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Deep brain stimulation for chronic pain

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Abstract

As a clinical intervention, deep brain stimulation (DBS) has provided remarkable therapeutic benefits for otherwise treatment-resistant movement and affective disorders including chronic pain. In this review, we concentrate on the experience of using DBS to treat chronic pain in Oxford. We provide a brief historical background as well as details of our methods for patient selection, surgical techniques and assessment. While the precise mechanisms of action for DBS remain uncertain, we describe how DBS can help for treatment-resistant chronic pain and have great potential to advance our general understanding of the human brain. In particular, we show how DBS can be used in conjunction with methods such as local field potentials and magnetoencephalography to map the underlying mechanisms of normal and abnormal oscillatory synchronization in the brain related to the pleasure of pain relief.

Keywords: Chronic pain, neuroimaging, magnetoencephalography, local field potentials, obsessive compulsive disorder, functional neurosurgery, amputation, neuropathic pain, thalamus, cingulate, periaqueductal gray, pleasure.

Introduction

Deep brain stimulation (DBS) has become the basis of important successful therapies for treating otherwise treatment-resistant movement and affective disorders such as Parkinson's disease, tremor, dystonia and chronic pain (1). Despite the long history of DBS, its underlying principles and mechanisms are still not clear but what is clear is that DBS directly changes brain activity in a controlled manner, the effects are reversible (unlike those of lesioning techniques) and that DBS is one of only a few neurosurgical methods that allows blinded studies (2).

Modulation of brain activity by way of direct electrical stimulation of the brain has been in use at least since 1870, when Fritsch and Hirtzig showed

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that stimulation of the motor cortex of the dog can elicit limb movement (3). Direct neuromodulation and recordings have since proved to be very useful for improving human neurosurgical procedures as first shown in 1884 by Horsley (4).

It is over fifty years since the initial studies used DBS in the hypothalamus to treat chronic pain (5). Around the same time ablative surgery of thalamic nuclei (ventral posterior lateral and medial, VPL/VPM) and adjacent structures was used for the alleviation of pain (6-9). This evidence led Hosobuchi to try stimulation of the VPM for treating anaesthesia dolorosa (10). Similarly, other groups were successfully experimenting with DBS of the thalamus (11-14). Some groups also reported some success with using DBS in the internal capsule (15-17).

Other DBS targets for chronic pain were identified over time, which included the periventricular and periaqueductal gray (PVG/PAG) regions. Reynolds and colleagues discovered that they could use PAG stimulation to induce analgesia during surgery in awake rodents (18,19). This was then translated into using DBS of the PVG/PAG in human patients (20-23).

Other targets such as the more medial thalamic nuclei including the centromedian-parafascicular complex came from investigations into inadvertent localisation errors and current spread from existing targets (24-27).

This rapid progress in electrical stimulation treatments for chronic pain and for movement disorders such as Parkinson's Disease led the United States Food and Drug Administration (FDA) to try to evaluate their merits. A symposium was organised (28), which found that DBS treatments for pain were both safe and effective (29, 30). The United States Medical Device Amendments of 1976 and an additional ruling in 1989 meant that DBS manufacturers were subsequently required to conduct clinical trials to demonstrate safety and efficacy.

Two multi-centre trials for DBS of chronic pain were conducted by Medtronic. The first trial in 1976 had 196 patients (using the Medtronic Model 3380 electrode) and a second trial in 1990 had 50 patients (using Model 3387) (31). The two trials were far from ideal as they consisted of prospective case series from various neurosurgical centres, which were not randomised or case controlled, and in addition had poor enrolment and high attrition. There were inconsistencies across centres in the selection of number of DBS targets, numbers of electrodes used per patient and stimulation parameters chosen. Heterogeneous case mixes with underspecified patient selection criteria, and subjective and unblinded assessment of patient outcomes added to the confusion.

The second trial tried to improve the data by limiting deep brain sites stimulated to two per patient and using visual analogue scores (VAS) to rate pain intensity for outcome assessment, but was on a much smaller scale with a mean of five and median of three patients treated per centre.

The study criteria for efficacy was that at least half of patients should report at least 50% pain relief one year after surgery. This was not met by either trial and FDA approval for analgesic DBS was therefore not sought by the device manufacturer (31).

As a consequence, during the last decade most of the research in DBS for chronic pain has gone on outside the US with only five centres outside the US having produced case series of more than six patients: (32-40).

These studies have in general been much better controlled and shown significant improvements for patients with primarily pain after amputation and stroke, and head pain including anaesthesia dolorosa, as documented below.

In addition to chronic pain states, there are other affective disorders with pain components that have been successfully treated with DBS. Patients with cluster headache have been successfully treated with DBS in the hypothalamus (41-43). Depression is another condition, where the targets have included thalamus (44, 45) and the subgenual cingulate cortex (46). Another recent study of DBS in the nucleus accumbens found a significant reduction in anhedonia in three patients with treatment-resistant depression (47). DBS for obsessive compulsive disorder have targeted the anterior internal capsule (48). DBS of the thalamus (49) and GPi (50) have been reported effective in treating Tourette syndrome.

It should, however, be noted that owing to the lack of good animal models of depression, obsessive compulsive disorder and Tourette syndrome, the mechanisms underlying these interventions are much more speculative than for example the targets used in

Parkinson's disease. We have previously argued that the MPTP model may also be useful (1), since many of the involved brain structures are also implicated in affective disorders as e.g. demonstrated by how severe depression can be reversibly induced by DBS for Parkinson's disease (51, 52). The ethical implications of DBS for the treatment of affective disorders should be carefully considered to avoid comparisons to the psychosurgery of last century – but it should be remembered that DBS is, in principle, reversible.

Mechanics of DBS surgery

The specific methods used for DBS vary between neurosurgical teams. Here we present the methods adopted in Professor Tipu Aziz' neurosurgical centre in Oxford and focus specifically on the selection and surgical procedures used for DBS for pain relief (see figure 1).

Patient selection

There are two main challenges to chronic pain patient selection for DBS, which is to determine that 1) the patient's pain is neuropathic and neither factitious nor psychogenic, and 2) this neuropathic pain is likely to be successfully treatable with DBS.

Assessment by a multi-disciplinary team consisting as a minimum of a pain specialist, neuropsychologist and neurosurgeon is essential to the patient selection process. Comprehensive neuropsychological evaluation forms best practice in patient selection for DBS to exclude psychoses, addiction and medically refractory psychiatric disorders and ensure minimal cognitive impairment (53-56).

Quantitative assessment of the pain and health related quality of life should be a requirement of the pre-operative patient selection process. Our preference is to use both VAS (scale 1–10) to rate pain intensity and the McGill pain questionnaire (MPQ) for pain evaluation (57, 58), the latter giving additional qualitative information. Quality of life is assessed using the Short Form 36 (SF-36) and VAS part of the Euroqol five-dimensional assessment tool (EQ-5D), (59-61). The patient records their VAS twice daily in a pain diary over a period of 12 days. The 24 VAS scores are reviewed to ensure consistency. The EQ-5D, SF-36 and MPQ are administered by the pain specialist pre-operatively. The MPQ is repeated on a separate occasion independently by the neuropsychologist and scored using the ranked pain rating index. Our experience is that certain items of the MPQ can predict a good response to DBS. In particular, over 80% of our patients who describe 'burning' pain have found benefit from DBS, regardless of whether VPL/VPM, PVG/PAG or both are stimulated.

The specific aetiology of the chronic pain is less important 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 pharmacological treatments. Surgical treatments may have been attempted, for example peripheral neuroablative or decompressive procedures for trigeminal neuralgia, however we do not consider failure of other neurostimulatory therapies a prerequisite for DBS.

Our preference is to trial DBS rather than SCS or MCS in carefully selected patients wherever the aetiologies of chronic pain are consistent with neuronal reorganisation at multiple levels of the central neuromatrix. Our experience of DBS for pain after limb or plexar injury includes ten successfully implanted patients to date (38, 40) has led us to consider DBS rather than SCS as first-line treatment for complex regional pain syndromes, in other words for plexar injuries and stump pain after amputation as well as phantom limb pain.

Overall, optimal patient selection includes expert opinion after multi-disciplinary assessment demonstrating quantitatively severe pain refractory to medication for at least one year with significantly impaired quality of life and likely neuropathic aetiology without predominantly spinal involvement. We do not advocate opiate or naloxone administration to determine suitability for DBS. Medical contraindications to DBS include uncorrectable coagulopathy obviating neurosurgery and ventriculomegaly sufficient to preclude direct electrode passage to the surgical target.

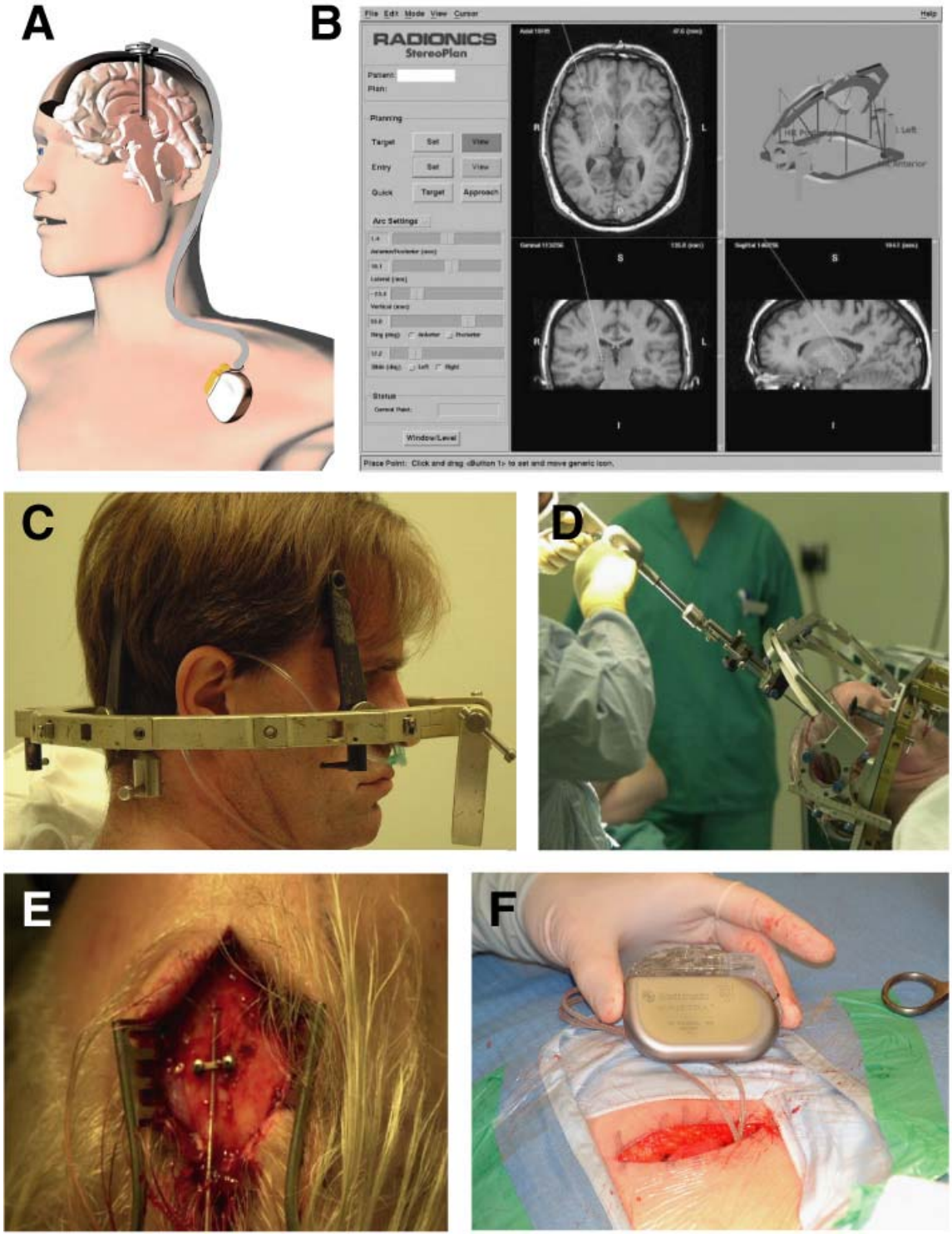

Figure 1. The neurosurgical procedures involved in DBS. A) Schematic of the principles of DBS. B) Illustration of the process of the neurosurgical pre-planning. C) Application of the Cosman-Roberts-Wells stereotactic head frame on the patient. Note that the base ring is parallel to the orbitomeatal line. D) The precise positioning of the electrode through perforating the calvarium with a twist drill. E) Securing the electrode to the skull with a titanium miniplate and screws. F) Placement of the implantable pulse generator in a subcutaneous pectoral pouch.

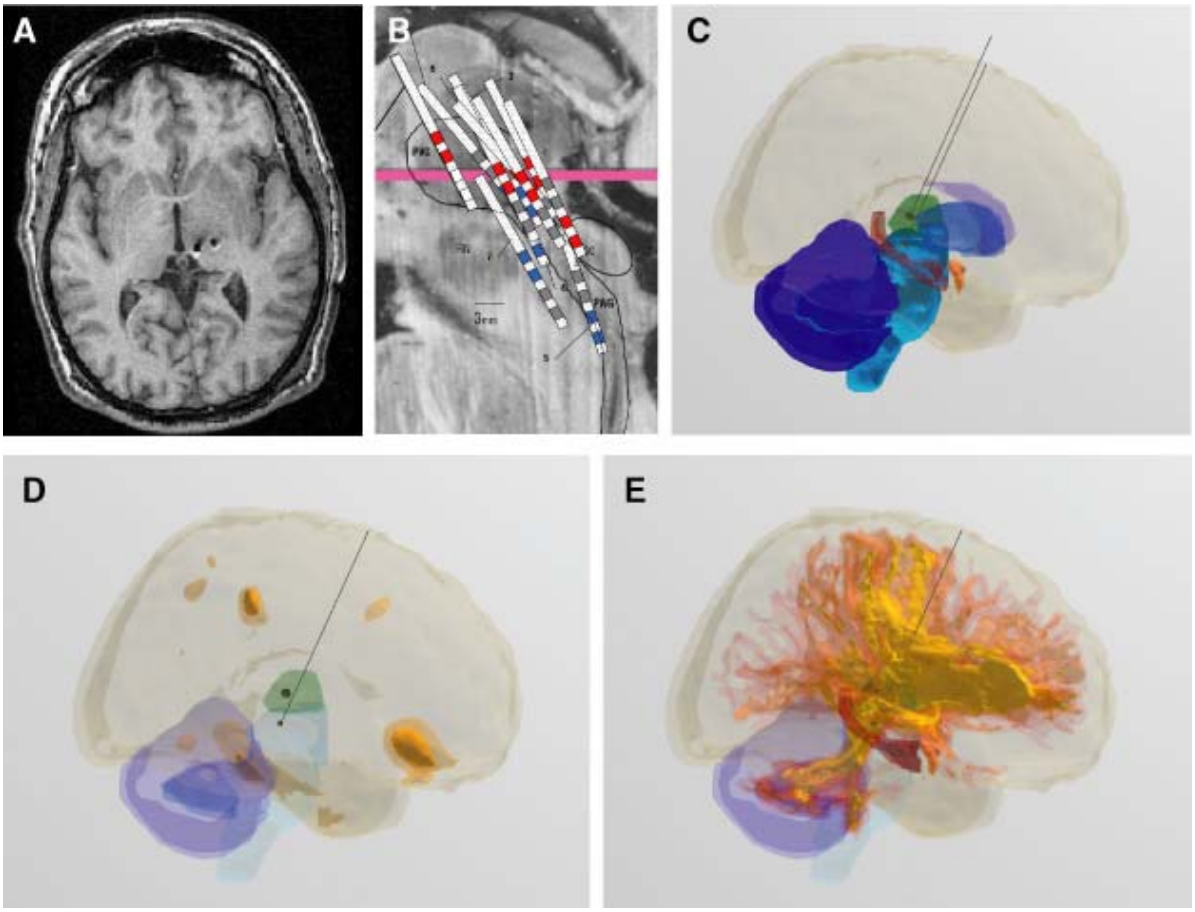

Figure 2. DBS for chronic pain. A) Axial MRI slice showing the implantation of electrodes in PVG/PAG and thalamus in a patient. B) Schematic illustration of the vertical placement of electrodes in the PVG/PAG in a series of chronic pain patients. C) Three-dimensional rendering of human brain showing the placement of the two electrodes in the PVG/PAG and thalamus, as well as some of the important subcortical structures. D) Three-dimensional rendering showing the whole-brain DBS induced activity from stimulation in the PVG/PAG. E) The connectivity of the PVG/PAG measured with diffusion tensor imaging.

Surgical procedures

A T1-weighted MRI scan of each patient's brain is performed several weeks before surgery. For surgery, a Cosman-Roberts-Wells base ring is applied to the patients' head under local anesthesia. A stereotactic computed tomography (CT) scan is then performed and using the Radionics Image Fusion® and Stereoplan® (Integra Radionics, Burlington, Mass) program the coordinates for the PVG and ventro-posterior lateral thalamus (VPL) are calculated. A double oblique trajectory is used with an entry point just anterior to the coronal suture and laterality of approach dictated by ventricular width. The PVG/PAG is proximally located 2–3 mm lateral to the wall of the third ventricle and 2 mm anterior to the level of the posterior commissure and distally the deepest electrode lay in the superior colliculus. The VPL is located 8-14 mm lateral and 5–8 mm posterior to the mid-commissural point, at the depth of the anterior/posterior commissure plane. After washing the patient's scalp with alcoholic chlorhexidine, a parasaggital posterior frontal scalp incision 3.0 cm from the midline is made contralateral to the side of pain.

The VPL is usually implanted with a Medtronic 3387 (Medtronic, Minneapolis, Minn) electrode with stimulation induced parasthesia in the area of pain. The PVG is also implanted with a Medtronic 3387 electrode with stimulation induced relief of pain or a sensation of warmth in the area of pain. The deepest electrode is noted to be in a satisfactory position if eye bobbing was induced at intensity of stimulation at least twice that required for sensory effects. The

electrodes are fixed to the skull with a miniplate prior to externalization. In most patients the electrodes are externalized for a week of trial stimulation.

Pain is assessed before surgery and during stimulation by a self-rated visual analog scale. If the patients are satisfied with the degree of pain relief, full implantation of a pulse generator is performed in the following week under general anesthesia.

Other surgical centres around the world use slightly different procedures with one of the main differences being the use of microelectrode recordings to improve the accuracy of targeting in stereotactic placement. Some of the benefits of this procedure include the potential for differentiation of gray and white matter locations, localization of white matter tracts with particular responses to stimulation, and real-time correction for intraoperative shifts in implantation sites. This procedure is, however, somewhat controversial and perhaps superfluous since studies have shown a good correspondence between the MRI-defined target and the proposed electrophysiology-derived map (62). Furthermore, a review comparing modern techniques with the older unguided lesioning procedures of the 1960s argued that the modern technique of multiple microelectrode passes for localization results in no significant difference in outcome and more intracranial haemorrhages (63).

Safety and complications

The safety of DBS and the procedure involved has been demonstrated in many world-wide trials and in the long-term follow-up in DBS for the treatment of chronic pain (64). The long-term efficacy of DBS depends on the generators where most will last around 3-5 years depending on the current demands of the pulse protocol; although in the case of dystonia this can be less than one year. Rechargeable pulse generators are available for spinal cord generators and are being trialled for DBS.

Stereotactic neurosurgical procedures always carry a significant risk and can lead to intracranial bleeding, usually in around 2.0-2.5% of DBS implants (65, 66). Other potential complications include hardware-related complications such as dislocation, lead fracture, and infection (6%). The infection rate is equal to that of other surgical procedures but may necessitate explantation of the stimulator (67). Stimulation-induced side effects (3%) are also quite common effects, such as paresthesia, dyskinesia, tonic muscle contractions and gait ataxia, as well as the less common effects like aggression (68), mirthful laughter (69), penile erection (70), depression (51) and mania (71). These side-effects are closely related to the location of lead/contact used for stimulation.

The principles of DBS

The similar therapeutic outcomes of DBS and neurosurgical lesions have been used for trying to understand the mechanisms of DBS. This in turn raises the deceptively simple general question of whether DBS inhibits or excites neurons, which we will address in the following.

Fundamentally, DBS of the normal and diseased brain must fundamentally depend on the stimulation parameters, the properties of the neural tissue and their interaction. In other words, these parameters include 1) the stimulation parameters including amplitude and temporal characteristics, 2) the physiological properties of the brain tissue which may change with disease state, and 3) the interactions between the electrode and the surrounding tissue arising from the specific geometric configurations.

The stimulation parameters of DBS of therapeutic value have been derived primarily by trial and error by using the near immediate effects on e.g. tremor, rigidity, paresthesia, bradykinesia, and chronic pain in patients on the operating table (72). The exact DBS parameters vary with treatment and targeted brain region but are usually between 1-9 volts stimulus amplitude; 60-240 μseconds stimulus pulse duration; monopolar cathodic; and either low (5-50 Hz) or high (130-180Hz) stimulus frequencies (73). Currently a charge-density limit of 30 μC/cm2 is used as a safety factor based on post-mortem studies of tissue damage (73). Most commercially available stimulators will allow for these parameters to be changed and fine-tuned over time but based solely on the patient's behavioural state. The technology is open-loop continuous stimulation which can not be adjusted real-time to the continuous changes in brain state of the individual patient. In some ways, the current

technology is like that of cardiac pacing technologies of twenty years ago, and the field is wide open for further innovation.

The physiological properties of normal and diseased brain tissue have variable electrical properties depending on the types of neurons and supporting glial cells which utilize different types of ion channels with variable voltage-sensitive properties. The most excitable neural elements are the myelinated axons (74, 75). The effect of DBS on the various neural elements depends on the nonlinear relationship between stimulus duration (pulse width) and amplitude (voltage or current) necessary to stimulate the neural element (74). The minimal current necessary to stimulate a neural element with a long stimulus duration is called rheobase, which is the amplitude threshold. The chronaxie time measurement is the minimum interval of time required to excite a neural element using half the intensity that elicits a threshold response. The chronaxie of myelinated axons is around 30-200 μsecs, while the chronaxies of cell bodies and dendrites are substantially larger at around 1-10 msec (76). This means that with usual DBS parameters, the postsynaptic responses are the result of activity from efferent axons rather than from cell bodies (77).

The geometrical configuration of neural elements in relation to the electrode is important for determining the effects of stimulation on local and global elements. For example, the orientation of the axons and the cell body is an important determinant of neural responsiveness (74). The distance of the neural elements from the electrode is also an important factor with both the rheobase and chronaxie rising in proportion to distance, such that the responsiveness of more distal elements is increasingly unlikely (76). The stimulation volume is not a fixed cylinder around the stimulation electrode but varies with electrode position and surrounding neural tissue. Usual clinical parameters lead to the stimulation of a large volume of neural tissue (75, 78). For example, modelling the excitability effects for STN stimulation using realistic white-matter pathways has shown that at 3V the stimulation spreads outside the STN proper and the pattern of excitation is consistent with known stimulation side-effects (78). Finally, currents from monopolar cathodes of more than eight times threshold may block action potentials in axons. This leads to the intriguing possibility that the effective stimulation from an electrode blocks activity in nearby elements and give rise to sub-threshold activity in distal elements, leaving the intermediate neural elements to be the most likely to receive the effects of stimulation and pass on to mono- and poly-synaptic connected brain structures.

The relative contribution of these parameters in determining the underlying mechanisms of DBS on local and whole-brain activity can be assessed experimentally in humans and other animals through direct neural recordings (79-83), neurochemistry (84, 85) and functional neuroimaging methods (86-88). In addition, computational modelling can be used to test and predict the effects of DBS on simulated neural elements (75, 78).

Functional neuroimaging

Unlike neurophysiological studies, functional neuroimaging methods allow for the study of the whole-brain activity elicited by DBS. The most widespread of these neuroimaging methods are positron emission tomography (PET) and functional magnetic resonance (fMRI), which can measure indirect changes of neural activity such as blood flow, blood oxygenation and glucose consumption. Presently it is not entirely clear how well these indirect measurements correlate with various aspects of neural activity but some progress has been made under normal physiological conditions (89, 90). This means that these methods entail a number of assumptions which may or may not prove to be important for interpreting the subsequent results.

In addition, fMRI studies clearly pose a large degree of risk to DBS patients since the large magnitude of the magnetic fields will interfere with active pulse generators and DBS electrodes. One study showed that extreme caution must be exercised when studying DBS with fMRI since strong heating, high induced voltage, and even sparking at defects in the connecting cable have been observed (91). It has also been shown that fMRI using the blood-oxygen level dependent (BOLD) signal as a measurement may be problematic, since near-infrared spectroscopy showed considerable variations in blood oxygenation in frontal cortex following GPi and thalamic

stimulation (92). Despite these important caveats, a case report has been published using fMRI to study STN stimulation in a patient with Parkinson's disease. The results showed increases in the BOLD signal in primary motor areas and decreases in supplementary motor areas during STN stimulation (93). It should be noted that safety guidelines and procedures have since been issued by DBS manufacturers.

Similarly, PET is not without health risks due to the ionized radiation, but has been used for measuring the effects of DBS. It should be noted, however, that the long acquisition times (on the scale of minutes) make the ensuing brain changes difficult to interpret, and investigators have to carefully address the potential movement artefacts when studying movement disorders.

Using PET to study DBS for affective disorders is less challenging in terms of potential movement artefacts. One PET study investigated the effects of hypothalamic stimulation for cluster headache in ten patients (94) and found that hypothalamic stimulation modulated the pain processing network. Another PET study used stimulation of subgenual cingulate cortex for treatment-resistant depression in seven patients showed marked reduction in mood symptoms in four patients (46). The results are harder to interpret given the small numbers of patients and the paucity of knowledge about the brain structures involved in depression, but suggest that the mode of functioning of DBS would appear one of modulating an existing network of interacting brain regions.

Single-photon emission computed tomography (SPECT) is another invasive neuroimaging technique which has been used to measure regional cerebral blood flow changes following DBS for chronic pain. In one study DBS for intractable neuropathic pain were assessed in three patients using SPECT (95). Pain relief was achieved in all patients with one patient had having electrodes in the VPL, another with electrode in the PVG, and one patient had electrodes in both targets. DBS consistently increased perfusion in the posterior subcortical region between VPL and PVG, regardless of the site of stimulation. Furthermore, thalamic and dual target DBS increased thalamic perfusion, yet PVG DBS decreased perfusion in the PVG-containing midbrain region and thalamus. Dual target stimulation decreased perfusion in the anterior cingulate and insular cortices.

In contrast to PET, SPECT and fMRI, magnetoencephalography (MEG) is non-invasive and almost without risks for use in patients, and can provide novel spatiotemporal information on the underlying whole-brain activity with the current density of MEG sensors affording sensitivity such that the spatial resolution is comparable to fMRI (typically around 5 mm3) but with much better temporal resolution (in milliseconds) (96).

The first MEG study of DBS was carried out in a patient with low-frequency PVG/PAG stimulation for severe phantom limb pain (88, 97). When the stimulator was turned off the patient reported significant increases in subjective pain. Corresponding significant changes in the elicited power of neural activity were found in a wide-spread network including the mid-anterior orbitofrontal and subgenual cingulate cortices; these areas are known to be involved in pain relief (98). Similarly, MEG of high-frequency hypothalamic stimulation for cluster headache showed a similar pattern of changes in neural activity in a wide-spread cortical and sub-cortical network including the orbitofrontal cortex (99). Due to its non-invasive nature and high spatial and temporal resolution MEG holds great promise in elucidating the underlying whole-brain neural mechanisms of DBS by for example measuring oscillatory communication between brain regions (100).

Synthesis of mechanisms

The experimental evidence collected so far allows for some conclusions to be drawn about the neural and systems level mechanisms of action of DBS. The effects of DBS do vary with the stimulation parameters (including frequency, amplitude, pulse width and duration); with the intrinsic physiological properties; and with the interactions between the electrode and the geometric configuration of the surrounding neural tissue and specific anatomy of the targeted region. DBS affects multiple neural elements including foremost myelinated axons and to a lesser degree cell bodies.

Overall, the weight of the evidence so far suggests that the most likely mode of action for DBS is through stimulation-induced modulation of brain

activity (1, 2, 101-103), rather than competing hypotheses such as synaptic inhibition (81), depolarization blockade (104) or synaptic depression (105).

Findings using DBS for chronic pain

To date over 1300 cases of DBS for chronic pain have been reported (33, 35, 38, 106-108). This compares to the nearly 4000 patients who have been implanted with spinal cord stimulators (SCS) (109, 110) and the nearly 400 patients with motor cortex stimulators (MCS) (111, 112).

Over the last decade, over 65 patients (70% men, mean age 51 years old) have been treated with DBS for chronic pain in Oxford with DBS of thalamus and/or PVG/PAG. We have published detailed results for the majority of implanted patients amenable to follow-up elsewhere (37-40, 113, 114). Approximately 70% of our patients gained pain relief during the week post-procedure and proceeded to full implantation. DBS remained effective for pain relief in over 60% of patients one year after surgery.

The Oxford data shows that DBS is superior to MCS for selected refractory pain syndromes (115), and that DBS is more appropriate than SCS for certain pain aetiologies. In particular, our results suggests that DBS is most effective in patients with pain after amputation, either phantom or stump, cranial and facial pain including anaesthesia dolorosa.

We also found very good efficacy of DBS for stroke patients complaining of burning hyperaesthesia (37) but overall less efficacy in patients with stroke, demonstrating the importance of patient selection.

We have also obtained good outcomes using DBS for facial and head pain including post-herpetic trigeminal neuralgia and anaesthesia dolorosa (39, 116), multiple sclerosis (107), genital pain, brachial plexus injuries and malignancy (38).

We are currently looking for new ways to improve to improve patient selection and thus outcomes. One intriguing possibility is the future use of autonomic measures as a potential objective markers (117), such as shown by the subjective preference for PVG/PAG stimulation over VPL/VPM in stroke together with the correlations revealed between cardiovascular effects, analgesic efficacy of DBS and burning hyperaesthesia.

It should, however, be noted that the complexity of chronic pain is such that the relief of one component of the chronic pain, for example burning hyperaesthesia, may unmask other pain components and thus may not overall lead to an quantitative reduction in pain scores. The large variability of results in case series to date reflects not just limitations in pain assessment tools and study design and execution, but also individual differences between patients as to what constitutes success. It is therefore important to include quality of life measures in outcome assessment to overcome the limitations of using VAS scores and pain questionnaires.

Conclusions

Deep brain stimulation is an important tool both for alleviating human suffering and for obtaining novel insights into the nature of fundamental brain function. Due to the existence of the robust MPTP translational model, DBS has so far proven most useful for controlling movement disorders as well as for controlling chronic pain. It is, however, imperative to find novel ways to treat affective disorders such as depression, which are far more prevalent than movement disorders in the general population (98).

Possible future innovations such as closed-loop demand-driven stimulators have great potential for transforming the therapeutic potential of DBS. Through the use of MEG and DBS we will come to understand the normal oscillatory activity of specific brain regions better (83), and such ‘neural signatures’ may come to help drive specific DBS interventions. We now also have potential evidence of such a neural signature of pain in DBS patients who showed characteristically enhanced low frequency (8-12 Hz) power spectra of both PVG/PAG and VPL/VPM LFPs when in pain (118). Further research is required to elucidate if such neural signatures could aid patient selection, in particular if combined with technical advances in MEG to characterise whole-brain functional neuronal connectivity (88).

In general, such research on feedback-driven neural protheses may open up for more advanced brain-computer interfaces, which can in time come to

help patients in a number of pathological states, such as helping patients with spinal cord injuries or even come to help to drive brain activity to help individuals in vegetative and minimally conscious states (119).

In this review we have tried to share our experience of what chronic pain patients to offer DBS and which targets to select. In our experience, successful indications include amputation, stroke, anaesthesia dolorosa, brachial plexus injuries and post-operative wound pain. We have shown how improving patient selection is essential to improving outcomes. In our view, DBS should only be performed in experienced, specialist centres willing to carefully study the patients and publish the results. The intensive experimental study of small groups of patients can help generate hypotheses creating opportunity for larger randomized, case-controlled, clinical trials.

Overall, DBS is a remarkable therapeutic tool which has great future potential both in terms of improving its clinical efficacy and in terms of understanding the fundamental mechanisms of normal human brain function.

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