Deep brain stimulation (DBS) is a standard treatment for selected patients with advanced Parkinson’s disease (PD). Randomized controlled studies have shown that DBS combined with medical therapy provides superior outcomes compared with medical management alone for the control of motor symptoms in advanced disease. There are currently 3 major DBS targets for managing PD symptoms. While thalamic stimulation is usually reserved for a few patients with tremor-predominant PD, subthalamic nucleus (STN) and globus pallidus pars interna (GPi) DBS can treat motor cardinal symptoms of the disease, including tremor, rigidity, and bradykinesia, and manage motor fluctuations.

Randomized comparisons between GPi and STN DBS showed similar outcomes for both nuclei. Concerns related to higher hemorrhage risk during microelectrode recording–guided GPi DBS surgery can make this a less-favored target by some centers. However, cognitive and behavioral adverse effects may be more common after STN DBS. In our center, we consider patients for both STN and GPi surgery and tailor the target choice to the patient’s goals and presentation. Although DBS is effective for symptom management, it does not prevent the progression of the disease. We present here the case of a patient in whom bilateral STN DBS was effective, but whose PD progressed with severe motor, particularly dystonic, features. Pallidal DBS may be a safe and useful strategy to manage dystonic features and behavioral complications of subthalamic stimulation and pharmacological management. While combined stimulation was quite successful in the reported patient, further studies with larger samples and longer follow-up periods will be necessary before recommending the addition of pallidal DBS as a routine strategy for patients previously implanted with STN DBS.

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**KEY WORDS** deep brain stimulation; dual target; globus pallidus; Parkinson's disease; subthalamic nucleus; functional neurosurgery
Case Report

We present the case of a 41-year-old man with an 8-year history of PD who was experiencing progressive disability despite optimal medical therapy. His major complaints were freezing of gait, rigidity, unpredictable off-periods, and severe dyskinesia. He underwent bilateral STN DBS and his symptoms were markedly improved, except for some residual mild bradykinesia on the left hand. At the 1-year follow-up, the levodopa equivalent daily dose (LEDD) of 2150 mg was reduced to 750 mg (−65%) (Fig. 1). Symptom control remained stable for 4 years after surgery, but as the disease progressed, the patient started to complain of left arm dystonia, initially only with strenuous exercise such as participating in a triathlon, which he continued to do annually. This was initially managed with botulinum toxin injections, but the left arm dystonia worsened, affecting other parts of the body and becoming painful, with an average pain reporting of 7 on a 0- to 10-point Numerical Rating Scale (NRS-11). Hardware failure was ruled out, and several trials to adjust stimulation parameters failed to improve his condition. Stimulation amplitude was increased until side effects were noted at 4.1 V and above, with worsening of left arm cramping. Although dopaminergic treatment and stimulation were still beneficial, the patient could not tolerate further amplitude or medication increases. In addition, he experienced worsening on-medication festination of speech and gait, the latter leading to falls. Moreover, he developed severe neuropsychological problems including inappropriate sexual behavior and impulsive spending, which caused significant financial, interpersonal, and family problems. With reduction in total daily levodopa equivalent (dopamine agonists were reduced by 55%), the neuropsychological symptoms resolved, but at the cost of motor worsening and marked dystonic postures.

At the age of 53 years (12 years after the first surgery), the patient’s quality of life was assessed using the EQ-5D, yielding an index score of 0.378, indicative of poor health status (the EQ-5D index score ranges from 0.109 to 1.0, in which a higher score indicates a better quality of life). Activities of daily living were assessed using the Movement Disorder Society–Sponsored Revision of the Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) Part II (score range 0–52), yielding a score of 25. Motor function was evaluated by an independent rater blinded to stimulation and medication condition with the MDS-UPDRS Part III (score range 0–112) during the on-medication/on-stimulation state, also yielding a score of 25 points. By the time of surgical consideration, the patient was presenting with dystonic symptoms involving the trunk and both sides. A decision was made to add bilateral GPi electrodes with the goal of treating these symptoms, but the patient did not believe he could tolerate an awake procedure again, particularly due to severe dystonic symptoms that could be worsened in a supine, fixed position. GPi electrodes were implanted under general anesthesia, with placement verification by intraoperative images with the O-arm (Medtronic Inc.) fused with the preoperative images and surgical plan in the StealthStation (Medtronic Inc.). New implantable pulse generators (IPGs) were implanted and connected to the leads in a second stage. One month after the pallidal leads were implanted, the IPGs were turned on. Stimulation parameters previously used for the STN were maintained (left STN: bipolar = 1–2–3+, amplitude = 4.0 V, pulse width [PW] = 120 μsec, rate = 130 Hz; right STN: bipolar = 1–2–3+, amplitude = 4.3 V, PW = 90 μsec, rate = 130 Hz). Pallidal stimulation parameters were set as monopolar initially (left GPi: monopolar = case+10−, amplitude = 1.5 V, PW = 60 μsec, rate = 130 Hz; right GPi: monopolar = case+8−, amplitude = 2.3 V, PW = 60 μsec, rate = 130 Hz), but were gradually titrated during follow-up visits. Stimulation parameters at the 6-month follow-up and stereotactic coordinates for both targets are presented in Table 1. Six months after surgery, motor outcome during on-medication/on-stimulation (STN and GPi) state measured by blinded ratings of MDS-UPDRS Part III was improved by 60%, mostly due to improvement in kinetic tremor and bradykinesia, activities of daily living (MDS-UPDRS Part II) by 44%, pain (NRS-11) by 42%, and quality of life by 82% according to the EQ-5D (Table 2). The LEDD was further reduced, by 55% (Fig. 1). Images of subthalamic and pallidal electrodes are displayed in Fig. 2.
Our report describes a patient who experienced significant benefit for several years following STN DBS. However, behavioral problems and painful dystonia gradually emerged over time. Impulse control disorders can be associated with long-term dopaminergic treatment, particularly dopamine agonists.\(^3\) Weintraub et al.\(^35\) reported an overall impulse control disorder prevalence of 13.6% in PD patients receiving dopamine-replacement therapy (compulsive sexual behavior, 3.5%; pathological gambling, 5.0%; compulsive buying, 5.7%; binge-eating disorder, 4.3%; 2 or more impulse control disorders combined, 3.9%). Decreasing dopamine agonists results in a less pulsatile dopaminergic stimulation and is associated with remission of or significant reduction in impulse control disorder.\(^19\)

Likewise, dystonia can occur as a complication of medical therapy in PD patients.\(^24,30\) It usually occurs as an off-period phenomenon and the lower limb, particularly the foot, is the most commonly affected location.\(^24\) However, it can also present as peak dose dystonia or diphasic dystonia. There are different approaches to control dystonia, including several pharmacological strategies, botulinum toxin injections, and DBS.\(^30\) Levodopa dose reduction or withdrawal usually improves “on” time dystonia, but other parkinsonian symptoms may worsen. In our case, neuropsychological problems resolved with reduction of dopamine agonists, but motor function worsened significantly. Moreover, dystonia became severely painful despite botulinum toxin injections. As subthalamic stimulation was still effective, we concluded that these leads should not be removed and replaced with pallidal leads. Rather, additional pallidal leads were implanted with the goal of improving motor function and dystonic symptoms.

According to the “classic” theory of how STN DBS works, stimulation orthodromically activates efferent axons. Adding pallidal electrodes might therefore be considered redundant and unlikely to add benefits in managing symptoms because subthalamic stimulation already influences GPi activity via the subthalamopallidal projection.\(^12\) However, recent work by Gradinaru et al.\(^11\) and Li et al.\(^16\) suggested that antidromic activation of afferents to the STN may contribute to DBS therapeutic effects. According to this view, GPi DBS might activate physiological mechanisms different from those of STN DBS, justifying the addition of GPi DBS in a patient such as ours.

### Table 1. Electrodes, stereotactic coordinates, and stimulation parameters 6 months after pallidal electrode implantation

<table>
<thead>
<tr>
<th>Location</th>
<th>Stereotactic Coordinates*</th>
<th>Stimulation Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>X</td>
<td>Y</td>
</tr>
<tr>
<td>STN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>+11.5</td>
<td>−2.8</td>
</tr>
<tr>
<td>Left</td>
<td>−12.3</td>
<td>−3.9</td>
</tr>
<tr>
<td>GPi</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>+25.3</td>
<td>+3.4</td>
</tr>
<tr>
<td>Left</td>
<td>−24.4</td>
<td>+2.1</td>
</tr>
</tbody>
</table>

* Tip of the electrode relative to the midcommissural point (mm).

### Table 2. Clinical outcomes 6 months after bilateral STN and bilateral GPi stimulation according to different rating scales

<table>
<thead>
<tr>
<th>Rating Scale</th>
<th>Score</th>
<th>Preop</th>
<th>6 Mos</th>
<th>Difference (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDS-UPDRS II</td>
<td>25</td>
<td>14</td>
<td>−44%</td>
<td></td>
</tr>
<tr>
<td>MDS-UPDRS III (on-medication)</td>
<td>25</td>
<td>10</td>
<td>−60%</td>
<td></td>
</tr>
<tr>
<td>Health status (EQ-5D index)</td>
<td>0.378</td>
<td>0.689</td>
<td>82%</td>
<td></td>
</tr>
<tr>
<td>Pain (NRS-11)</td>
<td>7</td>
<td>4</td>
<td>−42%</td>
<td></td>
</tr>
</tbody>
</table>

* Negative difference indicates improvement, except for EQ-5D index, for which a positive difference indicates improvement.

FIG. 2. Preoperative MR images were fused with postoperative CT. Subthalamic electrodes (located medially) and pallidal electrodes (located laterally) are indicated by the arrows.
ceding whether to offer Gpi DBS to this patient, we also considered another, simpler rationale. Targeting DBS in PD patients aims at stimulating as much of the motor corticobasal ganglia-thalamo-cortical loop as possible while minimizing spread of current to limbic or associative loops, or to adjacent structures such as the internal capsule.20,32 Adding Gpi DBS may allow for stimulation of additional motor fibers, which could not be captured from STN alone without spread of current to other undesired structures. A third rationale for adding Gpi DBS in our patient was the prominence of dystonia among his symptoms. Clinical observation has suggested that pallidal stimulation may be beneficial for dystonic symptoms,28 although subthalamic stimulation has recently been shown to also be effective for primary generalized and segmental dystonia.22,28

Prior reports have studied the possibility of co-targeting STN and Gpi in patients with PD. Peppe et al.23 reported no difference between subthalamic stimulation alone versus combined stimulation in 14 patients with PD. Allert et al. reported the case of a patient with PD in whom additional pallidal stimulation successfully corrected the failure of long-term subthalamic stimulation.1 Two major differences contrast our report from the former study. In the case of Peppe et al., all 4 electrodes had been implanted on the same day to directly compare the initial effects of single- and dual-target stimulation. In our patient, pallidal electrodes were implanted after 12 years to attempt to rescue long-term efficacy decline and complications associated with subthalamic stimulation. This difference points out the possibility that indeed there may be little advantage to simultaneously target the subthalamus and pallidum, but an opportunity exists for rescuing long-term limitations of subthalamic stimulation with pallidal leads. Second, the mean disease duration in the report by Peppe et al. was 13 years, while in our case the disease duration was 20 years at the time of surgery. Similar to our case, Allert and colleagues reported on a patient with young-onset PD in whom subthalamic stimulation initially improved motor function. However, in that case, symptom control declined faster and motor function was significantly impaired 4 years after subthalamic stimulation, whereas in our case significant impairment occurred almost a decade later.

Although the present report has strengths, such as blinded UPDRS ratings before and after implantation of pallidal leads, it also has limitations. First of all, it consists of a single-patient report and thus caution must be taken before generalizing this treatment to other patients. Furthermore, our case may not represent an ordinary case of idiopathic PD due to features such as young onset, rapid progression to motor fluctuation, and prominent dystonia, which can be associated with some genetic forms of parkinsonism.29 Unfortunately, this patient has not been submitted to genetic testing to exclude a genetic etiology. In addition, it was difficult to obtain on/-off-medication and on/-off-stimulation assessments separately for Gpi, STN, and both together. The patient travels a considerable distance to attend our clinic and would have to stay for an overnight medication washout. Furthermore, testing all combinations of stimulation, with time allowed for washout, would require very prolonged testing in an unmedicated and unstimulated or partially stimulated state. In that state, this patient developed a very deep off-stimulation and off-medication severe, painful dystonia. The patient previously agreed to limited testing of this kind, for purposes of clinical care, but we did not feel justified in performing more difficult and uncomfortable testing to provide novel scientific information. Moreover, the patient gave permission for videotapes to be made for clinical and scientific purposes, but he did not give permission for them to be published. Nevertheless, we were able to assess outcome measures with reliable and well-established tools such as EQ-5D, MDS-UPDRS Part II, and blinded MDS-UPDRS Part III assessments. Sixty percent is an exceptionally large improvement in medicated motor UPDRS score and may reflect several factors specific to this patient. The figure is not the average of a sample but rather for an individual patient and may therefore come from the tail of the statistical distribution. The likelihood that this case represents the tail of distribution is emphasized by patient selection. This patient was not randomly selected: to the contrary, he represents a very successful case of our center, and this influenced our decision to offer supplemental Gpi electrodes. Some individual characteristics may also explain his above-average response to DBS: his comparatively young age, his young age at onset, and very prominent off-medication and off-stimulation dystonia. Moreover, he is passionately devoted to physical exercise (for example, he continued to exercise heavily until shortly before the Gpi surgery). In addition, his on-medication UPDRS score may have been lowered by the medication reduction necessitated in his case by neuropsychiatric drug side effects.

In the past few years, outcomes of patients with PD after 8–10 years of subthalamic DBS have been reported,5,8,38 and the number of patients who have undergone long-term subthalamic stimulation is expected to increase. Managing symptoms in this population and identifying therapeutic approaches that might address limitations and complications of chronic subthalamic stimulation will become increasingly important. Pallidal DBS may be a safe and useful strategy to manage dystonic features and behavioral complications of subthalamic stimulation and pharmacological management. While combined stimulation was quite successful in the reported patient, further studies with larger samples and longer follow-up periods will be necessary before recommending the addition of pallidal DBS as a routine strategy for patients previously implanted with STN DBS.

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20. Matias. Drafting the article: Matias, Silva, Cooper. Critically revising the article: all authors.

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