Turning tables

Should GPi become the preferred DBS target for Parkinson disease?

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Half a decade ago, a provocative editorial envisioned a "rematch" between globus pallidus pars interna (GPi) and subthalamic nucleus (STN) deep brain stimulation (DBS) in the treatment of advanced Parkinson disease (PD).[1] The idea of a boxing bout between the 2 most common DBS targets for the treatment of PD summarized a decade-long controversy. While GPi had been the preferred target of ablative procedures for the treatment of advanced PD in the 1990s, the advent of DBS coincided with an overwhelming preference for the STN. Such instantaneous supremacy was originally supported by a theoretical rationale, namely the central role of the STN in the pathophysiology of PD,[2] but for over a decade it remained fundamentally based on preference more than evidence.

In fact, the first relevant head-to-head comparison between STN and GPi DBS left the choice of target to the investigators, based on their experience.[3] This otherwise seminal study, which led to FDA approval in 2002, showed significant motor benefits using bilateral stimulation of either STN or GPi. However, despite concerns about nonrandomized assignment to the 2 targets, the authors concluded "STN stimulation appears to be associated with a greater benefit and permitted a reduction in the consumption of levodopa." The added benefit of reducing medications is still perceived as a key advantage for STN DBS, even if many agree today that lowering the dose of dopaminergic therapy should not be the primary goal for surgery.[1] No randomized trial compared the benefits and adverse events of the 2 procedures in a substantial number of patients until the cooperative VA/National Institute of Neurological Disorders and Stroke–sponsored trial, which showed a substantial equality of motor outcomes.[4] In such a scenario, long-term results, including not only motor benefits but also the incidence of cognitive, mood, and behavioral side effects, become especially important deciding factors.[1]

In the current issue of *Neurology*®, Weaver et al.[5] filled part of this information gap, reporting DBS long-term outcomes in 159 patients originally enrolled in the cooperative VA trial. The authors followed for 36 months patients randomly assigned to GPi (n = 89) or STN DBS (n = 70), using the ON stimulation/OFF medications Unified Parkinson's Disease Rating Scale motor subscale as the primary outcome, and quality of life scales and neurocognitive function as secondary outcomes. Motor function improvement was significantly sustained up to 36 months both for GPi and STN stimulation, with similar and stable improvements between targets. However, quality of life subscales improvement and neurocognitive measures showed gradual decline over time, suggesting underlying progression of the nonmotor features of the disease.

In addition to these important, yet expected outcomes, this report offers 3 details that are worth deeper scrutiny. First of all, the faster decline of Mattis Dementia Rating Scale scores for STN than GPi patients suggests a cognitive disadvantage for those implanted in the STN. Stimulation-associated cognitive and behavioral problems already had been suggested by smaller series comparing the 2 targets.[6] Possible current spread to associative STN areas or surrounding areas with limbic connections has been postulated to justify these unwanted effects.[1] Further research is needed to clarify this issue, including the role of empirical, possibly excessive stimulation parameters.[7] Finally, the role of dopaminergic medications, typically maintained at higher levels in GPi implants, in maintaining cognitive function should not be underestimated.[8]

Reducing levodopa and equivalent medications has been classically perceived as a major advantage of STN DBS. In the current study, the initial medication reduction, expectedly greater in the STN group (35% vs 18%), was maintained at 36 months. However, the STN group (but not the GPi) gradually lost the additive effect of medication to stimulation. Such deterioration of the ON/ON benefits in STN patients over time was already known, in particular for balance and gait.[9] Nevertheless, a number of unan-

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swered questions arise: is it important or even desirable to reduce medications over the long term? Do medication and stimulation have a complementary or alternative role? Is GPi stimulation more compatible with long-term medical therapy? Is chronic STN stimulation interfering with dopaminergic stimulation?

A final thought-provoking observation regards the discrepancy of untreated scores (OFF stimulation/OFF medication) between the 2 study groups over time. While OFF/OFF motor scores gradually worsened in the STN group, they remained remarkably stable in GPi patients. This apparent lack of disease progression could be attributed to prolonged residual benefits of higher daily dopaminergic medication doses in the GPi group, although medications remained stable (albeit lower) in the STN group. While a disease-modulating effect of STN DBS was long postulated and never proven,[10] the GPi stimulation has received little or no attention in this sense.

The only serious limitation of this study appears to be the fairly large number of dropouts, which account for approximately 50% of those originally randomized in the study, slightly more for the STN group. While this attrition determined a downgrade of the evidence level to Class III, the reported population is comparable to the baseline study group in demographic and clinical terms. It is obviously impossible to determine whether the subjects who abandoned the study might have provided a different set of outcomes.

The controlled evidence emerging from this study assigns to GPi an important round in the "rematch" with STN. Motor outcomes being equal, the lack of ON/ON motor and cognitive deterioration over time is clearly a very desirable long-term benefit for any DBS candidate. In the absence of severe resting tremor, which probably remains more sensitive to STN stimulation, GPi DBS is becoming an increasingly frequent and important option. If the art of making medical decisions reflects a continuous struggle between evidence- and preference-based practices, this study will inject more reliable evidence in delicate long-term decisions, based until now almost exclusively on the preference and personal experience of the DBS provider.

DISCLOSURE

The author reports no disclosures relevant to the manuscript. **Go to Neurology.org for full disclosures.**

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