Deep-brain stimulation

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Deep-brain stimulation (DBS) is a clinical intervention that has provided remarkable therapeutic benefits for otherwise treatment-resistant movement and affective disorders. The resulting direct causal manipulation of both local and distributed brain networks is not only clinically helpful but can also help to provide novel fundamental insights into brain function. In particular, 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. The precise mechanisms of action for DBS remain uncertain but here we present an overview of the clinical efficacy of DBS, its neural mechanisms and potential future applications.

Keywords: chronic pain, dystonia, essential tremor, globus pallidus interna, local field potentials, magnetoencephalography, neuroimaging, obsessive–compulsive disorder, Parkinson's disease, pedunculopontine nucleus, subthalamic nucleus

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

Here we first review the proven clinical efficacy of DBS for movement, affective and non-movement disorders, as well as the safety and potential complications of DBS. We then show how translational research has led to novel DBS targets for Parkinson's disease, specifically addressing the recent promising development of a new target in the brainstem nucleus, the pedunculopontine nucleus (PPN).

We then review some of the relevant experimental evidence for the underlying mechanisms for DBS. This forms the basis of the proposed model for how DBS might work. Finally, we review some of the future perspectives for refining and expanding DBS.

DBS is not, however, only a remarkably useful clinical intervention but the causal, interventional nature of DBS also has great potential to help us unravel the fundamental mechanisms of human brain function. This potential can be harnessed by combining DBS with noninvasive neuroimaging methods, such as magnetoencephalography (MEG), which offer the possibility of mapping the spatio-temporal unfolding of DBS-elicited whole-brain activity, including the normal and abnormal oscillatory synchronizations.

DBS for movement disorders

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 demonstrated that stimulation of the motor cortex of the dog can elicit limb movement [2]. Direct neuromodulation and recordings have since proved to be very useful for improving human neurosurgical procedures, as first shown in 1884 by Horsley [3].

Parkinson's disease is the most common movement disorder and the second most common neurodegenerative disease, affecting 1% of the population over 65 years of age [4]. The cardinal clinical manifestations of Parkinson's disease include resting tremor, akinesia, rigidity, gait abnormalities and postural imbalance. The main pathological finding in Parkinson's disease is degeneration of dopamine neurons in the substantia nigra pars compacta and the presence of intracytoplasmic inclusions known as Lewy bodies.

DBS for treating movement disorders has mainly targeted the structures in the basal ganglia [5], since Hughlings Jackson's primate research and patient observation led him to suggest that unstable basal ganglia activity led to chorea [6]. From a surgical point of view, one of the first demonstrations of the importance of specific parts of the basal ganglia came from the initial discovery in 1953 that ligation of a patient's anterior choroidal artery caused infarction of the globus pallidus [7].

Yet, the most important discovery probably came from human drug users who were exposed to the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which caused degeneration of dopaminergic neurons in the

substantia nigra [8,9]. This has since become the basis of the highly successful MPTP model for the study of the pathophysiology of Parkinson's disease [10].

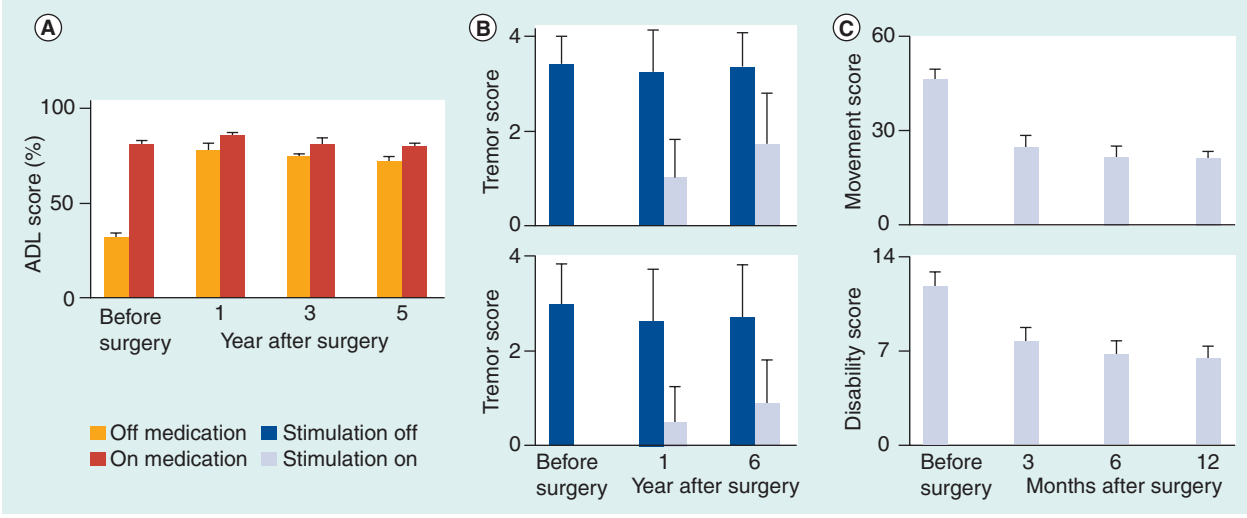
This MPTP model has highlighted the internal globus pallidus (GPi) and subthalamic nucleus (STN) as safe and efficacious targets for Parkinson's disease [11,12]. The long-term effects of using high frequency (130–185Hz) DBS for Parkinson's disease are well documented (Figure 1A) [13,14]. Substantial improvements in the symptoms of Parkinson's disease (as measured by motor and daily living scores) [15], as well as reductions in the patients' level of medication for Parkinson's disease have been found in extensive DBS trials for Parkinson's disease [14,16,17]. Currently, the majority of all DBS implantations to treat Parkinson's disease are within the STN. In addition, translational research has identified the PPN as a potential new target for parkinsonism in monkeys [18–21] and humans [22–24].

Another movement disorder, essential tremor, is usually treated with DBS in the ventral intermediate nucleus of the thalamus (Vim) [25,26], while the DBS targets for tremor in Parkinson's disease are the GPi and STN [27,28]. Long-term effects of DBS in Vim have shown an average tremor reduction of over 80% in the majority of patients [29,30]. Thalamic DBS was found to significantly improve tremor compared to thalamotomy and to have fewer adverse effects [31]. A large multicenter study demonstrated continued improvements in tremor ratings in patients with essential tremor after 6 years of follow-up (Figure 1B) [32].

By contrast, the preferred target for dystonia, including spasmodic torticollis (cervical dystonia), is the GPi [33–35], but another potential site might also be the STN [36]. The DBS parameters for dystonia differ from Parkinson's disease with a broader pulse width (200–400 µs) and higher voltage (typically between 2.2 and 7 V) leading to rapid battery consumption [37]. Blinded controlled GPi trials have shown 30–50% improvements in patients over 12 months (Figure 1C) [38].

Patient selection criteria for DBS depends on factors such as the correct diagnosis of movement disorder, age, cognitive state and disease stage for selecting those who will obtain maximum benefits from the neurosurgery with the least amount of adverse effects.

Figure 1. Long-term outcomes of deep-brain stimulation for movement disorders.



(A) Scores on the Schwab and England scale for activities of daily living (ADL) at baseline and 1, 3 and 5 years after surgery with medication on (red) and off (yellow) for 49 patients with Parkinson's disease. A score above 70% indicates complete independence and a score below this threshold indicates the need for a caregiver. Off-medication scores were significantly improved at 1, 3 and 5 years ($p < 0.001$) [14]. **(B)** Outcomes of deep-brain stimulation (DBS) on (light blue) and off (dark blue) for essential tremor using rating scale subscores for upper limb action tremor (top) and upper limb postural tremor for the hemibody contralateral to surgery (lower) for 37 patients with essential tremor. Significant improvements were found when comparing stimulation on and off ($p < 0.00001$) [32]. **(C)** Long-term outcome for dystonia using the mean scores for the movement (upper) and disability (lower) subscales of the Burke–Fahn–Marsden dystonia scale before and 3, 6 and 12 months after surgery for 22 patients with dystonia. Significant long-term improvements were found on stimulation compared with scores before surgery ($p < 0.001$) [38].

DBS for pain & other affective disorders

Treatment of affective and other non-movement disorders with DBS has so far been based mostly on human research since few, if any, effective translational animal models exist. 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 demonstrated, for example, by how severe depression can be reversibly induced by DBS for Parkinson's disease [39,40]. 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.

It is over 50 years since the initial studies used DBS in the hypothalamus to treat chronic pain [41]. More recent efficacious targets have been found in the thalamus [42–44] and the periventricular/periaqueductal gray region (PVG/PAG) [45–48]. However, following two failed clinical trials, US FDA approval was not sought by device manufacturers [49]. During the last decade only five centers outside the USA have produced case series of more than six patients [50–58]. These studies have shown significant improvements for patients with primarily pain after amputation and stroke, and head pain including anesthesia dolorosa. Patients with cluster headache have been successfully treated with DBS in the hypothalamus [59,60].

Other affective disorders that have been successfully treated with DBS include depression, where targets have included the thalamus [61,62] and the subgenual cingulate cortex [63]. Another recent study of DBS in the nucleus accumbens found a significant reduction in anhedonia in three patients with treatment-resistant depression [64]. DBS for obsessive–compulsive disorder has targeted the anterior internal capsule [65]. DBS of the thalamus [66] and GPi [67] has been reported to be 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.

Mechanics of DBS

The specific methods used for DBS vary between neurosurgical teams. Here we present the methods adopted in Professor Aziz's lab in Oxford and focus specifically on the procedures used for DBS for pain relief (Figure 2).

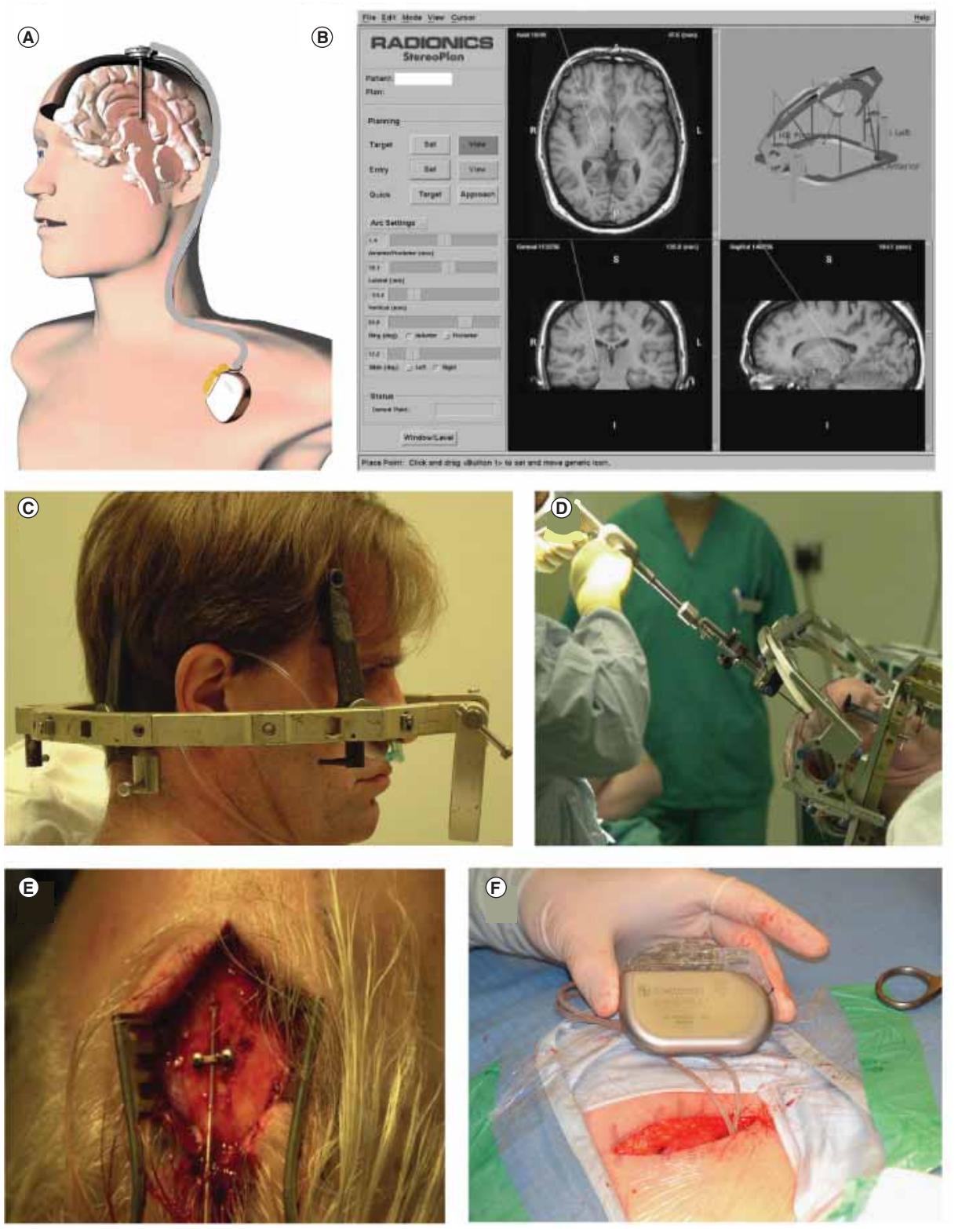
A T1-weighted MRI scan of each patient's brain is performed several weeks before surgery. For surgery, a Cosman–Roberts–Wells base ring is applied to the patient's head under local anesthesia. A stereotactic computed tomography scan is then performed and, using the Radionics Image Fusion® and Stereoplan® (Integra Radionics, Burlington, MA, USA) 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 the laterality of approach is 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. Distally the deepest electrode lay in the superior colliculus. The VPL is located 12 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 (Figure 3).

The VPL is usually implanted with a Medtronic 3387 (Medtronic, Minneapolis, MN, USA) electrode to enable stimulation-induced parasthesia in the area of pain. The PVG is also implanted with a Medtronic 3387 electrode to allow 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 a stimulation intensity 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 the following week under general anesthesia.

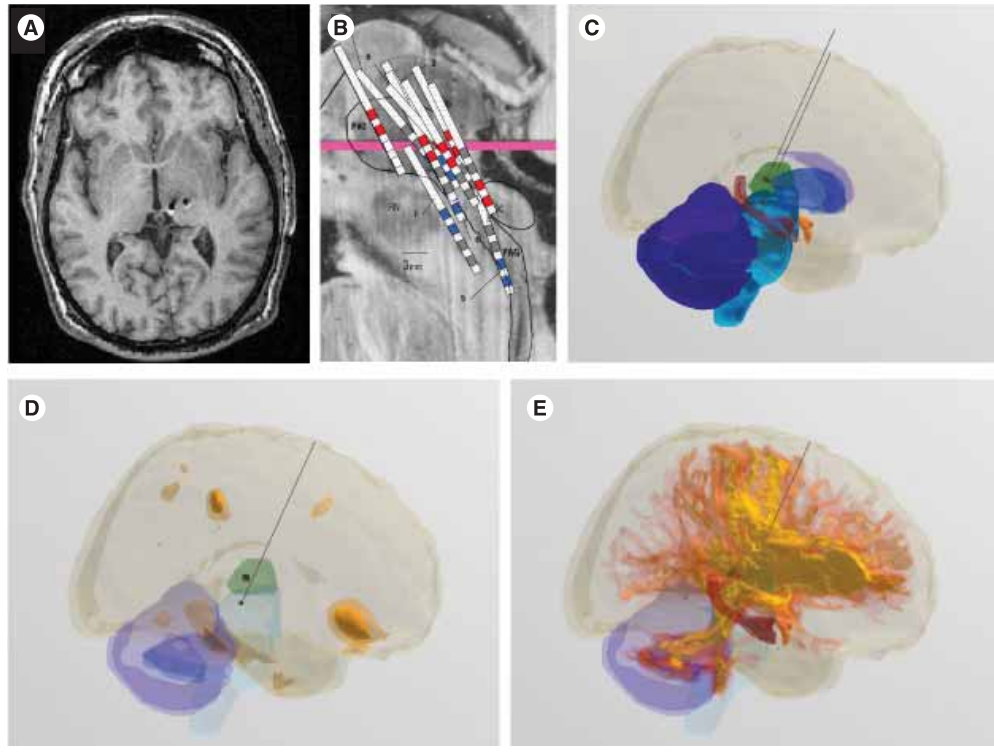
Other surgical centers around the world use slightly different procedures with one of the main differences being the use of microelectrode recordings to improve the accuracy of targeting in stereotactic placement. Some of the benefits of this procedure include the potential for differentiation of gray 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

Figure 2. Neurosurgical procedures involved in deep-brain stimulation.



(A) Schematic of the principles of deep-brain stimulation. **(B)** Illustration of the process of the neurosurgical preplanning. **(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 3. Deep-brain stimulation for chronic pain.



(A) Axial MRI slice showing the implantation of electrodes in the periventricular/periaqueductal gray region (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)** 3D 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)** 3D rendering showing the whole-brain, deep-brain stimulation-induced activity from stimulation in the PVG/PAG. **(E)** The connectivity of the PVG/PAG measured with diffusion-tensor imaging.

controversial and perhaps superfluous since studies have shown a good correspondence between the MRI-defined target and the proposed electrophysiology-derived map [68]. 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 but more intracranial hemorrhages [69].

Safety & complications

The safety of DBS and the procedure involved has been demonstrated in many worldwide trials and in the long-term follow-up in DBS for the treatment of chronic pain [70]. 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 1 year. Radiofrequency, rechargeable pulse generators are available for spinal cord generators and are being trialed 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 [17,71]. 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 [72]. Stimulation-induced side effects (3%) are also quite common, such as paresthesia, dyskinesia, tonic muscle contractions and gait ataxia, as well as the less common effects such as aggression [73], mirthful laughter [74], penile erection [75], depression [39] and mania [76]. These side effects are closely related to the location of lead/contacts used for stimulation.

Translational research

Current DBS therapies have already been transformed by translational research, which may also help to identify safe and effective new brain targets as well as new stimulation paradigms to treat movement and affective disorders.

New treatments for Parkinson's disease have come mainly through use of the MPTP model in primates [9,10]. Initially, lesions of the STN in primates were shown to be efficacious and safe in alleviating the symptoms of Parkinson's disease by two research groups at roughly the same time [11,12]. Subsequent DBS of the STN in the MPTP primate was also successful [77]. Similarly, human studies using DBS stimulation of the STN have been shown to be as safe and efficacious as GPi stimulation [78], although there are more known psychiatric side-effects with STN stimulation. This is possibly due to the fact that the STN is a smaller volume than the GPi, and that STN stimulation may also involve nonmotor regions of the STN and adjacent areas [79]. The therapeutic benefits of both STN and GPi stimulation do not usually exceed those of dopaminergic medications [80] but they have at least two main advantages: reducing medication and its side-effects and reducing the time spent with Parkinsonian symptoms when the medication is less effective.

This led us to search for a target that could also help with the gait disturbances and akinesia in Parkinson's disease, and potentially alleviate the resistance to dopaminergic medication and akinetic symptoms in the late stages of Parkinson's disease, progressive supranuclear palsy and multisystem atrophy. The PPN had emerged over a number of years as a promising target for DBS in Parkinson's disease, especially since it lies outside the basal ganglia and has no dopaminergic pathways.

Animal studies in rats and cats had shown that stimulation of the PPN increases (and inhibition decreases) movement [81–83], and that this region degenerates in akinetic disorders such as Parkinson's disease, progressive supranuclear palsy and multisystem atrophy. PPN also shows increased uptake of labeled 2-deoxyglucose in MPTP-treated primates [84]. This uptake is reduced after STN lesions, which can reverse akinesia in MPTP-treated primates, and lesions of the PPN in normal primates can induce akinesia [85–87].

Following these studies, we demonstrated that microinjections of the GABA antagonist bicuculline into the PPN of MPTP-treated primates can alleviate akinesia [88]. We also showed that motor activity can be influenced by DBS in the PPN in normal primates [18], although this study used an electrode designed for human implantation and might have been confounded by stimulation of nearby structures such as the superior cerebellar peduncles.

These studies strongly suggested that the PPN might be a potential target for alleviating Parkinson's disease, and we therefore implanted a custom-made macroelectrode designed specially for primates. We found that low-frequency DBS (5–10 Hz) reversed akinesia as effectively as dopaminergic treatment [20].

Subsequent human studies confirmed that stimulation of the PPN is effective in alleviating the symptoms of Parkinson's disease [22–24]. This new target offers hope of alleviating the symptoms of treatment-resistant Parkinson's disease, and indeed potentially any patient with intractable locomotor and postural akinesia. Furthermore, the very low stimulation frequencies required to drive the PPN could potentially extend the battery life of the pacemaker, which will greatly improve the cost effectiveness, the treatment and perhaps even make the treatment viable for use in developing countries.

The example of the PPN clearly illustrates how scientifically grounded translational research can help to bring important laboratory findings to bear on the alleviation of human suffering. Translational research can thus help us study the mechanisms that underlie the effects of DBS, the pathophysiological mechanisms and circuitries underlying the disorders, as well as the possible side effects of DBS.

Principles of DBS

The similar therapeutic outcomes of DBS and neurosurgical lesions have been used to try 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 depend on the stimulation parameters, the properties of the neural tissue and their interaction. In other words, these parameters include:

- Stimulation parameters including amplitude and temporal characteristics
- Physiological properties of the brain tissue that may change with disease state
- Interactions between the electrode and the surrounding tissue arising from the specific geometric configurations

The stimulation parameters of DBS that are of therapeutic value have been derived primarily by trial and error using the near-immediate effects on, for example, tremor, rigidity, paresthesia, bradykinesia and chronic pain in

patients on the operating table [89]. The exact DBS parameters vary with treatment and targeted brain region but are usually between 1 and 9 V stimulus amplitude; 60 and 240 µs stimulus pulse duration; monopolar cathodic; and either low (5–50 Hz) or high (130–180 Hz) stimulus frequencies [90]. Currently a charge-density limit of 30 $\mu C/cm^2$ is used as a safety factor based on post-mortem studies of tissue damage [90]. Most commercially available stimulators will allow for these parameters to be changed and fine-tuned over time, but based solely on the patient's behavioral state. The technology is open-loop, continuous stimulation that cannot 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 20 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 that utilize different types of ion channels with variable voltage-sensitive properties. The most excitable neural elements are the myelinated axons [91,92]. 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 [91]. 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 µs, while the chronaxies of cell bodies and dendrites are substantially larger at around 1–10 ms [93]. This means that with usual DBS parameters, the postsynaptic responses are the result of activity from efferent axons rather than from cell bodies [94].

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 [91]. 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 [93]. 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 [92,95]. For example, modeling the excitability effects for STN stimulation using realistic white-matter pathways has shown that at 3 V the stimulation spreads outside the STN proper and the pattern of excitation is consistent with known stimulation side effects [95]. 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 gives rise to subthreshold 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 polysynaptic 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 [96–100], neurochemistry [101,102] and functional neuroimaging methods [103–105]. In addition, computational modeling can be used to test and predict the effects of DBS on simulated neural elements [92,95].

Neurophysiological recordings

Evolution appears to have preserved many of the general principles for neural processing across species and, thus, data from other species such as rats and nonhuman primates are highly relevant for understanding the mechanisms of DBS. We concentrate here on *in vivo* studies in primates [106], while we will not discuss the results of the many studies in rodents of which there are other good reviews [107].

A number of research groups have used MPTP-treated primates to study the effects of STN stimulation on activity in GP neurons [96,108]. High-frequency STN stimulation was found to cause activation in STN efferent fibers, while the multiphasic response patterns found are suggestive of mono- and polysynaptic activity in other parts of the basal ganglia [96]. Similar results were found in the study using single STN stimulation, which induced a short-latency excitation followed by a weak inhibition in neurons in the external segment of the pallidum (GPe) and a short-latency, very short-duration excitation followed by a strong inhibition in GPi

neurons. These findings suggest that more complex polysynaptic responses dominate over monosynaptic responses in the GPi [108].

Human studies of STN stimulation have primarily used local rather than distal recordings. Distal recordings were used in a study in a dystonic patient who had previously undergone a nonbeneficial DBS GPi implantation and was now being implanted with thalamic DBS. The patient was anesthetized during the recording of seven thalamic neurons subjected to GPi stimulation [99]. Four of the tonically active thalamic neurons were inhibited, while the activity of three low-frequency neurons remained unchanged, which is consistent with the previous findings in monkeys [97].

Interestingly, when recording local field potentials (LFPs) from the GPi and the STN in four awake Parkinson's disease patients after neurosurgery, it was found that there were strong increases in β (15–30 Hz) oscillatory activity in the STN when the patients were without dopaminergic medication, which subsequently decreased when taking medication but led instead to spontaneous synchronization at frequencies in the γ band [109]. A subsequent study showed that therapeutic effective STN stimulation above 70 Hz suppresses activity in the GP in the β band at approximately 20 Hz [100].

This suggests that Parkinson's disease might be linked to an abnormal and potentially deleterious synchronization of basal ganglia output in the β frequency band of approximately 20 Hz [110]. Further evidence of the origin of these oscillations was recently obtained in a study of intraoperative LFP and neuronal spike recordings in the STN of 14 Parkinson's disease patients, which showed that the LFP β-oscillatory activity is generated mostly through spiking activity within the dorsal portion of the STN [111].

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 PET and functional MRI (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 [112,113]. This means that these methods entail a number of assumptions that 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 demonstrated 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 [114]. 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 the frontal cortex following GPi and thalamic stimulation [115]. 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 [116]. 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 artifacts when studying movement disorders.

Several PET studies have taken the necessary precautions to study the effects of DBS in movement disorders. In a group of patients with Parkinson's disease, STN stimulation led to increased blood flow in the thalamus, GP and midbrain (including the STN) and reduced blood flow in frontal parietal and temporal cortices [104]. Similarly, a PET study of Vim stimulation in patients with essential tremor showed increases in blood flow in the thalamus and the cortical targets of thalamic output [103].

Using PET to study DBS for affective disorders is less challenging in terms of potential movement artifacts. One PET study investigated the effects of hypothalamic stimulation for cluster headache in ten patients [117] and found that hypothalamic stimulation modulated the pain-processing network. Another PET study used stimulation of the subgenual cingulate cortex for treatment-resistant depression in seven patients, and showed a

marked reduction in mood symptoms in four patients [63]. 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 suggests that the mode of functioning of DBS would appear to modulate an existing network of interacting brain regions.

In contrast with PET and fMRI, MEG is noninvasive 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 mm^3) but with much better temporal resolution (in milliseconds) [118].

The first MEG study of DBS was carried out in a patient with low-frequency PVG/PAG stimulation for severe phantom limb pain [105,119]. 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 [120]. Similarly, MEG of high-frequency hypothalamic stimulation for cluster headache showed a similar pattern of changes in neural activity in a widespread cortical and subcortical network, including the orbitofrontal cortex [121]. Owing to its noninvasive 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 [122].

Synthesis of mechanisms

The experimental evidence collected so far allows for some conclusions to be drawn about the neural, and systems-level mechanisms of DBS action. The effects of DBS 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 [1,123–125], rather than competing hypotheses such as synaptic inhibition [98], depolarization blockade [126] or synaptic depression [127].

The similar therapeutic effects of DBS and lesioning are thus likely to be achieved through different mechanisms. The modulation is likely to come about through the local effects of the DBS electrode on the neural activity in the DBS target, which is passed on to mono- and polysynaptic network connections. Taking STN stimulation as an example [124], near the electrode a small volume of the applied field will activate projection neurons and a larger volume will activate afferent inputs, while projection neurons in the volume formed by the difference between these two volumes are suppressed by the stimulation-induced trans-synaptic inputs. The output of STN stimulation will thereby result in high-frequency glutaminergic inputs to the GPe and GPi, and it is possible that many neurons in the GPe will be antidromically activated through their afferent inputs in STN [96]. Further spread of activation to GPi axons and the lenticular fasciculus are also likely, which in turn can generate specific changes in the oscillatory neural activity between the cortex and the basal ganglia. Experiments have shown that high-frequency STN stimulation leads to the suppression of all activities in the GPi that are below 40 Hz, whereas frequencies below 30 Hz are maximally potentiated by STN stimulation at 25 Hz [100].

Future perspective

DBS 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. 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 [120]. We have previously suggested that translational research using DBS and the MPTP model in primates may also be useful for the treatment of affective disorders given the pivotal role of the basal ganglia not only in movement but also in affect [1].

Other 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 [100], and such 'neural signatures' may come to help drive specific DBS interventions.

Executive summary

Introduction

- Deep brain stimulation (DBS) in select brain regions has become the basis of highly successful therapies for treating otherwise treatment-resistant movement and affective disorders.
- DBS is not only clinically useful but can also help us understand fundamental brain function.

DBS for movement disorders

- Modulation of brain activity by way of direct electrical stimulation has been in use at least since 1870.
- Development of novel DBS targets depends on translational research; the 1-methyl-4-phenyl-1,2,3, 6-tetrahydropyridine (MPTP) model has been critical for the study of the pathophysiology of Parkinson's disease.
- The thalamus, internal globus pallidus and subthalamic nucleus (STN) are established DBS targets for treating many movement disorders.

DBS for pain & other affective disorders

- DBS targets for chronic pain include the thalamus and the periventricular/periaqueductal gray region.
- Other affective disorders, such as depression, are increasingly being treated with DBS but are more speculative given that we are currently lacking good animal models for these disorders.

Mechanics of DBS

- Surgical procedures for DBS as adopted by Professor Aziz are described in detail.
- Other centers use microelectrode recordings which are, however, controversial given that they are more time-consuming without significant differences in outcome and give rise to more complications.

Safety & complications

- Safety of DBS has been established in many worldwide trials and in long-term follow-up studies.
- DBS, like all stereotactic neurosurgical procedures, always has a significant risk.

Translational research

- STN DBS is currently the most used DBS procedure, as such it is a good example of translational research transforming neurosurgery.
- Recently, animal research has identified pedunculopontine nucleus DBS as a potential treatment for Parkinson's patients not helped by other treatments.

Principles of DBS

- Careful animal experimentation has demonstrated that STN DBS is both safe and efficacious.
- DBS fundamentally depends on the stimulation parameters, the properties of the neural tissue and their interaction.
- These parameters include: stimulation parameters (e.g., amplitude and temporal characteristics), physiological properties of the brain tissue, which may change with disease state, and interactions between the electrode and surrounding tissue.

Neurophysiological recordings

- Evidence from *in vivo* studies in primates is reviewed.
- Results show that Parkinson's disease might be linked to an abnormal and potentially deleterious synchronization of basal ganglia output in the β-frequency band of approximately 20 Hz.

Functional neuroimaging

- Functional neuroimaging methods allow for the study of the whole-brain activity elicited by DBS.
- Magnetoencephalography (MEG) and PET are the most important methods, while functional MRI should be avoided since it presents a large degree of risk to DBS patients.
- Owing to its noninvasive 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.

Synthesis of mechanisms

- DBS affects multiple neural elements including foremost myelinated axons and to a lesser degree cell bodies.
- The weight of evidence suggests the most likely mode of action for DBS is through stimulation-induced modulation of brain activity.

Future directions

- DBS is both an important tool for clinical use and for obtaining novel insights into the nature of fundamental brain function.

In general, such research on feedback-driven neural prostheses may open the way for more advanced brain–computer interfaces, which could help patients in a number of pathological states, such as those with spinal cord injuries, or even helping to drive brain activity in individuals in vegetative and minimally conscious states [128].

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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