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Review

The latest evidence on target selection in deep brain stimulation for Parkinson's disease

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ABSTRACT

Deep brain stimulation (DBS) is one of the most promising neuromodulatory techniques to gain momentum over the last 20 years, with significant evidence showing the benefit of DBS for Parkinson's disease (PD). However, many questions still exist pertaining to the optimal placement of stimulation contacts. This paper aims to review the latest and most relevant studies evaluating subthalamic nucleus (STN) and globus pallidus interna (GPi) stimulation. Additionally, it aims to shine a light on several of the lesser-known targets with mounting evidence of efficacy. Referenced literature for the main body of the article was gathered from Medline and PubMed databases. Results were limited to "full text", "English language" and publications from 1999 onwards. Case reports were excluded. The current evidence irrefutably demonstrates the benefits of both STN and GPi DBS on Unified Parkinson's Disease Rating Scale (UPDRS) III motor scores, with very similar outcomes seen after 1–2 years. Currently, it appears the greatest differences lie in the associated adverse effects. STN DBS was associated with a greater reduction in dopamine replacement therapy, but also appeared to have more negative effects on speech and mood. Meanwhile, in regards to alternative targets, the pedunculopontine nucleus has shown promising improvement in axial symptoms, while the ventral intermediate nucleus has demonstrated significant efficacy at suppressing tremor, and the caudal zona incerta may be superior to the STN and GPi in improving UPDRS-III scores. Due to the complexity of Parkinson's disease, an individual disease profile must be determined in a patient-by-patient fashion such that appropriate targets can be selected accordingly.

1. Introduction

While science and technology have allowed significant advances in our understanding of the human body and disease, relatively little advance has been made in our understanding of the circuitry of the brain and its ailments. In the nineteenth century, American poet Emily Dickinson wrote "The brain is wider than the sky", a metaphor which still rings true today. Although first described in the 1950s,[1,2] deep brain stimulation (DBS) in the modern era owes much to the seminal publications of Benabid[3,4] in the late 1980s concerning the Grenoble experience. While the mechanism of action continues to be elucidated, a variety of clinical applications are now firmly established and others show significant promise. Of these, Parkinson's disease (PD) has become the best studied and most common indication for DBS and a variety of targets have been utilised.

This article will review in detail the most recent evidence supporting these primary DBS targets, and may assist DBS teams in target selection based on individual patient profile.

2. Background

PD is a syndrome characterised by motor disturbance that manifests as tremor, rigidity, bradykinesia and gait disturbance. It is also associated with non-motor features, which can include cognitive impairment, falls, sleep disturbance and autonomic disturbance.

Dopamine replacement therapy (DRT) has long formed the mainstay of treatment for PD. The UK National Institute for Health and Clinical Excellence guidelines[5] recommend commencing one of three first-line drug classes (levodopa, dopamine agonists, or monoamine-oxidase-β inhibitors) once symptoms are interfering with everyday life.

Unfortunately, medical therapies are associated with a limited therapeutic window, which progressively shortens with duration of treatment. Furthermore, they have been associated with significant adverse effects, which include dyskinesias and motor fluctuations. Consequently, as evidence regarding its efficacy grows, increasing interest is being placed on the potential of DBS as a primary therapeutic option. Recent large-scale studies comparing DBS to best medical therapies have revealed 6 month results favouring DBS when assessing motor function and quality of life outcomes.[6,7]

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Typically, medical therapies and DBS are used in conjunction, and may in fact have a synergistic effect. While further evidence emerges regarding the specific indications and timing for DBS, the Australian Working Group has released clear and concise referral guidelines[8] for care providers to help identify and refer potential candidates. In brief, the guidelines state that DBS is indicated for patients who show an improvement in symptoms with levodopa, but who demonstrate motor fluctuations and/or dyskinesia which are poorly controlled with optimal medical therapies, or who have medication-refractory tremor, or who are intolerant of medical therapy.

While mounting evidence exists for early DBS, at this stage it is usually undertaken only once significant disabling motor fluctuations are well established.[9,10] This is likely to change following the findings of the EARLYSTIM study which randomly assigned 251 patients with early motor complications to DBS plus medical therapy or medical therapy alone (mean disease duration of 7.5 years). It revealed significant benefit of DBS plus medical therapy for each of the measured outcomes, including quality of life, motor disability, activities of daily living, levodopa-induced motor complications, and time with good mobility and no dyskinesia.[10]

Contraindications to STN DBS are the presence of significant cognitive impairment or psychiatric/medical comorbidity. Prior ablative surgery or DBS to another target are not necessarily contraindications.

The two most common targets for DBS, which aim to counter the cardinal features of PD, are the subthalamic nucleus (STN) and the globus pallidus internus (GPi). Both are components of the cortico-basal ganglia-thalamo-cortical loop.[11] Intuitively, it follows that the cardinal motor features of PD are thought to arise secondary to pathology within this circuit. However, the mechanisms underpinning reduction in motor features following stimulation to these areas remain unclear. The two general and opposing schools of thought are that DBS either produces[1] a functional inhibitory effect allowing normalisation of motor networks,[12] or[2] a range of complex neural excitatory effects acting within the target neurons themselves alone, with or without stimulation of nearby neurons and axons.[13]

Regardless of the mechanism, one of the key considerations in the delivery of DBS is targeting, which forms the focus of this paper. As our understanding of the pathophysiology of PD grows, new and more specific targets are being trialled with varying success. At this stage, it is no longer adequate to apply a one-technique-fits-all approach, and specific analysis of each symptom is now important to select the best target to apply treatment. The areas found to be most effective in ameliorating the dopamine-sensitive symptoms and hence the two areas with the most clinical evidence are the STN and the GPi. As pathology mapping techniques improve, research is beginning to investigate novel targets outside the cortico-basal ganglia-thalamo-cortical axis, which are showing improvement in the non-dopaminergic deficits such as falling, psychiatric morbidity, and bowel and bladder dysfunction.

Aside from target selection, there are other key variables that are currently being researched, including bilateral *versus* unilateral stimulation, optimising electrical stimulation parameters, general *versus* local anaesthesia for electrode insertion[14] and the role for microelectrode recording in improving target accuracy.

3. Potential targets for DBS

All referenced literature for the main body of this article was gathered from the Medline database. Results were limited to "full text", "English language" and publications from 1999 onwards. The majority of key references were published in the last 5 years. Case reports were not included.

In analysing the effect of DBS for each target, the most commonly used scoring system was the Unified Parkinson's Disease Rating Scale (UPDRS), which assesses the severity of symptom classes of PD (Table 1).[15]

Another of the key PD severity scoring systems is the Parkinson's Disease Questionnaire-39. It consists of 39 items aggregated into 8 scales for mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication and bodily discomfort. It has been shown to have satisfactory reproducibility and significant association with clinical measures.[16]

4. STN and GPi

Evidence supporting the efficacy of STN and GPi stimulation is the broadest of any of the targets. Particularly in the last 5 years, this evidence has unequivocally demonstrated the efficacy of stimulation to these two areas in alleviating motor symptoms. Naturally, determining which of these targets is associated with the greatest improvement has become the next challenge. The principle findings of several large trials comparing these two targets is discussed in this section.

The aforementioned significant improvements in motor symptoms associated with stimulation of the STN were evident in a multicentre randomised control trial (RCT) of 136 patients by Okun et al.[17] All patients were implanted with bilateral devices, but the control group devices were not activated for 3 months, at which time the primary outcome measure between the cohorts was the change in "on" time without dyskinesias. Those in the stimulation group (n = 101) recorded a mean improvement in daily "on" time of 4.27 hours. Interestingly, the control group also revealed a mean improvement in daily "on" time of 1.77 hours ($p = 0.003$), attributed to the "microlesion" effect associated with electrode implantation. Efficacy was also reflected in UPDRS-III scores at 3 months, whereby patient scores off-medication/on-stimulation improved by 39%, a result consistent with other large and recent RCTs.[10,18] Other secondary outcome measures revealed that in the stimulation-on group, there was a relatively greater reduction of UPDRS-IV score, greater reduction in DRT dose, and reduction in depression scores when compared to the control group. A significant improvement of UPDRS-III was then seen in the control group at 6 months (3 months after commencing stimulation). Verbal fluency deficits, a frequent cognitive side effect reported in other large studies of STN DBS implantation, were seen in both the stimulated and control groups. Logically, the authors associate this with surgical implantation.

The Veterans Affairs Cooperative Studies Program (CSP) 468 study[19] was a multicentre, randomised, blinded trial which showed similar improvements (25.3%) in UPDRS-III scores on-stimulation, off-medication at 24 months post STN implantation (n = 152). This landmark study also compared these findings with results of UPDRS-III scores in patients with GPi implantation (n = 147), and found that that there was no significant difference between targets at 24 months ($p = 0.5$). Notably, while it is commonly reported in the literature that falls and problems with mobility are slightly more common with STN DBS, this result was not significantly reflected in this paper.

Aside from motor scores, there were no significant differences in quality of life or adverse effects between groups at 24 months. Of the significant differences, average DRT use decreased more with STN stimulation than GPi stimulation (408 mg *versus* 243 mg respectively; $p = 0.02$). Sub-scores of neurocognitive function and mood revealed similar and non-significant slight decrements for all measures, except those for processing speed index (as measured by the Wechsler Adult Intelligence Scale) and the