

Deep brain stimulation in Parkinson's disease: Looking back, looking forward

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Patients with Parkinson's disease (PD) may present with prodromal (e.g. hyposmia, sleep disorders, constipation), motor (e.g. tremors, rigidity, bradykinesia, postural dysfunction) and non-motor (e.g. cognitive dysfunction, depression) symptoms.¹ Treatment is symptomatic, targeting motor and non-motor manifestations, but there is presently no effective disease modifying treatment.¹ Although PD therapies have primarily been focused on supplementing dopamine, which has improved survival and quality of life of PD patients,^{1,3} other neurotransmitter systems (e.g. serotonergic, cholinergic and noradrenergic) are also dysfunctional, especially for the non-motor symptoms.^{1,4,5} By the time patients reach the later stages of PD, many of them would have developed significant gait and balance difficulties, dysarthria, dysphagia and motor fluctuations like wearing off and levodopa-induced dyskinesias (LID), as well as non-motor symptoms such as orthostasis, depression, dementia and psychosis.^{1,2,6,7}

In addition to dopamine supplementation, other medical therapeutic options for the motor symptoms include anticholinergic agents, monoamine oxidase B inhibitors (e.g. selegiline and newer drugs such as rasagiline, safinamide and zonisamide), catechol-O-methyl transferase inhibitors, adenosine A2A inhibitors (such as istradefylline) and amantadine. Non-motor symptoms are treated with atypical antipsychotics, selective serotonin reuptake inhibitors, selective norepinephrine inhibitors, tricyclic antidepressants and anticholinesterase inhibitors.^{1,2,8,9}

Patients in the later stages of PD often do not respond to (or respond less well to) therapeutic adjustments,¹ and other strategies may need to be considered, e.g. enteral levodopa and surgery.^{1,10,11} Invasive (thalamotomy, subthalamotomy, pallidotomy) and noninvasive (MRI focused ultrasound) lesioning procedures may be useful to ameliorate the motor manifestations of PD.^{1,12,13} Non-lesioning surgical therapy, i.e. deep brain stimulation (DBS), has been shown to decrease dopaminergic

requirements, improve "ON" period motor function, activities of daily living and quality of life, and ameliorate LIDs.⁷ DBS is typically considered when patients demonstrate the wearing-off phenomenon or LIDs.^{1,2}

Neurosurgical interventions targeting the thalamus, globus pallidus and subthalamic nucleus (STN) to treat PD were based upon previous observations and interventions in animal models and PD patients, starting with James Parkinson's observation that the tremors of 1 of his 6 patients disappeared after a stroke.¹⁴ Albe-Fessard, and later, Benabid, observed that high frequency stimulation (100-200 Hz) in the ventrointermediate nucleus of the thalamus (Vim) reduced tremors in PD patients.^{15,16} Anatomical and physiological studies indicated overactivity of the globus pallidus pars interna (GPi) and STN in PD patients. Lesioning these structures in animal models ameliorated PD signs in animal models.^{14,16,17}

Benabid's pioneering work on chronic stimulation of the Vim to treat tremors in PD, essential tremors and extrapyramidal dyskinesias¹⁸ later led to DBS of the STN and GPi to treat motor manifestations and LIDs, respectively, in PD patients.^{17,19,20} DBS of the STN and GPi have both been shown, in several highly powered randomised controlled trials to markedly reduce "OFF" medication motor severity (by 30–50% of the motor scale of the Unified Parkinson's Disease Rating Scale, or UPDRS); increase daily "ON" time (by 2–5 hours); and improve LIDs, activities of daily living and quality of life, compared to best medical treatment.^{7,21} There is consistent evidence from observational follow-up studies showing sustained improvement of motor symptoms of up to 10–15 years and beyond, but what is unclear is whether there is long-term benefit on progression to disability or indeed, if early DBS improves the clinical progression or long-term outcome in PD patients.⁷

DBS to the STN and GPi both improve the motor symptoms of PD. STN stimulation allows a greater reduction in medications, whereas GPi stimulation

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directly reduces LIDs.²¹ Consisting of uni- or bilateral stimulating electrodes stereotactically implanted into the targets identified above (i.e. deep brain structures) and connected to an implantable pulse generator (IPG) emplaced subcutaneously on the chest wall,²² the clinician adjusts the parameters of stimulation by means of a handheld device placed over the IPG. Adjustments are made to the number and configuration of anodal (positive) or cathodal (negative) electrode contacts turned on, the voltage or current of the stimulation pulse, the duration of each pulse width (charge-balanced pulse) and the frequency of the pulses.²² DBS is believed to act via several different mechanisms. These include local and network-wide electrical and neurochemical effects of stimulation and modulation of oscillatory activity and synaptic plasticity. Some have postulated that DBS engenders neuroprotection and neurogenesis as well.²²

The Vim is not considered a suitable DBS target in PD, as it does not sufficiently improve bradykinesia and rigidity, though it remains an eminently suitable target for the treatment of essential tremors.²²⁻²⁴ DBS of the STN has the added advantage of reducing drug-refractory tremors.⁷ The time course of response after DBS varies according to symptoms—of the order of seconds for relief of tremor, and minutes to hours for amelioration of rigidity and bradykinesia. It usually takes hours to days for a less profound relief of axial symptoms after DBS.²² It is uncertain if, and to what extent, DBS alters either long-term outcomes or clinical progression of the disease.⁷

Cai et al. followed up 94 PD patients who received bilateral STN DBS over 10 years.²⁴ Their data were consistent with other long-term follow up studies, i.e. with reduction in dopaminergic medication requirements and motoric improvements (decreased “OFF” time), but did not appear to appreciably improve LIDs.²⁴ This is not surprising, as the GPi is thought to be a better target for the treatment of LIDs.²⁵ Movement Disorders Society (MDS)-UPDRS II and III scores increased from the fifth year after DBS, which is consistent with other studies, in which improvements in UPDRS motor scores became blunted, and “ON” medication motor scores declined below baseline levels by the fifth year.⁷ Assessment of PD motor scores in the “OFF” condition are accepted as a surrogate marker of the underlying severity of the disease, i.e. progression of the disease.⁷ It is thus unfortunate that Cai et al. only assessed the MDS-UPDRS II and III for their PD patients in the “ON” state.

DBS is now considered a mainstay of PD treatment, with promising new targets being investigated,

such as the zona incerta, which ameliorates refractory tremor;²⁶ the substantia nigra pars reticulata and pedunculopontine nucleus to improve axial symptoms and the freezing of gait.²⁷ What remains to be definitively determined with conventional DBS is when to perform it in PD patients, and whether it confers any neuroprotective benefit.

Finally, conventional (open loop) DBS, which continuously delivers stimulation within fixed programmed parameters, is disadvantaged by requiring periodic adjustments, having limited motoric improvement, short battery life and manifesting side effects such as dyskinesia (from stimulation at a time when it is not needed).²⁸ Adaptive DBS, with real-time modification to stimulation parameters based on neural signals that co-vary with the severity of motor signs or to stimulation-induced adverse effects, may not only improve motor function and reduce side effects but prolong battery life.²⁸

Declaration

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