Deep brain stimulation for the treatment of movement disorders

Abstract

Aim: To explore the principles behind deep brain stimulation (DBS), its efficacy and future uses.

Method: Research for this paper was carried out using Medline, Google Scholar and UBC’s e-library. Search phrases included: deep brain stimulation, movement disorders, Parkinson’s disease (PD), essential tremor (ET), dystonia and adenosine hyperpolarisation. Papers were limited to those published in English between the years 1995 and 2011, except for adenosine-related articles.

Overview: DBS has been approved to treat PD, ET and dystonia. It is an alternative to medication and has replaced ablative surgery. DBS sends electrical impulses to brain nuclei via electrodes. This causes functional inhibition, thus eliminating tremors. The mechanism of action is not known but theories include: hyperpolarisation of overactive neurons; modification of malfunctioning feedback loops; and, down-regulation of hormones and neurotransmitters. These mechanisms are target independent; thus, DBS is being studied to treat non-movement disorders.

Conclusion: Despite not understanding DBS’s mechanism of action, its effectiveness is replicable and it has provided patients with clinical improvement. It is currently being studied for use in non-movement disorders. DBS is becoming safer and more effective as patient selection criteria are refined, surgical techniques are improved and patient care evolves. It is expected to become a more common intervention for ET, PD and dystonia.

Introduction

Before the advent of deep brain stimulation (DBS), treatment options for individuals with essential tremor (ET), Parkinson’s disease (PD) and dystonia were limited to medication and ablation of abnormally functioning nuclei in the brain. While effective, both of these options had significant side-effects, such as cognitive impairment and dyskinesia.1 DBS is a surgical procedure in which electrodes are implanted into specific parts of the brain. These electrodes emit electrical impulses, which cause functional inhibition of the target nuclei, thus minimising tremors. The procedure was developed in the 1990s1 and approved by the Food and Drug Administration (FDA) in the US for the treatment of ET, PD and dystonia in 1997, 2002 and 2003, respectively.5 Although DBS has helped tens of thousands of patients,1 the exact mechanism of action is not fully understood.3 Because of its target-independent mechanism of action, research is ongoing to assess its safety and efficacy in other diseases.1,3,4 Since DBS is a relatively new procedure, formal guidelines for candidate selection, assessment and post-operative care have yet to be developed and globally adopted.5 This paper aims to explore the general principles behind DBS, its efficacy and possible future uses.

What is deep brain stimulation?

To deliver DBS, three components must be surgically implanted in the patient: an implanted pulse generator (IPG); an extension; and, a lead. The lead is a polyurethane-coated wire that terminates in four platinum iridium electrodes. When connected, the IPG sends electrical impulses through the extension to the implanted lead in the brain. These impulses have the effect of functionally inhibiting the desired nuclei, thus allowing the patient to be tremor free.3 In ET, PD and dystonia, the FDA-approved nuclei are, respectively: 1) the subthalamic nucleus (STN) and globus pallidus internus (GPI); 2) the ventrolateral intermedius portion of the thalamus (Vim); and, 3) the GPI and Vim.6

Interventional procedure of deep brain stimulation

For DBS to be successful, the electrodes must be accurately and precisely implanted in the specified nuclei. To accomplish this, a computer-based stereotactic localising system is utilised. The patient’s head is rigidly fixed to the stereotactic frame under local anaesthesia. It is then scanned using magnetic resonance imaging (MRI) or computed tomography (CT) to determine the distances between the frame’s known geometry and the target brain structures. The data gleaned from the scan is used to create an ‘atlas’ of the patient’s brain. This atlas enables the computer to assign either Cartesian or polar co-ordinates to the target structures depending on the type of stereotactic frame being used.

To ensure that the surgeon’s instrument is aimed correctly at the target nuclei’s co-ordinates, it is placed in an instrument guide affixed to high precision Vernier scales. Once this has been completed, the surgeon drills a burr hole approximately 14mm in diameter in the skull to allow access to the brain. To optimise the lead’s placement, the patient is kept conscious in order to provide feedback. Occasionally, a microelectrode is used to augment lead placement by stimulating and creating recordings of the target area. The permanent electrode is then implanted. Once this has been completed, the patient is put under general anaesthesia and the IPG and extension are implanted. The extension is attached to the end of the lead and runs subcutaneously behind the ear and down the neck to the IPG, which is implanted below the clavicle or, less commonly, in the abdomen.1,3,7 In the weeks post surgery, the IPG can be programmed transdermally to modify the voltage, frequency and duration of the electrical pulses sent to the lead. This programming allows the healthcare team to cater to the patient’s individual needs and to account for any changes in the patient’s disease.1,8 Typical IPG settings are 2.0-3.5V at 130Hz with a duration of 60ms.8

Mechanism of action

Although the mechanism by which DBS acts is not fully understood, there are several theories, all of which are believed to be target independent (i.e., not limited to the GPI, Vim and STN).3,8 The three most widely accepted sub-mechanisms are discussed below.

Increased adenosine causing neuronal hyperpolarisation

Studies postulate that tremors are caused by increased neuronal excitation and that DBS is able to normalise the neuronal activity through hyperpolarisation. DBS causes astrocytes adjacent to electrodes to release adenosine triphosphate (ATP), which catabolises to adenosine. This ligand then binds to the adenosine A1 receptor, a G-protein coupled receptor (Figure 1, #2). The ligand/receptor interaction results in the guanine nucleotide exchange factor (GEF)-mediated allosteric activation of the Gαi1/2/3 protein’s α-subunit by exchanging guanine diphosphate (GDP) for guanine triphosphate (GTP) (Figure 1, #2). The G-proteins dissociate into Go-GTP and Gβγ dimers, which activate a number of secondary signalling pathways. Most importantly, the Gβγ-mediated activation of potassium-ion channels and inactivation of P/Q- and N-type voltage-gated calcium-ion channels (Figure 1, #4) cause neuronal hyperpolarisation (Figure 1, #5). These downstream signalling events result in reduced excitatory transmission, thereby reducing uncontrolled movements.3,4 Clinical outcomes from DBS and ablative procedures are similar; however, it is important to note that DBS is easily reversed by discontinuing the electrical impulses. Confirmation that adenosine plays a main role in DBS’s efficacy was achieved by injecting adenosine A1 receptor agonists intrahalamically, which produced the same reduction in tremor.9,10

High frequency electrical stimulation alters feedback loop

It is suspected that tremors may also be due to disregulation in the dopaminergic nigrostriatal system. This alteration affects the normal feedback loop of the corticospinal pathway and the sensorimotor
system, causing the feedback loop to be under-dampened, leading to oscillatory neuronal firing, which manifests as tremors. In order to overcome this, DBS provides electrical pulses, which cancel out the unwanted oscillations by restoring the feedback loop to its normally critically damped state.8,11

Down-regulation of local neurotransmitters and/or hormones
An in vitro study exposed isolated GH3 and PC12 culture cells to high frequency electrical stimulation (HFS). GH3 cells are found in the pituitary and normally secrete growth hormone and prolactin,12 while PC12 cells are from adrenal medulla and mediate the transport of noradrenaline13 and release dopamine.14 The study demonstrated that the cells significantly decreased their production of prolactin, dopamine and norepinephrine when exposed to HFS. The authors postulate that this down-regulation leads to local functional inhibition of the stimulated nuclei and thus elimination of the offending tremor.15

Treatment efficacy
A meta-analysis of DBS’s effect on PD’s clinical manifestation conducted by Benabid et al. compared the outcomes of 18 studies. It compared the Unified Parkinson’s Disease Rating Scale (UPDRS) of patients pre- and post-operatively. Specifically, it analysed parts II and III of the UPDRS, which measure the activities of daily living and motor function, respectively. The study found that patients’ scores improved by 50% for UPDRS II and 52% for UPDRS III on average. Partial results of their findings are shown in Table 1.8

Indications and contraindications
A formal set of candidate selection guidelines has yet to be developed and implemented. However, a set of generally accepted criteria exists and is as follows:4,5,16

- patient has medically refractory ET, PD or dystonia, which significantly interferes with quality of life;
- no existing cognitive deficits;
- no untreated or disabling psychiatric illness;
- no cardiac pacemaker or defibrillator;
- regular follow-up visits to allow for tuning of the IPG module;
- realistic expectations of the surgical outcome; and,
- no general surgical contraindications.

If the patient had undergone previous ablative surgery for their movement disorder, DBS is still an option, provided that the target nuclei have not been destroyed. Having a history of an unsuccessful DBS surgery is not a contraindication, as DBS does not permanently alter the target structure. Even if the same nuclei are targeted, the ineffective electrode does not need to be removed provided it is at a minimum of 2mm from the newly implanted electrode.8

Risks and side effects
As with any surgical procedure, complications and unwanted effects may arise. The major risks associated with DBS are: haemorrhage;
confusion; and, problems with the lead. Issues with the lead are generally due to fracture, misplacement or migration. Cognitive deficits are serious potential complications to consider when thinking about DBS as treatment. Worsening of the cognitive deficit may be caused by trauma induced by the surgical procedure itself. When considered in conjunction with the tremors, these deficits may point to atypical PD or degeneration of additional systems whose symptoms can only be temporarily warded off by DBS as the condition worsens over time.8

Fortunately, with increasing experience and improvements in patient selection, and pre-, intra-, peri-operative and long-term care, these risks have declined to the point where the mean morbidity rate is 3-4%.1

A 10-year retrospective study into the short- and long-term outcomes of DBS showed that it was a safe procedure with a low rate of adverse events (Table 2).17 Of the initial group who received DBS in this study, 7.8% had revision due to: decreased effect; low efficacy; infection; and, lead fracture or migration.

The future of deep brain stimulation
Currently, DBS is only approved by the FDA for the treatment of PD, ET and dystonia. However, due to its success and target-independent nature, DBS is being studied for a number of conditions that are not limited to movement disorders (Table 3).1,3

Limitations
The most significant limitation of the studies analysed was that there were no control groups to compare against DBS. The studies compared unmedicated pre-DBS and unmedicated post-DBS patients.6,11,17 Although there was an improvement compared to the baseline, it would have been beneficial to see the gains made against conventional medication to highlight the advancements made by DBS. Additionally, many studies were conducted retrospectively, possibly introducing bias into the results.5,7,11,18 Other studies, while they showed consistent data, were based on relatively small sample sizes or reported data from a single institution, which may mean that the findings are not generalisable.1,5,6,7,11

Table 1: UPDRS II and UPDRS III percent improvement pre and post DBS.

<table>
<thead>
<tr>
<th>Study</th>
<th>Improvement</th>
<th>UPDRS II</th>
<th>UPDRS III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krack et al.</td>
<td>73%</td>
<td>71%</td>
<td></td>
</tr>
<tr>
<td>Kumar et al.</td>
<td>30%</td>
<td>58%</td>
<td></td>
</tr>
<tr>
<td>Limousin et al.</td>
<td>58%</td>
<td>60%</td>
<td></td>
</tr>
<tr>
<td>Pinter et al.</td>
<td>N/A</td>
<td>45%</td>
<td></td>
</tr>
<tr>
<td>Houeto et al.</td>
<td>55%</td>
<td>67%</td>
<td></td>
</tr>
<tr>
<td>DBSPDSG</td>
<td>N/A</td>
<td>51%</td>
<td></td>
</tr>
<tr>
<td>Lopiano et al.</td>
<td>68%</td>
<td>57%</td>
<td></td>
</tr>
<tr>
<td>Volkman et al.</td>
<td>N/A</td>
<td>67%</td>
<td></td>
</tr>
<tr>
<td>Østergaard et al.</td>
<td>64%</td>
<td>64%</td>
<td></td>
</tr>
<tr>
<td>Simuni et al.</td>
<td>42%</td>
<td>47%</td>
<td></td>
</tr>
<tr>
<td>Pahwa et al.</td>
<td>27%</td>
<td>28%</td>
<td></td>
</tr>
<tr>
<td>Krack et al.</td>
<td>66%</td>
<td>66%</td>
<td></td>
</tr>
<tr>
<td>Rodríguez et al.</td>
<td>43%</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>Hamani et al.</td>
<td>58-42%</td>
<td>50-49%</td>
<td></td>
</tr>
<tr>
<td>Fraix et al.</td>
<td>49%</td>
<td>57%</td>
<td></td>
</tr>
<tr>
<td>Kleiner-Fisman et al.</td>
<td>50%</td>
<td>52%</td>
<td></td>
</tr>
<tr>
<td>Deuschl et al.</td>
<td>39%</td>
<td>41%</td>
<td></td>
</tr>
<tr>
<td>Goodman et al.</td>
<td>30%</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Risks and side effects of DBS.

<table>
<thead>
<tr>
<th>Intra-operative</th>
<th>Peri-operative</th>
<th>Long-term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasovagal response</td>
<td>2.5%</td>
<td>Headache</td>
</tr>
<tr>
<td>Syncope</td>
<td>1.2%</td>
<td>Confusion</td>
</tr>
<tr>
<td>Isolated seizure</td>
<td>1.2%</td>
<td>Hallucinations</td>
</tr>
<tr>
<td>Severe cough</td>
<td>0.9%</td>
<td>Isolated seizure</td>
</tr>
<tr>
<td>Intracerebral haemorrhage</td>
<td>0.6%</td>
<td>Intracerebral haemorrhage</td>
</tr>
<tr>
<td>Transient ischaemic attack</td>
<td>0.3%</td>
<td>Large subdural haematoma</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>0.3%</td>
<td></td>
</tr>
</tbody>
</table>
Table 3: Other conditions being studied for DBS.

- Spasmodic dysphonia
- Orthostatic tremor
- Meige syndrome
- Cluster headache
- Short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT)
- Trigeminal neuropathy
- Trigeminal neuralgia
- Chronic paroxysmal hemicranias
- Chronic pain
- Tourette’s syndrome
- Aggressive behaviour
- Depression
- Obsessive-compulsive disorder
- Epilepsy
- Camptocormia
- Restless legs syndrome
- Obesity/addictions
- Disorder of consciousness
- Alzheimer’s disease

Conclusion

Over the past 20 years, DBS has provided significant clinical improvement to patients with movement disorders. Despite not completely understanding DBS’s mechanism of action, its effectiveness has been replicated in multiple studies. As a result of its success, and owing to its target-independent nature, it is being studied for use in many other non-movement disorder-related conditions. Additionally, DBS is becoming safer and more effective as patient selection criteria are refined, DBS surgical techniques improve and DBS patient care evolves. This exciting intervention has proven highly effective and will likely become a more frequently used procedure in the future. There is promising potential to affect even more conditions that currently have no treatment.

References

18. Leksell Stereotactic System® [photograph]. Stockholm: Elekta AB (publ); c2011. 1 photograph: colour, 700x450 pixels.
19. Figure 1: Neuronal Hyperpolarisation [diagram]. Dublin: Derek Thong; 2011. 1 diagram: colour, 282x772 pixels.