

## Comparison of pallidal and subthalamic deep brain stimulation for the treatment of levodopa-induced dyskinesias

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Deep brain stimulation (DBS) can relieve dyskinesias effectively and safely. This modality is applied most commonly in the treatment of dyskinesias associated with levodopa therapy for Parkinson disease. The subthalamic nucleus (STN) and globus pallidus internus (GPi) are the most common surgical targets. Deep brain stimulation of the GP has a direct antidyskinetic effect, whereas relief of dyskinesias by DBS of the STN depends on postoperative reduction of dopaminergic medications. Outcomes are similar for DBS in these two sites despite the different mechanisms by which the stimulation relieves dyskinesias. Deep brain stimulation of the STN has become the surgical treatment of choice in many movement disorders programs but this modality has not been compared with DBS of the GPi in randomized controlled trials, and the superiority of one site over the other remains unproven. In the absence of data demonstrating superiority, selection of the stimulation target should be individualized to meet the needs of each patient. Selection of the target should be based on the patient's most disabling symptoms, response to medications (including side effects), and the goals of therapy, with consideration given to the different antidyskinetic effects of DBS of the STN and GPi.

**KEY WORDS** • Parkinson disease • globus pallidus • subthalamic nucleus • thalamus • levodopa

The introduction of levodopa in the 1960s<sup>5</sup> provided dramatic relief of symptoms for many patients with PD and had a profound impact on surgical therapies for this disease. Parkinson disease became viewed as a medical rather than a surgical disorder.<sup>2</sup> Within a decade, however, the limitations of levodopa became apparent. It did not prevent disease progression and was frequently associated with complications and side effects, including progressive shortening of the duration of action with predictable loss of drug effect throughout the day ("wearing off"); unpredictable, abrupt loss of drug effect throughout the day ("on-off" fluctuation); and involuntary movements (dyskinesias and dystonias). These complications are observed in as many as 50% of individuals who have been treated with levodopa for more than 5 years and in as many as 70% of people who have been treated with levodopa for 10 years or more.<sup>23</sup> For many patients these complications may be as disabling as the symptoms of the underlying disease and may compromise the utility of levodopa in the management of PD.

Dyskinesias can be functionally and cosmetically disabling. Reduction of dyskinesias improves motor function and the performance of activities of daily living, and it can

have a significant beneficial effect on the self-esteem of individuals who are affected by these involuntary movements. Dyskinesias associated with levodopa therapy for PD can be alleviated by adjustment of the medication dose. In some cases this requires reduction of dopaminergic medications at the expense of loss of control of cardinal PD symptoms. Individuals whose PD is managed in this fashion are faced with a difficult choice between accepting more severe dyskinesias with better control of PD symptoms or less severe dyskinesias with worse control of PD symptoms. Surgical treatment can be very helpful for these individuals.

Reduction of dyskinesias by surgery can be accomplished in either of two ways. Surgical intervention (for example, DBS of the STN or subthalamotomy) can be aimed directly at reducing PD symptoms, with the hope that medications can then be reduced to provide relief from levodopa-related side effects including dyskinesias. Alternatively, surgical intervention (for example, pallidotomy, DBS of the GPi, thalamotomy, and thalamic DBS) can be aimed at treating the dyskinesias directly. In contemporary practice, DBS has become the preferred surgical treatment for movement disorders.<sup>7</sup> Deep brain stimulation of the STN and the GPi has become the preferred surgical treatment for dyskinesias associated with PD. In this review these two variations of DBS treatment will be discussed in detail.

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*Abbreviations used in this paper:* DBS = deep brain stimulation; GP = globus pallidus; GPi = GP internus; PD = Parkinson disease; STN = subthalamic nucleus.

### *Selection of the DBS Target*

Deep brain stimulation of the STN is the surgical treatment of choice for PD in many centers. Numerous studies have demonstrated the effectiveness of this treatment in attenuating the cardinal symptoms of PD. In general, DBS of the STN does not appear to have a direct antidyskinetic effect but allows many or most patients to reduce their antiparkinsonian medications, with an accompanying reduction in side effects, including dyskinesias. The presence of persistent or worsened dyskinesias after DBS of the STN usually indicates a need to reduce dopaminergic medications. The primary disadvantage of this operation as a treatment for dyskinesia is its indirect mechanism of action on these symptoms: dyskinesias improve only if medications can be withdrawn or reduced after DBS of the STN. If a sufficiently good response of PD symptoms to DBS of the STN to allow medication reduction postoperatively is not attained, the dyskinesias will continue unabated. In addition, this treatment is sometimes associated with persistent dyskinesias, which may be a side effect of stimulation, even in the setting of medication reduction.

In contrast, DBS of the GPi appears to have a direct antidyskinetic effect. Patients undergoing this procedure typically do not receive lower doses of medications postoperatively, yet they show significant improvement of dyskinesias. Patients who obtain good relief of PD symptoms with medications but who are bothered by dyskinesias may do well with DBS of the GPi because they can continue PD medications at preoperative levels but experience relief of the dyskinesias. Treatment with DBS of the GPi can be especially useful for individuals in whom dyskinesias are a dose-limiting side effect of medications. Direct treatment of dyskinesias with DBS of the GPi can widen the therapeutic window for dopaminergic medications and permit more aggressive drug therapy. Medication therapy may, in fact, have a synergistic effect with DBS of the GPi,<sup>3,11</sup> which is not seen after DBS of the STN.<sup>3</sup>

Selection of the target site may also be influenced by growing recognition that withdrawal of medications after DBS for PD may not be desirable or possible for all patients. Neuropsychological, cognitive, and psychiatric dysfunction seem to occur more often after DBS of the STN than of the GPi.<sup>33</sup> Some of these abnormalities appear to be related to postoperative medication withdrawal because they can be reversed by reinstatement of the drugs.<sup>8,14</sup> This argues for the relative superiority of pallidal DBS because it can provide good relief of motor symptoms without the reduction of medications that is usually necessary to relieve dyskinesias after DBS of the STN.

Selection of the target should be based on the patient's most disabling symptoms, response to medications (including side effects), and goals of therapy, with consideration given to the different antidyskinetic effects of DBS of the STN and GPi. If dyskinesias are a patient's most disabling symptom, then DBS of the GPi can be offered with the knowledge that regardless of changes in medication therapy after surgery there is a high likelihood that dyskinesias will improve. The possibility also exists that relief of dyskinesias, if they are a dose-limiting side effect, by DBS of the GPi might widen the therapeutic window for dopaminergic agents and allow more aggressive phar-

macological therapy of PD, as has been shown after pallidotomy.<sup>28</sup> In contrast, the same individual undergoing DBS of the STN must hope for a sufficiently good response to DBS that his or her medications can be reduced postoperatively. If the response of parkinsonian symptoms to DBS of the STN is inadequate or if withdrawal of medications precipitates or exacerbates nonmotor symptoms, continued medication therapy will be necessary and the individual will continue to suffer disabling dyskinesias. If a patient is affected primarily by medication side effects other than dyskinesias, DBS of the STN may be the preferable approach because it allows postoperative reduction of medications.

### *Technical Considerations*

For the most part, similar surgical methods are used to implant DBS systems for the treatment of dyskinesias and for cardinal symptoms of PD. A few subtle differences exist for implantation of pallidal DBS systems; these variations are used because of possible differential antidyskinetic effects of stimulation at different sites within the GP. Implantation of leads is typically performed while patients are in the "off-medication" state to reduce dyskinesias that can cause motion artifacts during preoperative imaging (for example, magnetic resonance imaging or computerized tomography studies) or during intraoperative microelectrode recording, or that might cause a patient to slip out of pin fixation in the stereotactic frame.

The lead implant for DBS of the STN or GPi can be guided using computerized tomography, magnetic resonance imaging, and/or ventriculography. Microelectrode recording has not been proven to be essential but it is useful for confirmation of proper target location. For both STN and GPi, identification of kinesthetically responsive cells for a somatotopically relevant portion of the body confirms proper electrode location. This confirmation is particularly useful for the STN because it is a small target surrounded by structures that can give rise to "dose-limiting" stimulation-related side effects from a malpositioned electrode.<sup>35</sup> Microelectrode recording in the GPi is useful for identification of the pallidal base and the medial border of the pallidum, because lead placement that is too medial will predispose the patient to undesirable, "dose-limiting" stimulation of the internal capsule. The pallidal base can also be identified indirectly by locating the optic tract underlying the GPi with microelectrode recording or stimulation. Macroelectrode stimulation of STN and GPi by using the DBS lead or a dedicated macrostimulation electrode confirms proper electrode position by the absence of adverse stimulation side effects and, typically, by improvement in parkinsonian symptoms.

Studies conducted in acute cases indicate that two different sites may exist within the GPi, at which stimulation has opposite effects on dyskinesias and response to levodopa.<sup>1,16</sup> It is unclear whether these different zones are of practical significance in the long-term management of disease, but the presence of these different functional zones in the GPi should be kept in mind during surgical planning, selection of stimulation electrode, positioning of stimulation lead within the GPi, and during postoperative programming. The presence and locations of pro- and antidyskinetic sites within the GPi are somewhat variable

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from patient to patient.<sup>16</sup> In general, stimulation of the ventral pallidum relieves levodopa-induced dyskinesias but may worsen akinesia, which indicates general antagonism of levodopa effects (although the beneficial effects of levodopa on rigidity are not affected by ventral pallidal DBS). Dorsal GPi stimulation seems to mimic the action of levodopa: gait, akinesia, and rigidity improve, and it is possible in some patients to induce dyskinesias in the off-medication state. Stimulation of the middle portion of the GPi seems to provide a good compromise between these two extremes.

Two DBS stimulation leads are commercially available at this time. One is a four-contact lead with 1.5-mm spacing between adjacent contacts and a total array span of 10.5 mm (model 3387; Medtronic Neurological, Inc., Minneapolis, MN) and the other is a four-contact lead with 0.5-mm spacing between adjacent contacts and a total array span of 7.5 mm (model 3389; Medtronic Neurological, Inc.). Implantation of a lead with larger intercontact spacing (model 3387; Medtronic Neurological, Inc.) provides greater leeway in lead positioning and postoperative programming. If the surgeon chooses to implant a lead with close contact spacing, care must be taken to place it near the midpoint or ventral in the GPi to provide stimulation of the "antidyskinetic" functional zone within this structure. In contrast, a lead with larger intercontact spacing can be positioned to span a greater length of the GPi, with stimulation "sublocalization" accomplished during postoperative programming. Wider rather than narrower contact spacing may be advantageous for pallidal stimulation because of interpatient variability in locations of pro- and antidyskinetic regions within the GPi.

### **Postoperative Programming: GPi**

The general approach to programming DBS systems is similar for DBS of the STN and of the GPi, that is, the goal is to provide the best possible relief of cardinal symptoms of PD. In general, programming should be initiated in the off-medication state. This may require that antiparkinsonian medications be withheld for at least 12 hours (usually overnight) prior to a programming session. After programming to achieve the best relief of symptoms is completed, the patient should take his or her PD medications and return for reassessment, with special attention being paid to dyskinesias. These symptoms may vary on a diurnal basis and be better in the morning and worse in the afternoon. Monitoring for development of dyskinesias is sometimes best accomplished in the afternoon, particularly after the patient has taken several doses of antiparkinsonian medications.<sup>19</sup> If programming in the off-medication state provides good relief of PD symptoms and is not associated with the development of dyskinesias in the on-medication state, no further adjustment of stimulation is necessary. Alternatively, if the patient returns for reassessment in the on-medication state and dyskinesias are noted, reprogramming will be needed.

An added element of programming flexibility is present in patients whose primary complaint is levodopa-induced dyskinesias. Symptoms in these individuals can sometimes be managed easily by performing all programming in the on-medication state when dyskinesias are present, with DBS programming efforts being directed specifically

ly at reducing the dyskinesias. Care must be taken to ensure that beneficial medication effects are not antagonized and that off-medication symptoms are not exacerbated when using this approach.

As noted earlier, different regions in which stimulation has opposite effects on dyskinesias appear to exist within the GPi. Dyskinesias may be induced by stimulation of the dorsal GPi<sup>1,16</sup> and relieved by stimulation of the ventral pallidum, although some variability in this response exists among patients. In general, the best relief of dyskinesias is achieved using deeper contacts, but this may antagonize some of the beneficial effects of levodopa (especially in treating bradykinesia). Fortunately, the antidyskinetic effects of DBS of the GPi occur at lower amplitudes than those required to inhibit levodopa effects, so relief of dyskinesias can usually be accomplished without antagonizing the beneficial effects of medications for other PD symptoms. Use of deep contacts for treatment of dyskinesias may be appropriate for individuals in whom this is the primary symptom, and may widen the therapeutic window for levodopa so that any inhibition of medication effects by DBS can be balanced by an increase in medication. If ventral pallidal stimulation provides adequate relief of dyskinesias but results in loss of beneficial medication effects, a compromise can generally be found by using contacts near the central portion of the GPi, which usually provides good relief of dyskinesias as well as tremor, rigidity, and bradykinesia.<sup>1,16,19</sup> Alternatively, bilateral pallidal DBS systems can be programmed asymmetrically by using a more proximal contact on one side and a more distal contact on the other.<sup>1</sup>

### **Postoperative Programming: STN**

Programming DBS of the STN for the relief of dyskinesias is aimed at relieving the cardinal symptoms of antiparkinsonianism to allow subsequent reduction of antiparkinsonian medications. This modality mimics the effects of levodopa in many regards and the effects of DBS of the STN are best seen in patients in the off-medication state. Withholding antiparkinsonian medications for at least 12 hours (usually overnight) is sufficient to achieve a satisfactory off-medication state for most patients. After programming to achieve reduction of bradykinesia, rigidity, and tremor is completed, patients should take their regular doses of antiparkinsonian medications. During the subsequent on-medication state, patients should be reevaluated for side effects of the combination of DBS of the STN and medications, particularly dyskinesias. The time from latency to onset of dyskinesias may be minutes to hours. Patients should be able to contact the programming physician for several hours following the procedure in the event that disabling dyskinesias occur after stimulation adjustment.<sup>15,35</sup> During the first few weeks and months after surgery, as stimulation is adjusted to provide the best relief of parkinsonian symptoms, medication doses are titrated downward, and dyskinesias tend to resolve. Persistent dyskinesias are generally treated by reduction of medication.

In some instances, especially during the first few weeks after DBS implantation, dyskinesias may be precipitated by DBS of the STN. The most effective electrode contact for long-term therapy is often that which produces dyski-

nesias in the early postoperative period.<sup>15,35</sup> Reducing medication levels typically alleviates the dyskinesias, but if medication reduction results in worsening of PD symptoms, medication doses may need to be increased and stimulation amplitudes reduced. Over time (days to weeks or months), the threshold for induction of dyskinesias typically increases and stimulation amplitude can then be increased to provide better relief of PD symptoms, allowing decreases in medication doses and attenuation of levodopa-induced dyskinesias. Occasionally, stimulation using the most effective (that is, the most “prodyskinetic”) contact precipitates dyskinesias that cannot be controlled except by reduction of stimulation intensity. In this case, programming the stimulation system to use a more proximal or distal contact in a monopolar configuration or reprogramming to a bipolar configuration sometimes widens the therapeutic window of stimulation to allow good relief of PD symptoms without producing dyskinesias. Addition of an active DBS contact dorsal to the STN may also provide better control of dyskinesias (W Marks and S Heath, unpublished data).

### *Mechanisms of Action*

**Pallidal Stimulation.** The specific mechanism of pallidal DBS in reducing dyskinesias is unknown. The current view of basal ganglia circuitry indicates that reduction of activity in the ventral GPi (for example, with pallidotomy), which reduces akinesia, should worsen dyskinesias. In fact, lesioning of the ventral pallidum provides good relief of dyskinesias.<sup>1,16</sup> This observation has led some authors to suggest that dyskinesias arise from abnormal patterns of neuronal activity within the GP and that relief of dyskinesias by surgical intervention is a result of modification of these patterns of activity.<sup>1,16,36</sup> Surgical modification of this patterned activity might be accomplished through direct neuronal inhibition (for example, with surgical lesioning or focal electrical stimulation) or, in the case of DBS, by activation of axons close to the stimulation electrode, which in turn produces downstream inhibition that interferes with patterned output from the GPi.<sup>36</sup> Dyskinesias might also arise from an abnormal balance of activity within different functional zones of the GP.<sup>1</sup> Ventral pallidal stimulation, which is typically antidyskinetic, might relieve dyskinesias by suppressing an abnormal mixture of activity, perhaps by attenuating disequilibrium between striatopallidal and subthalamopallidal inputs.<sup>16</sup>

The anatomical and physiological basis of discrete functional zones within the GP in which DBS may have opposite effects, as described earlier, has not been fully characterized. Stimulation through dorsal and ventral pallidal contacts might selectively activate different fiber tracts with differing downstream effects. For example, stimulation through ventral DBS contacts might activate fibers in the ansa lenticularis, whereas stimulation through dorsal contacts might activate the lenticular fasciculus.<sup>16</sup> Alternatively, differential DBS effects might be mediated through effects on the subthalamopallidal tract, which projects to the dorsal GP externus and GPi. Dorsal GPi stimulation might inhibit this projection and would be expected to improve PD symptoms and induce dyskinesias.

**Stimulation of the STN.** Compared with DBS of the GPi, in the STN this procedure seems to have a more straightforward effect in relieving dyskinesias. Deep brain stimulation of the STN mimics the effects of levodopa on parkinsonian motor symptoms and allows reduction of dopaminergic medication, secondarily relieving dyskinesias as medications are reduced or withdrawn postoperatively. According to my observations, attenuation of dyskinesias is sometimes seen in the early postoperative period after implantation of DBS electrodes in the STN in the absence of reduction of medications. This indicates a direct antidyskinetic effect of manipulation of the STN (or directly superior tissues), but long-term relief of dyskinesias generally requires reduction of medications.

The specific site of action in stimulation of the STN is unknown. Some data indicate that the best effect at the lowest intensity is achieved not by stimulation of neurons within the STN but by stimulation of tissue dorsal to it, which might affect the pallidothalamic bundle, the pallidosubthalamic tract, and/or the zona incerta.<sup>34</sup> Other data indicate that the most effective contact location appears to be within the anterodorsal portion of the STN, although current could spread from this location into the directly superior fields of Forel and zona incerta.<sup>26</sup> The observation that an active DBS contact dorsal to the STN may provide better control of dyskinesias (indicative of a direct antidyskinetic effect) supports the notion that activation of structures dorsal to the STN is important in providing relief of parkinsonian symptoms by DBS of the STN (W Marks and S Heath, unpublished data).

### *Outcomes of DBS of the STN and GPi for Dyskinesias*

Consistent with their different mechanisms of action, DBS of the GPi tends to decrease and DBS of the STN tends to increase peak dose dyskinesias immediately after the treatment.<sup>24</sup> Long-term follow up conducted after postoperative medication adjustment reveals that DBS, whether in the STN or GPi, provides good relief of dyskinesias associated with PD. Published reports indicate that DBS of the STN reduces dyskinesias from 41 to 83%; the mean reduction of dyskinesias is 56% (derived from eight published reports of outcomes of this treatment).<sup>3,6,13,14,17,18,20,27</sup> In comparison, DBS of the GPi reduces dyskinesias from 47 to 88%; a mean reduction of 73% (derived from seven published reports).<sup>3,6,9,18,20,21,32</sup> Outcomes of DBS of the STN and GPi cannot be compared directly because the data are derived from nonrandomized, non-controlled case series, with one exception. Burchiel, et al.,<sup>3</sup> reported a small randomized series comparing DBS of the STN and GPi. In this series, dyskinesias decreased 67% in the STN group and 47% in the GPi group. This difference was not statistically significant. Complications, morbidity, and deaths associated with DBS for the treatment of dyskinesias are associated with DBS in general<sup>25,31</sup> and are not unique to the treatment of dyskinesias.

### *Thalamic DBS for Parkinsonian and Nonparkinsonian Dyskinesias*

The GP and STN are the most common targets for DBS used to treat dyskinesias. This is true for the following reasons. 1) Dyskinesias are common in patients with PD. 2) Parkinson disease is a relatively common movement dis-

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order. 3) Deep brain stimulation of both the GPi and the STN is approved by regulatory agencies for the treatment of symptoms of PD. Deep brain stimulation of the thalamic ventral intermediate nucleus is approved for the treatment of parkinsonian and essential tremor and has also been used as a primary treatment for dyskinesias associated with PD.<sup>4,10,30</sup> In general, thalamic DBS is less effective than interventions in the pallidum and STN for the relief of parkinsonian dyskinesias,<sup>30</sup> and it is not widely used for this purpose. Thalamic stimulation seems most effective if the electrode is positioned slightly more medially, posteriorly, and deeply than it is typically placed for treatment of tremor. The region stimulated by an electrode in this location may include the centre median and parafascicular complex.<sup>4</sup> Thalamic DBS has been reported on a limited basis for the “off-label” treatment of nonparkinsonian dyskinesias<sup>22</sup> (these forms of dyskinesias may be categorized more accurately as dystonias).<sup>12</sup>

### CONCLUSIONS

Deep brain stimulation can relieve dyskinesias effectively and safely. Dyskinesias treated most commonly with DBS are those associated with PD, and the STN and GPi are the typical surgical targets. Although the STN has become the surgical target of choice for DBS in many movement disorders programs, comparisons of the outcomes of DBS of the STN and of the GPi have not been made in randomized controlled trials, and therefore the superiority of DBS of the STN remains unproven.<sup>29,33</sup> Deep brain stimulation of the GPi and of the STN has different mechanisms of action but appears comparable in its ability to reduce dyskinesias associated with PD. In the absence of data demonstrating superiority of one site over another, selection of the stimulation target should be individualized to meet the needs of each patient. The choice of target should be based on the patient’s most disabling symptoms, response to medications (including side effects), goals of therapy, and taking into account the different antidyskinetic effects of DBS of the STN and GPi.

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