No differences in neuropsychological outcomes between constant current and voltage current subthalamic deep brain stimulation for Parkinson's disease

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The current available devices for deep brain stimulation (DBS) therapy allow clinicians to use current or voltage between the electrical parameters to improve symptoms. Constant current stimulation may have the putative advantage to avoid the variations in stimulation current delivery that is caused by variations in brain tissue impedance. Although constant current systems might be safer, no strong evidence is available to support this hypothesis or its clinical superiority versus constant voltage (1).

A recent study has delved into the cognitive and behavioral outcomes of subthalamic nucleus (STN) DBS in Parkinson's disease (PD) patients using a constant current rather than a constant voltage amplitude (2). This article expands upon previous finding reporting the outcome of the open-label randomized controlled trial of a constant current DBS device which found improvements in patient reported good quality "on" time compared to a delayed stimulation control group (3). The new study (2) supplements the former limited neuropsychological data presented (3), and examines the cause and impact of verbal fluency declines following surgery, which is the most consistent and persistent cognitive decline reported in DBS patients (4).

In their study, Tröster *et al.* (2) take their investigation one step further, and provide a detailed and focused evaluation of the verbal fluency declines (which are mild but relatively pervasive following either STN or globus pallidus internus, GPi, DBS), and were found also in their constant current STN DBS investigation. By capitalizing on the delayed stimulation paradigm (one group of patients started stimulation immediately after surgery whereas the other group 3 months following surgery), the investigators could tease apart whether a microlesion/implantation effect or a stimulation effect was the potential underlying cause of the verbal fluency declines at 3 months following the surgery, and which remained for both groups until at least 12 months. The 90-day outcome comparing the stimulation group to the delayed stimulation control group demonstrated the expected outcomes of declines in verbal fluency tasks (letter fluency, semantic fluency, and switching fluency) and processing speed (Stroop Color Word Test) for the stimulation group. However, the delayed stimulation group also demonstrated declines in semantic and switching fluency, and initiation/perseveration on the Dementia Rating Scale, suggesting that these findings were secondary to a microlesion/implantation effect. The distinction between these findings implies that several consistently reported cognitive side effects of this surgical intervention may be amenable to potential changes to aid in reducing the surgical impact, such as differences in targeting (e.g., avoiding the lateral ventricles or the head of the caudate nucleus), and/or patient- or symptom-tailored electrode

placement. Several of the more persistent cognitive side effects (e.g., letter fluency processing speed) may benefit from programming parameter modifications to reduce stimulation of nearby structures or to more accurately focus or steer the stimulation and reduce the cognitive side effect profile of the surgical intervention. The letter and semantic fluency declines were not related to levodopa reductions, age, complex attention measures, or communication satisfaction following surgery.

While the authors acknowledge that the exact underlying mechanism of change for verbal fluency declines is not known they hypothesize that declines in processing speed and switching/executive function are likely related to these consistently reported changes. Verbal fluency tasks tap a unique executive functioning ability that likely relies at least in part on the individual's inability to switch to a new category. Switching was one of the most consistently clinically significant declines noted in the sample with 43% of patients and these declines persisted for the entire sample 1 year following surgery, lending credibility to the idea that the stimulation itself, whether it is constant current or constant voltage induced stimulation, may be exacerbating and/or leading to persistent decline.

DBS outcome studies generally find mild improvements in mood following the surgical intervention, regardless of the target site; however, the largest randomized US study to date found that STN DBS resulted in mildly increased depressive symptoms while GPi DBS revealed mild mood improvements following surgery (5). The current study revealed that depression scores improved for both the stimulation and the delayed stimulation control STN DBS groups but the stimulation group demonstrated a larger magnitude of improvement in mood. These improvements persisted until the longer follow-up evaluation (1 year for the stimulation group, and 9 months for the delayed stimulation group) with 39% of the patients reporting a clinically significant improvement in mood. Taken together these finding suggest both a surgical and a stimulation effect on mood following implantation.

The Holy Grail for DBS care team members is to be able to determine the algorithm to predict who at baseline will derive the best motor outcomes with the least neurobehavioral side effects. Although many attempts have been made to determine the predictive risk factors for poor motor or cognitive outcome, the answer remains elusive. Tröster *et al.* (2) made an attempt to unlock the portion of this mystery relating to the prediction of neurobehavioral outcome, but the quest remains unfulfilled. They were unable to replicate or expand upon previous work by Smeding *et al.* (6) and found that a composite of attention measures, age, and dopaminergic medications did not predict cognitive outcome on a screening instrument or a composite of executive function and memory tests at 90 days following surgery. It is likely that this elusive question will not be answered until a large comprehensive DBS registry is developed.

This initial open-label trial of constant-current stimulation focused on stimulation of the STN for the treatment of advanced PD motor symptoms. To date, current controlled stimulation has not been evaluated in GPi DBS, which according to a recent meta-analysis[4] may be a safer surgical alternative to STN in terms of its neurocognitive and neurobehavioral profile. The meta-analysis revealed that STN DBS led to cognitive declines in more domains than was found for studies investigating GPi DBS, and a greater reduction in depression symptomatology following GPi versus STN. However, the findings in GPi DBS are based on a small literature, and the efficacy and side effect profiles will require further evaluation using both methodologies and both surgical sites.

Okun *et al.* (3) acknowledges that the overall study design of the parent study was an open-label randomized trial lacking blinding of the randomization of group selection which limits the ability to determine the magnitude and potentially the cause of the motor changes. Tröster *et al.* (2) do not discuss this limitation as it relates to the neurobehavioral outcome. Due to the lack of blinding, a nocebo effect may be postulated as a potential issue for consideration for the delayed stimulation control group at 90 days; however, most cognitive scores did not show a significant change at 90 days, and only the DRS initiation/perseveration subscores demonstrated a decline for only the delayed stimulation control group. In neuropsychological testing, particularly over a 3-month time-frame, practice effects are of greater concern, and the authors appropriately acknowledge and deal with this issue through the use of randomized alternative measures and caution when interpreting non-clinically significant memory improvements in the stimulation group on follow-up evaluations.

The results of the present investigation are promising and add to the literature that DBS, whether it is constant current or constant voltage stimulation, is a safe and effective surgical alternative to medical management. While this investigation demonstrates that constant-current neurostimulation for PD

is a safe and efficacious treatment in terms of the neurobehavioral outcomes, it does not compare the cognitive a behavioral outcome of this new treatment modality directly to the standard constant voltage treatment; however, it is clear that cognitive profiles appear very similar. It is likely that since the impedance of the brain tissue is most variable first weeks after the surgery, that once these variations have stabilized, the outcome profiles will likely be very similar between the two methods.

The St. Jude Medical Neuromodulation constant-current stimulation electrodes differ in another manner from the voltage controlled electrodes. The constant-current electrodes contain two center contacts which are segmented instead of four concentric rings of stimulation found in the standard voltage controlled electrodes. The two center contacts are segmented into three divisions which can be activated or deactivated to steer the current away from the areas that might produce unwanted side effects. This difference was not discussed within the current investigation (2) as it was a not a direct comparison of the methods of stimulation or devices. The difference in programing parameter options and the potential for improved ways to control the direction of the current spread may lead to a reduced side effect profile including potentially reduced cognitive changes. Future direct comparisons of the two methods including stimulation parameters, lead placement, and surgical trajectory may be beneficial in teasing apart the most efficacious treatment options for patients with advanced PD and offer personalized treatment tailoring the DBS target sites and devices to the patient symptom presentation.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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