Neuropsychological outcomes from deep brain stimulation—stimulation versus micro-lesion

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As one of the most pivotal innovations in neurotherapeutics, deep brain stimulation (DBS) has transformed the treatment of patients with Parkinson's disease over the last 30 years (1). The most common targets of DBS used to treat symptoms of Parkinson's disease include the globus pallidus pars internus (GPi), subthalamic nucleus (STN) and to a lesser extent the ventral-intermediate nucleus of the thalamus (VIM). Since the development of STN DBS for Parkinson's disease in 1993, numerous studies have demonstrated the many motor benefits of stimulation (2,3). DBS of the STN results in lessening motor fluctuations, reduction of dyskinesias by more than 50%, and marked improvements up to 40–60% in OFF symptoms such as tremor, bradykinesia and rigidity, which results in improvement in the patients' quality of life (4,5). DBS is typically well tolerated but can be associated with side effects. Although reports vary, STN DBS has been associated with multiple areas of cognitive decline, most consistently demonstrated in changes in verbal fluency. In a recent meta-analysis of available data, patients with STN stimulation were found to have mild deficits in psychomotor speed, memory, attention, executive functions, and overall cognition with more moderate declines in both semantic and phonemic verbal fluency (6). The etiology of these cognitive declines is likely multifactorial with a contribution from the underlying neurodegenerative nature of Parkinson's disease. However, patients with DBS regardless of the target (STN or GPi), show more cognitive decline when compared to patients undergoing treatment with best medical therapy as measured in processing speed, working memory, and other neuropsychological testing (7). Attempts to topographically map the human STN have suggested that placement of the DBS electrodes within the anterior aspect of the ventral STN is related to additional neuropsychological sequelae (8).

The benefits and side effects of DBS are largely dependent on electrode placement within the brain and adjacent brain structures and networks. There have been an increasing number of investigations regarding the effects of various specific stimulation parameters on both motor and non-motor symptoms. Earlier studies illustrated higher amplitude stimulation corresponded to decreased attention while increased pulse width improved delayed memory (9). Comparisons of different rates of STN stimulation have shown that high frequency stimulation (130 Hz or higher) worsened verbal fluency while low frequency stimulation (less than 130 Hz) appeared to improve verbal fluency (10). The authors hypothesized that low frequency stimulation activated frontal pathways while high frequency deactivates them.

Up until recently, the only approved DBS device available in the United States was the Activa system from Medtronic (Medtronic Minneapolis, MN, USA). Although the system was upgraded in order to have the capability to program in either constant voltage or constant current mode, many

clinicians were most familiar with programming their DBS patients using constant voltage. The rationale behind the use of constant current is to deliver a stable amount of current that accommodates for changes in impedance that may fluctuate over time. Impedance can vary due to local changes in the electrical properties of the tissue surrounding the electrode, including the encapsulation around the electrode that is thought to increase the tissue resistance (11). A multi-center open-label clinical trial that utilized the St. Jude constant current system was completed in 2010. This study demonstrated that constant current bilateral STN DBS with the St. Jude system produced significant improvements in "good quality on time" defined as on time without troublesome dyskinesias when compared to a delayed stimulation cohort that was implanted but not actively stimulated until after 3 months after surgery. This improvement in motor symptoms was sustained at 1 year of follow up (12). In October 2016, the FDA approved the St. Jude Infinity (St. Jude Plano, TX, USA) constant current DBS system for use in the United States. Now with two DBS systems available in the United States for implantation, many centers are considering the potential advantages or disadvantages of constant current stimulation when deciding on which system to choose.

The recently published article, "*Neuropsychological outcomes from constant current deep brain stimulation for Parkinson's disease*" by Tröster *et al.* examined the effects of constant current STN DBS on cognition and mood, using data from the original 136 patients within the multicenter study that utilized the cohort of delayed stimulation patients as the control group (13). A battery of various neuropsychological tests were administered to both the constant current active stimulation group and control group 1–4 weeks prior to surgery, as well as at 3 and 12 months after implantation. The data showed that although there was not much of a difference in many of the tests within the neuropsychological battery, at 3 months, the active stimulation group had a decline in the verbal fluency, processing speed, and attention/working memory compared to the delayed stimulation group. Once the control group's stimulation was activated after 3 months, the pooled cognitive testing of all of the stimulated patients (now including the delayed stimulation and original active stimulation groups) also showed a statistically significant decrease in the overall verbal fluency compared to baseline. Although results varied by the specific verbal fluency test, approximately 16–40% of this study's patients demonstrated changes in verbal fluency. The authors did suggest a possible micro-lesion effect on cognition since both the control and stimulated groups did demonstrate declines in category and switching verbal fluency. These results are similar to previous studies, including the larger NINDS/VA CSP-468 study that examined the cognition of 84 patients who underwent bilateral constant-voltage STN stimulation with a similar neuropsychological battery at baseline and at 6 months (7). This study showed that there was a decline in both processing speed and working memory when compared to patients treated with best medical therapy. Thus, the results reported in Tröster *et al.*'s recent study does not suggest a qualitative difference in cognitive side effects from constant current stimulation as opposed to constant voltage based on historical data. The Tröster study does suggest that both the surgical procedure and STN stimulation contribute to these deficits. The control group (no stimulation) did show significant deficits in some measures of verbal fluency but also showed trends in all of the same tests as the stimulation group. It is likely that these did not reach statistical significance because there was a much smaller sample size in the control group and the deficits were smaller in magnitude. Together, these data suggest that disrupting the STN (or neighboring structures) with either stimulation or a micro-lesion leads to specific psychological deficits. This is further supported by the study of Wojtecki *et al.* who reported that driving or activating this pathway with low frequency stimulation can improve verbal fluency (10). Now with the capability of directional steering of stimulation, further studies are needed to investigate the role of whether honing stimulation with directional steering lessens the side effects of DBS on cognition and behavior.

In summary, the study by Tröster *et al.* adds additional confirmation that STN DBS in Parkinson's disease patients results in declines in verbal fluency and Stroop tasks. These declines appear to be due to both high frequency stimulation and a micro-lesion effect from surgery. Deficits from STN DBS appear to be similar whether stimulation is programmed by constant current or constant voltage.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest

to declare.

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