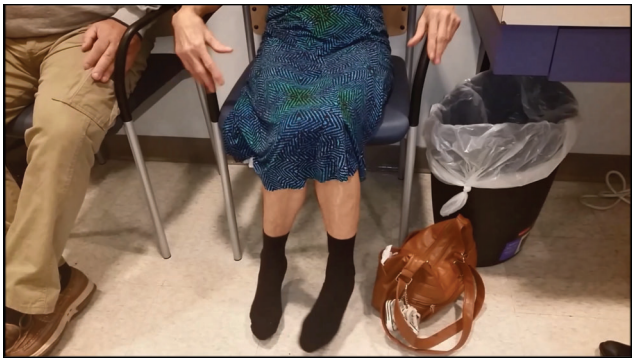
(Vim) nucleus of the thalamus can address unilateral tremor in PD, it does not impact rigidity, akinesia, or levodopa-induced dyskinesia meaningfully.[1,2] Bilateral Vim stimulation also raises concern for exacerbating speech impairment and gait imbalance.[3] To address the totality of motor fluctuations in advanced PD with DBS, clinicians have favored the implantation of the globus pallidus interna (GPi) and subthalamic nucleus (STN), although at varying rates over time. Traditionally, of these two targets, the STN is thought to provide greater tremor control.[4] Indeed, STN stimulation was shown to be equivalent to Vim stimulation for PD tremor in a small series of patients with significant rest and action tremor.[5] However, STN stimulation has also been associated with a concern for worsening depression and higher rates of suicide attempt.[6] The patient under discussion suffered from significant resting and postural tremor, and has a concerning history of depression and suicide attempt, making the ideal surgical target unclear based on these perhaps dogmatic views. Should Vim be selected at the risk of leaving akinesia and rigidity unaddressed? If the STN is targeted, will the patient be exposed to an unacceptable increased risk of suicidality or depression in the name of tremor reduction? If GPi is selected to avoid possible worsening of mood disorder with STN stimulation, can the patient be assured that her significant tremor will respond to DBS?

Clinical Solution

The patient was discussed extensively within the multidisciplinary DBS team, consisting of a movement disorders neurologist, functional neurosurgeon, and neuropsychologist. Her therapist provided supporting information regarding the stability of her depression. The patient was counseled extensively regarding the risks and benefits of DBS, and the concerns of exacerbating neuropsychiatric deficits with STN stimulation, or failing to address non-tremor symptoms with Vim stimulation. A decision was made to offer the patient magnetic resonance imaging-guided bilateral GPi DBS. She underwent surgery without complication. Initial programming showed an improvement in her MDS-UPDRSIII of 55% in the on-stimulation/off-medication state compared with her off-stimulation/off-medication state (MDS-UPDRSIII scores of 24 and 53, respectively), with significant improvement in tremor severity and constancy (Video 1). Long-term follow-up is not yet available.

Gap in Knowledge

The debate over the merits of GPi and STN stimulation in PD have been extensively catalogued. Ultimately, the collective body of evidence suggests that the two targets are similar in their motor benefits, but STN may be superior to GPi in regards to economic profile (fewer battery replacements) and medication reduction; GPi is superior to STN in regards to dyskinesia control and medication flexibility.[7] These considerations were not the most pressing sources of debility or risk for the patient under discussion. Informal discussions with DBS clinicians would suggest that of these two targets, STN treatment remains the preferred choice for PD patients in need of significant tremor control, and a target to avoid in patients with significant comorbid psychiatric illness. What evidence supports these biases?



Video 1. Rest tremor prior to and immediately after initial programming of bilateral globus pallidus interna (GPi) deep brain stimulation. Left GPi settings were (c+,2–) at 2 volts, pulse width 90 μs, and frequency 180 Hz. Therapy current was 1.883 mA. Right GPi settings were (c+,10–) at 2 volts, pulse width 90 μs, and frequency 180 Hz. The therapy current was 2.677 mA.

There are limited reports on the effect of GPi stimulation in cases of severe PD tremor or benign tremulous PD. A review of cases of rigorously defined benign tremulous PD implanted at the Mayo Clinic over a 14-year period showed no cases of GPi implantation (15 patients with Vim and STN stimulation were identified).[8] This likely reflects a target selection bias stemming from the historical use of Vim stimulation for tremor, and STN stimulation for PD tremor. This is in spite of evidence of improvement in severe tremor in patients undergoing pallidotomy.[9] Retrospective reviews provide some support for GPi and STN target equivalency in tremor reduction. Katz et al.[10] reviewed the Veterans Administration (VA) Cooperative Studies Program #468 by analyzing the response of different PD motor subtypes to GPi and STN stimulation. They analyzed tremor dominant (TD), postural instability gait difficulty, and intermediate subtypes. TD subtype was determined by a cumulative UPDRS tremor subscale score 1.5 times greater than that of the subscale items for balance and gait. TD patients experienced greater mean overall improvement, as measured by the UPDRSIII, after GPi DBS than after STN DBS. However, the discrepancy in improvement was mainly accounted for by improvement in gait. Tremor subscales showed no significant difference in improvement based on target.[10]

A few prospective randomized trials have attempted to compare GPi and STN stimulation directly. A single-center study of 23 patients randomized to GPi and STN stimulation, with blinded assessment after 1 year, found UPDRS tremor subscores in either group showed no statistical difference.[11] Larger, more recent studies have shown a similar equivalency in tremor reduction. The aforementioned VA study found that stimulation at either target provided similar overall motor benefits.[12] However, no analysis of tremor subscale was provided in the initial reports of outcomes at 6 and 24 months after DBS. A subset of these patients was followed at 36 months and showed similar overall UPDRSIII improvement, while specifically reporting

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tremor subscale scores which showed equal improvement between STN and GPi groups.[13]

Other large prospective randomized trials provide conflicting evidence regarding target equivalency for improving PD motor symptoms. The COMPARE trial analyzed cognition and mood changes between STN and GPi stimulation as its primary outcome, but in secondary analysis UPDRS motor scores showed no significant difference between groups.[14] The NSTAPS study, did find a greater mean improvement in the secondary outcome measure of UPDRSIII motor scores in the off-medication state after STN DBS than GPi.[15] However, neither prospective study commented on GPi and STN benefit for tremor specifically. When the evidence of clinical outcomes is reviewed, clinicians' preference in treating severe PD tremor with STN DBS has little support.

Perhaps tremor should not be regarded as a guiding feature of target selection as our clinical dilemma suggests. What then of our perception of the adverse psychiatric effects of STN stimulation? In a large, multicenter survey of patients with STN DBS, Voon et al.[6] found that the risk of suicide in the first postoperative year is elevated. Attempted suicides were associated with postoperative depression, being single, and a prior history of suicide attempt and impulse control disorder.[6] The association of STN stimulation and increased suicide risk is controversial. A careful analysis of the VA cooperative study found no increased risk of suicidal ideation postoperatively, nor between STN and GPi groups.[16]

Postoperative depression, as a risk factor for suicidality, has also been evaluated with mixed results. The VA cooperative study did suggest a small but statistically significant worsening of depressive symptoms 2 years after STN DBS, but those with GPi DBS showed slight improvement.[12] The aforementioned COMPARE trial found no difference in visual analog mood subscales between GPi and STN groups.[14] Two retrospective studies investigated whether a history of preoperative depression was more likely to lead to postoperative depression. A 2002 retrospective review of 24 STN DBS patients, 12 of whom had depressive episodes prior to surgery, found five patients with a persistent depressive episode postoperatively, in spite of significant motor benefit.[17] Four of these patients were among those with presurgical depression. A larger retrospective review of 110 patients with DBS, to either the STN or GPi, showed that those with a history of presurgical depression had higher postsurgical Beck Depression Inventory scores than those without a history of depression.[18] The study was not designed to detect a difference between the surgical targets.

Additionally, aggressive medication reduction in the postoperative period appears to be related to the incidence of apathy and depression, suggesting that if there is a correlation between STN DBS and worsening depression, it may be a result of aggressive medication reduction and not the stimulation per se.[19] Indeed, four out of five of the patients in the 2002 review of STN DBS who experienced postoperative depression were noted to have had a >60% reduction (and in one case complete withdrawal) of their levodopa.[17] Other studies have shown an improvement in depressive symptoms in the first 6 months after STN DBS, suggesting that effective stimulation and careful postoperative medication management should not be expected to have negative consequences on mood.[20]

In conclusion, further research is needed to provide evidence-based guidelines for target selection for DBS in advanced PD. The available evidence suggests that STN and GPi DBS are equivalent for PD tremor reduction. Clinicians' bias towards STN targeting for tremor reduction either fails to recognize that equivalency, or represents a practical experience that has failed to be recognized in the literature. Similarly, a more definitive understanding of the effects of stimulation targets on depression and suicidality would offer clinicians and patients a more accurate assessment of possible psychiatric risk when deciding to proceed with an elective invasive surgery.

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