not traditionally treated by DBS, for example visceral pain in which PAG changes are described using functional neuroimaging [187, 188], have the potential to be ameliorated by DBS and are worthy of further study.

Investigations both into the mechanisms of DBS and using deep brain recording to elucidate pain processing mechanisms have yielded considerable advances. Future insights will arise from complementary information gathered using new technologies. Diffusion tensor imaging using magnetic resonance imaging to trace neuronal connections has shown connectivity between PAG and thalamic structures, and may elucidate differential somatotopic connections [189, 190], and also have the clinical utility to aid targeting in functional neurosurgery [191]. MEG enables whole brain changes to be mapped with spatial resolution comparable with functional magnetic resonance imaging but with a temporal resolution of the order of milliseconds [94]. Our initial investigations have revealed activation of pain processing neocortical areas during analgesic DBS having filtered out artifactual interference from stimulation [111, 112, 192]. Therefore, global MEG measurements combined with local deep brain recording hold promise for revealing much about pain processing and DBS-related mechanisms, beyond wider neurosurgical applications [193], towards identifying predictors of efficacy, and enhancing treatments. Nevertheless, complimentary functional neuroimaging modalities such as single photon emission computed tomography have roles in characterizing whole brain changes with DBS with excellent deep brain structure penetration compared with present MEG studies, albeit with more limited temporal resolution and characterization of metabolic correlates of neuronal function [113].

The large variability of results in case series of DBS for pain to date reflects not just limitations in pain assessment tools and study design and execution, but individual differences between patients as to what constitutes success. A good outcome may be the removal of a particular component of pain, for example burning hyperaesthesia, without quantitative reduction in pain scores. Such pain relief may serve to unmask other types or components of pain elsewhere, such as muscular allodynia, as has been described after stroke [194]. Conversely, complete pain eradication by DBS may even accompany unease, motor complications, or other sequelae precipitating intolerance of stimulation. Thus, clinicians must characterize patients' pain qualitatively, as well as quantitatively, and investigators should endeavor to include quality of life measures in outcome assessment.

Contemporary case series suggest that between 25 % and 50 % of patients successful during trial stimulation do not experience long-term success beyond 1 year after surgery. To address this predicament, alongside improving case selection, further challenges are to identify predictors of long-term efficacy and to investigate the putative phenomenon of tolerance. Progressive increases of stimulus amplitude or insertion of a second electrode have proven unhelpful [184]. Our experience [79], and that of others [195], is that tolerance is often overcome by subtle alterations of pulse width by 30–90 μs or frequency by 5–15 Hz, or both, and by either cycling stimulation or having stimulation breaks—periods off DBS lasting from days to months as required. Such experience is in contrast to DBS for movement disorders where it has been established that rebound of tremor with time can be overcome by ramping up thalamic stimulation parameters [196]. It is possible that the unmasking of other discomfort such as muscular allodynia by relief of burning hyperaesthesia can be overcome by "deramping" DBS. A good positive correlation found between frequency and amplitude in long-term follow-up of poststroke pain DBS and a reduction in both amplitudes and frequencies of stimulation over time in patients achieving pain relief supports such a hypothesis [79].

There remain groups of patients presently refractory to thalamic or PAG DBS or whose pain, for example whole body pain lacking distinct somatotopy or pain after spinal cord injury, makes them poor candidates for the procedure. We have successfully implanted DBS into the anterior cingulate cortex in such patients with the rationale of reducing the emotional saliency of pain perception while not seeking to alter its nociceptive component [82, 197]. Such work draws upon a wealth of literature, and our own positive clinical experience of anterior cingulotomy for cancer pain [38, 198]. We expect that anterior cingulate DBS will not only become established as a viable novel target in DBS for chronic pain, but also that its use and related translational investigations will yield many neuropsychological insights into emotion, attention, and executive function.

As clinical indications and clinician and patient awareness of DBS continue to increase, the costs of both the technology and its implantation will decrease, making the therapy more widely available. While it is unlikely that DBS will be as widespread and inexpensive as cardiac pacemakers, it may be comparable in cost to SCS within 5 years. A priority is to demonstrate cost-effectiveness by ensuring rigorous and evidence-based studies of DBS for pain and redressing the challenges of past failed trials. A combination of tailored evidence-based methods on intensively studied small cohorts must occur alongside the co-ordination of multicenter clinical trials with standardized selection, implantation, and outcome data collation protocols. Only then can DBS for pain become re-established as a widely used therapy rather than one reserved for a select handful of experienced, specialist centers willing to carefully study their patients and publish their results.

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Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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