Deep Brain Stimulation: an underused panacea?

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Summary

Deep brain stimulation (DBS) enables structures in the brain to be stimulated electrically by an implanted pacemaker after a minimally invasive neurosurgical procedure and has become the treatment of choice for Parkinson's disease refractory to or complicated by drug therapy. Many clinical indications for DBS now exist including dystonia and tremor in movement disorders; depression, obsessive-compulsive disorder and Tourette's syndrome in psychiatry; epilepsy, cluster headache and chronic pain. DBS is a standard and widely accepted treatment for Parkinson's disease after two decades of experience, but for most other clinical indications it remains restricted to a handful of experienced, specialist centres. Current challenges highlighted include consideration of referral for DBS by clinicians and the securing of funding for its use from National Health Service healthcare providers.

Deep brain stimulation (DBS) is neurosurgery that enables brain structures to be stimulated electrically by a pacemaker implanted under the skin. In the 1980s, over a decade after its first use in pain,[1] implantable DBS of the thalamus was performed to suppress tremor in Parkinson's Disease (PD) refractory to drug treatments.[2] Primate-based research soon afterwards identified the subthalamic nucleus, a basal ganglia structure, as a putative brain target for both ablation and DBS.[3,4] Alongside the resurgence of thalamic DBS and basal ganglia lesional surgery[5,6] and improvments in neurostimulator technology, scientific discoveries from primate research cultivated a renaissance in neurosurgery for PD in the 1990s resulting in increasing use of DBS over the last decade. Its efficacy in PD has been demonstrated robustly by clinical trials with multiple novel brain targets having been discovered recently. Several other indications for DBS now exist such as tremor and dystonia in movement disorders; psychiatric disorders like obsessive-compulsive disorder (OCD), depression and Tourette's syndrome; cluster headache, epilepsy and chronic pain.[7]

Devices

At present, only one commercial manufacturer (Medtronic Inc, Minneapolis, MN, USA) produces deep brain electrodes widely used for DBS. Two models are currently available - the 3387 and the 3389. Both are quadripolar electrodes, having four electrical contacts with the brain.

Several stimulation parameters can be altered in DBS, in particular voltage, frequency and pulse width. Stimulation can be monopolar or bipolar over any combination of the four contacts of each electrode and multiple contacts can be specified as anodes or cathodes. The DBS electrode is secured to the skull and connected to a lead tunneled to the chest or abdomen where a pulse generator (pacemaker) is implanted under the skin. Recent developments include commercially available transcutaneously rechargeable pulse generators, which will be included in a new DBS platform being introduced by Medtronic, and the potential entry of other device manufacturers from related fields like spinal cord stimulation. Detailed device issues are described elsewhere.[8,9]

Efficacy

As several decades of clinical experience with established drug treatments have accrued so patient subgroups refractory to medical therapies have been identified, not just in PD, chronic pain and epilepsy, but also in other movement disorders including dystonias, tremor, Tourette's syndrome, psychiatric disorders of depression and obsessive-compulsive disorder (OCD) and cluster headache. These disorders have all been successfully treated by DBS after failed drug treatment (Table 1).[7] Each is summarised below.

Parkinson's disease

PD is a slowly progressive, neurodegenerative disease characterised by tremor, rigidity, bradykinesia and postural instability. It is common in middle or late life with prevalence rising to 1% in people over 60

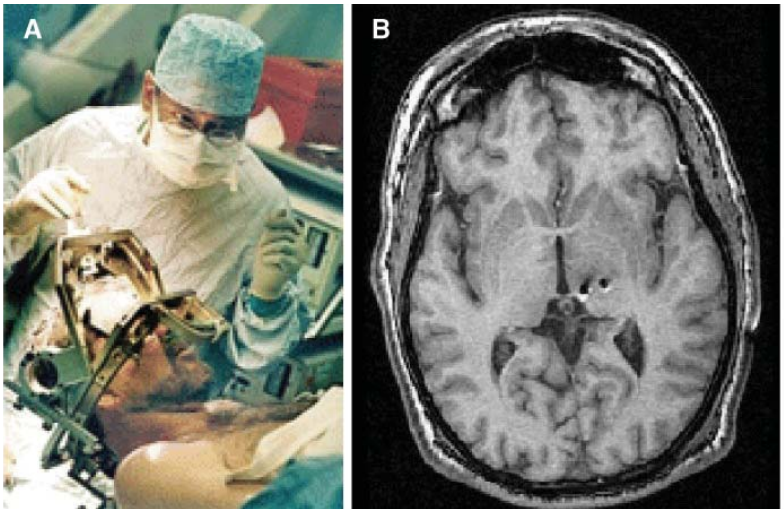

Figure 1: (A) Intra-operative awake deep brain stimulation; (B) axial MRI of deep brain stimulators for pain in situ.

Table 1. Clinical indications for deep brain stimulation, approximate numbers of patients treated worldwide and common brain structures targeted.

Indication	Patients treated	Deep brain targets
Parkinson's disease	40,000	Globus pallidus internus, subthalamic nucleus
Chronic pain	2,000	Ventral posterior medial and lateral thalamic nuclei, Periventricular and periaqueductal grey matter
Tremor (not including Parkinson's disease)	1,000	Ventralis intermedius thalamic nucleus, Zona incerta
Dystonia	500	Globus pallidus internus
Cluster headache	100	Posterior hypothalamus
Epilepsy	50	Anterior thalamic nucleus
Tourette's syndrome	100	Ventromedial thalamic nuclei, Anterior limb of internal capsule, Globus pallidus internus
Obsessive-compulsive disorder	100	Anterior limb of internal capsule
Depression	50	Subgenual cingulate cortex, Anterior limb of internal capsule

years of age. Established basal ganglia brain structures currently targeted for PD DBS include the globus pallidus interna (GPi), Ventralis intermedius nucleus of the thalamus (ViM), and subthalamic nucleus (STN), over 30,000 patients having been implanted to date.[10]

GPi has traditionally been targeted mainly for dyskinesia symptoms, STN for levodopa refractory patients and ViM for tremor. Despite its smaller size, the STN recently gained dominance over GPi as the surgical target of choice for PD due to reports of favourable motor outcomes.[11] A 156 patient randomised, controlled, multi-centre trial of STN DBS versus medical treatment alone showed a 25% benefit in motor function and 22% improvement in quality of life outcomes at six months after.[12] Sustained benefit with STN DBS has also been described after five years of follow-up.[13,14] GPi and STN have been compared at four year follow-up,[15] however long-term, back to back, randomised, blinded, controlled trials of the two surgical targets are yet to be completed.[16]

The pedunculopontine nucleus (PPN) has been discovered in the last decade as a deep brain target, stimulation of which reduces gait abnormalities and postural instability.[17] Like the STN, its clinical utility has been realised by non-human primate research.[18,19] Initial results favour its use in PD patients blighted most by postural instability, in PD-plus syndromes of multiple system atrophy and progressive supranuclear palsy and in those with symptoms not ameliorated by STN stimulation alone.[20]

Tremor

Tremor is the involuntary, rhythmic oscillation of a body part. Essential tremor prevalence varies greatly throughout the world and can be up to 2%. DBS can alleviate contralateral limb tremor in essential tremor, Holmes' tremor, cerebellar tremor, tremulous multiple sclerosis and tremor after head injury.[21] For trunk, head and voice tremors, bilateral DBS is considered.[22] Brain targets considered in patients refractory to medication are the ViM and the zona incerta (ZI).

Sustained and consistent motor improvements with ViM DBS have been shown six years after surgery in 19 patients with essential tremor.[23] Quality of life improvements have also been demonstrated in 40 patients one year after surgery.[24] In multiple sclerosis, patient selection is paramount.[25] Distal limb tremor responds best to ViM DBS and proximal limb tremor to ZI DBS.[26] Post-operative benefits in motor function for 88% of patients and in daily functioning for 76% have been shown in a systematic review of 75 multiple sclerosis.[27] Brain targets in DBS for head injury depend upon the prevailing movement disorder with excellent results described in the small numbers of cases reported.[28]

Dystonia

Dystonias are disorders of involuntary sustained muscle contractions that can affect certain body regions or be generalised. They may begin in childhood or young adulthood, often progressing from focal limb involvement to a severe generalised form, or manifest in later adulthood when they are usually focal or segmental and frequently craniocervical (spasmodic torticollis). Prevalence of early onset dystonias is up to 50 per million with a greater, up to 0.01%, prevalence of the late onset type. DBS is considered for children refractory to medical therapy, usually by anticholinergic, dopaminergic or benzodiazepine treatments, and adults refractory to botulinum toxin injections.

Stimulation of the posteroventral GPi is performed for primary dystonias.[29] GPi DBS is particularly effective in childhood dystonias,[30] and in those patients carrying a mutation in the DYT1 gene.[31] Secondary dystonias are less responsive.[32] Moderate benefits have also been observed with ViM but not STN DBS.[33] Motor improvements are often not fully realised until weeks to months later.[34] Sustained motor and quality of life improvements without cognitive impairment have been shown three months after surgery in a prospective, multi-centre trial of 40 patients,[35] and three years after surgery in 58% of patients in a trial of 22 patients.[36]

Depression

Depression is extremely common. Lifetime prevalence for major depressive disorder has been estimated at 16%, half of all patients having reduced function and role impairment. Patients with major depressive disorder are twice as likely to die as those who are not depressed. One trial of DBS in drug refractory depression targeted the subgenual cingulate cortex bilaterally, four out of six patients showing improvement.[37] Another targeted the anterior limb of the internal capsule as for OCD in five patients,[38] three patients showing a greater than 50% symptom improvement. Both studies were uncontrolled and had less than one year of follow-up. While DBS for severe depression appears promising, further studies are required to confirm efficacious targets and successful outcomes.

Obsessive compulsive disorder

OCD can manifest at any age, but first onset is usually in a person's third decade. Prevalence is 0.8% in adults and lower in children. About 10% of patients are refractory to pharmacotherapy and frequently become housebound. The anatomical target for DBS derives from the success of the lesional procedure of anterior capsulotomy that improves symptoms in approximately half of patients treated.[39] Long-term outcomes for bilateral DBS of the anterior limb of the internal capsule and adjacent ventral striatum have been reported by two groups. In one study, blinded assessment of four patients followed up for at least 21 months after surgery revealed significant improvements in three patients.[40] In another study, of ten patients evaluated three years after surgery, seven showed a one third or greater percentage reduction in symptoms and six had an improvement in activities of daily living.[41]

Tourette's syndrome

Tourette's syndrome has 0.1-1% prevalence, usually affecting children and adolescents. It is more common in people with autistic spectrum disorders and is characterised by motor and vocal tics. Simple tics typically involve one muscle group and complex tics may mimic a purposeful movement such as an obscene gesture. Simple vocal tics are sounds or noises like grunting and complex vocalisations include echolalia and coprolalia, the latter affecting 10% of patients. For most sufferers, symptoms decline in adulthood, but DBS may be considered for those with debilitating tics refractory to drugs such as neuroleptics and anti-convulsants.

Brain regions targeted for DBS have included the medial intralaminar thalamic (centromedian and parafascicular) nuclei (three patients)[42] and case reports of stimulation of the anterior limb of the internal capsule,[43] and GPi.[44-46] With this initial experience and experience of ablative surgery for Tourette's syndrome,[47] criteria for DBS suitability have been proposed.[48]

Epilepsy

Epilepsy is a debilitating neurological condition affecting 50 per 100,000 people with higher prevalence in children and the elderly. Symptomatic

epilepsy is estimated to reduce life expectancy by up to two decades. Sudden death in medically refractory epilepsy is 0.5% and highest in young adults. Neurosurgical treatment is considered after poor seizure control despite trial of at least three antiepileptic medications.

DBS of the anterior thalamic nuclei has been undertaken by several groups. In one study, five of six patients had improvements in their seizures over an average follow-up period of five years.[49] In another study, four of five patients showed significant reductions in frequency and severity of seizures after 6-36 months without adverse complications.[50] A third study showed significantly reduced seizures in all four patients over an average 44 month follow-up period.[51] Putative targets of stimulation may depend upon seizure localisation and also include the STN, caudate, hippocampus, cerebellum, hypothalamus and medial intralaminar thalamic nuclei.[52]

Cluster Headache

Cluster headache is characterised by severe unilateral periorbital pain with concomitant autonomic sequelae of vasodilatation and periorbital oedema. Prevalence is less than 1% with men more commonly affected. DBS can be performed for cluster headache refractory to medical treatments, targeting the ipsilateral posterior hypothalamus. After mean follow-up of almost two years, 13 out of 16 patients were reported symptom free or almost headache free in the largest study to date.[53] Another group has reported three of six patients considerably improved.[54] Initial reports appear extremely successful.[55]

Chronic pain

Chronic pain presents a considerable burden to society, occurring in cancer, stroke, trauma and failed surgery. It may affect as many as one in five people. DBS has been undertaken for almost four decades. Targets have included the internal capsule and medial intralaminar thalamic nuclei, but most current treatments target the ventral posterolateral and ventral posteromedial thalamic nuclei (VPL/VPM) and periaqueductal and periventricular grey matter (PAG/PVG). 1300 recipients of DBS for pain have been reported.[56,57] Chronic pain aetiologies with good outcomes in contemporary series are stroke,[58] amputation,[59] anaesthesia dolorosa,[60,61] and plexopathies with success also seen in multiple sclerosis[62] and malignancy.[63]

Safety

As an intracranial neurosurgical procedure, DBS has small but significant risks. Aside from multidisciplinary assessment to determine suitability for the procedure, the patient must be refractory to medical treatment and able to give informed consent (where appropriate) to risks of stroke (1-3%), seizures (<1%), death (0.1%), skin erosion, lead breakage and the need for implantable pulse generator (IPG) revision surgery every one to ten years depending upon indication, and infection (3%) - a small proportion of cases requiring complete removal of the DBS system.[56,64-66] Patients should also be counselled for the possibility that they may derive no benefit from DBS or not tolerate it well, again necessitating its removal. Likelihood of this varies from indication to indication, but it should be emphasised when treating less established indications.

Indication and target specific complications can arise, for example dysarthria with bilateral ViM DBS,[67] altered libido with medial thalamic stimulation,[42] and anxiety with PAG/PVG DBS.[57] A full list of such specific complications is beyond the scope of this review and is discussed elsewhere.[9,68] However, their incidence with DBS is usually smaller than for the same target if lesioned, and furthermore DBS confers adjustability and reversibility.

The limited lifespan of IPGs is accentuated by disorders requiring large voltages or pulse widths and high frequencies of stimulation. For OCD and depression 5 to 10 volts is required requiring IPG changes almost yearly, and for dystonia large pulse widths are often used requiring IPG replacements approximately every 3 years. Stimulation failure due to IPG charge loss is an emergency in dystonia as relapse with respiratory compromise can be sudden and require intensive care.[69] New rechargeable IPGs coming to market are still likely to need replacement every nine years.

Cost-effectiveness

DBS is clearly a specialised treatment. In the British National Health Service, national tariffs for procedures are set and in 2007 pre-operative assessment was priced at over £1,000, surgery at approximately £21,000, replacement IPGs at over £8,000 and clinic follow-up visits at £800. Considering equipment alone, a stereotactic frame costs £80,000 and a computer planning station £65,000, their estimated lifespans being three years. A single electrode lead, extension, IPG and patient DBS controller cost around £12,000. To put the figures in context, Britain prices a cardiac pacemaker implantation at around £3,000 and a spinal discectomy similarly.[70]

Despite, or perhaps because of, its expense few studies have been published regarding the cost-effectiveness of DBS. A North American analysis of PD made several assumptions to suggest that DBS for PD may be effective with quality of life improvements of at least 18% over medical treatment alone.[71] For STN DBS in PD, a German study of 46 patients attributed 32% increased healthcare costs for the first post-operative year due to surgical and equipment expense, but 54% cost reductions for the second post-operative year concomitant with significantly improved motor outcome measures and reduced medications. The results suggest that the procedure is highly cost-effective after the first year and overall,[72] findings supported by other studies.[73,74] Two British studies have been conducted in dystonia and multiple sclerosis tremor. For dystonia, quality of life measures of 26 patients were used to demonstrate a quality adjusted life year (QALY) improvement of almost one year with DBS at a cost of £34,000 per QALY.[65] In contrast, one small study for multiple sclerosis suggested that benefits in 15 patients did not justify the high costs of DBS.[75]

One North American study sampled hospitals in the year 2000 when 88% of PD surgery performed was DBS and in 1996 when no DBS was performed.[76] Intriguingly, younger age, Caucasian ethnicity, private insurance, higher socioeconomic status, teaching hospital status and smaller annual hospital caseload all favoured DBS. Furthermore charges for DBS were 2.2 times higher than for ablative surgery, with lower charges made by higher-volume hospitals. These larger-volume hospitals also had superior short-term outcomes. Such results may reflect the early years of the treatment's diffusion from experimental status in academic settings to widespread uptake by many neurosurgical units.

Further, larger cost-benefit and cost-utility analyses with longer-term follow-up are required for each indication to verify the findings of these preliminary studies described. It is noteworthy that factors of scale could account for cardiac pacemakers being relatively inexpensive in comparison to cerebral ones. Present high costs of DBS are therefore likely to be reduced by its increasing uptake.

Discussion

Two distinct issues remain to be unequivocally determined in DBS: treatment effectiveness for indications other than PD and treatment mechanism. Discussions of mechanism vary both in emphasis from the electrophysiological to the neurochemical and by target and indication, and are presently not well understood.[77] There are also considerable practical difficulties in implementing evidence-based medicine methods when undertaking surgery for medically refractory disorders.[7]

In contemporary ablative neurosurgery there are no prospective, randomised, double-blind, placebo-controlled trials of any procedure and none is likely. Sham burr holes and lesions are considered unethical.[78] Thus, even in the era of evidence-based medicine, surgical procedures can become accepted upon little more than intuitive appeal to the 'educated eye'.[79] The uncertainty in novel indications for DBS necessitates independently reviewed and well-designed trials with heterogeneity and differences in peri-operative management controlled for where possible. Such control is admittedly difficult in patient groups who are by definition refractory to medical treatment and have frequently tried other therapies as well.

Initial claims for therapeutic success in novel indications for DBS should ideally be confirmed by blinded studies. DBS does however enable electrodes, and thus treatments, to be switched off, in principle facilitating intra-patient double-blinded trials. Such a trial was elegantly conducted in a case of OCD.[80] A similar method favoured for evaluating treatment outcomes in small groups and single cases is the N-of-1 trial. A randomised, placebo-controlled intra-patient trial is conducted whereby the patient receives paired sessions during which each intervention occurs once. Session order is randomised and effects of treatment or placebo compared between sessions. The valid-

ity of N-of-1 trials using analgesic outcome scores has been demonstrated for DBS in chronic pain.[81]

Further challenges in supra-specialist surgery with its geographically wide referral patterns are poor recruitment to trials and loss of patients to follow-up. Amid the myriad challenges, it should be emphasised that absence of 'class A' evidence from multi-centre, randomised, controlled clinical trials is not evidence of absence of efficacy. As videos taken before and after DBS for movement disorders demonstrate, some treatments have dramatic effects unlikely to reflect biases. Treatment effects can be therefore inferred from well designed case series and non-randomised cohort studies.

Particular advances in DBS will come from technological improvements. Improvements in IPG battery life and rechargeable IPG technology will reduce the frequency of further procedures in those patients presently requiring frequent IPG changes. Miniaturisation will reduce the invasiveness of the procedure and improve cosmesis. Improvements in the resolution and safety of neuroimaging may enhance targeting of deep brain structures such that targets within the target for certain symptom constellations or disorders of particular body regions could be addressed more specifically. Telemedicine may reach DBS, with remotely controlled equipment programmable during videoconferencing or over the internet avoiding patient time spent travelling to follow-up clinics. Remotely downloaded data from personal digital assistants could be used to record symptoms and assess outcomes. The field is likely to benefit from novel approaches commenced by several device manufacturers, mirroring the competitive leaps made in cardiac pacemakers four decades ago.

Amidst the exciting advances outlined above, long-term results from randomised controlled clinical trials currently underway will begin to clarify debates over which brain targets are best for which symptoms and also of timing of surgery in relation to disease progression. As more becomes known about the limitations of DBS, its current status will shift from panacea in medically refractory patients to therapeutic tool in a complex repertoire including pharmacotherapy, lesioning surgery and emerging molecular and cellular technologies. A wealth of current research into gene therapy, cellular transplantation and nanotechnology may begin to gain clinical utility, add to the gamut of functional neurosurgical treatments that might become available and clarify the therapeutic role of DBS. Such innovations show much promise, but require robust demonstration of their safety and efficacy in animal models before progression to clinical trials.[19]

Conclusion

DBS is brain surgery and is thus often regarded as a last resort treatment. However, as evidence continues to gather concomitant with mechanistic understanding, and the number of indications increases, we expect that patient, clinician and commercial interest in the technique, as assessed by treatments performed, research investment, scientific publications and market indicators, will continue to proliferate. The evidence for consideration of referral for treatment for many debilitating diseases is persuasive.

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