EDITORIAL

Responsive Deep Brain Stimulation: A New Hope for Controlling Stimulation-Induced Dysarthria in Essential Tremor

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Thalamic deep brain stimulation (DBS) is highly effective for essential tremor (ET); however, stimulation-induced side effects may diminish the overall therapeutic outcome. One of the most common side effects in both ET[1] and Parkinson's disease (PD) is stimulation-induced dysarthria (SID). Although the exact mechanism of SID is not fully understood, it is hypothesized that SID may result from unintended stimulation of adjacent brain tissue surrounding the target area or the target area itself.[2] This unintended stimulation can interfere with normal speech function, leading to difficulties in articulation, phonation, prosody, and respiration that characterize dysarthria.

In some patients, SID may manifest before achieving full control of the target symptom, thereby narrowing the therapeutic window of DBS. In this scenario, the physician and patient typically must reach a compromise between symptom control and side effect management. This delicate balance is crucial for optimizing the patient's quality of life, because inadequate symptom control or intolerable side effects can severely impact daily functioning.

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Various programming strategies have been suggested in the literature to address SID. For the currently available DBS systems, these strategies include amplitude reduction, contact adjustment, interleaving stimulation, directional stimulation, low frequency/pulse width, or bipolar stimulation. All these approaches shape the electrical field for more precise stimulation and have been recently reviewed in the literature both for thalamic DBS in ET and subthalamic nucleus DBS in PD.[3,4] In severe cases, an on-demand stimulation approach, where patients switch between predefined stimulation settings with their programmer, is often an unsatisfactory option.

Another way to overcome DBS-induced side effects in general and SID in particular is on-demand DBS via a closed-loop system.[5] At present, these systems are available only in experimental settings. Here, in contrast to conventional DBS (cDBS) with permanent stimulation, the on-demand activation of DBS depends on a recorded biomarker. In adaptive DBS (aDBS), this biomarker is directly recorded via the implanted electrodes. In a pilot study, SID was less severe in PD patients treated with aDBS with electrodes sensing for β-activity located in the subthalamic nucleus.[6] In contrast to aDBS, responsive DBS (rDBS) delivers stimulation on demand based on peripheral markers. On-demand approaches are particularly promising for side effect management and have the potential to reduce SID while maintaining symptom reduction.

In this issue of *Movement Disorders*, Cernera et al[7] present novel and intriguing data in a pilot study on this clinically relevant topic. The authors compared SID between rDBS and cDBS in eight unilaterally implanted ET patients. The concept of rDBS of Cernera et al[7] involves using electromyography sensors to detect tremor activity contralaterally to the implanted electrode and only activate stimulation when tremor occurs, thereby potentially minimizing unnecessary stimulation and its associated side effects. The authors demonstrated better intelligibility using rDBS than cDBS in their patient cohort.

Furthermore, rDBS appeared to be well tolerated by ET patients, at least in the experimental setting.

Despite these undoubtedly interesting findings, the data presented in this study must be interpreted with caution because of several limitations. First, the sample size of eight patients is relatively small (although sufficient for a proof-of-principle study), none had a voice tremor component, and only two of eight patients experienced SID under their regular DBS treatment. Second, and more importantly, during the rDBS stimulation, patients performed the speech testing with their upper extremities at rest, resulting in minimal tremor in the extremities and, consequently, minimal stimulation activation. This is evident from the very low total electrical energy delivered (TEED) to the brain during this condition. The low TEED observed in the rDBS condition suggests that patients received little to no stimulation during the speech tasks, which could confound the results. Therefore, the rDBS condition closely resembles the OFF-stimulation condition, where by definition, no SID is present.[8] Therefore, this pilot study merely demonstrates that rDBS has the potential for a "seamless transition" between activated and inactivated DBS based on the tremor signal. In line with this, the authors suggest investigating rDBS under more naturalistic conditions in future trials where patients communicate and simultaneously engage in daily activities. In such activities, tremor and speech will occur simultaneously or in close succession, allowing for a more accurate assessment of the potential of rDBS.

In such validation studies involving larger cohorts and long-term effects, the outcome parameters to quantify SID need to be more carefully chosen. At present, robust parameters or questionnaires to reliably detect the severity of SID are not available. Automatic speech analysis via machine learning for dysarthria quantification may help to close this gap in the future.[9] A recent research showed the promising potential of automated speech analysis in a real-world setting[10] that could be applied to continuously assess the extent of SID. More research is, therefore, needed in both directions: novel on-demand DBS techniques and robust methods for SID quantification.

In conclusion, Cernera et al[7] address a clinically significant problem and propose a potential solution for overcoming SID in the future. Their pilot study may serve as another starting point for future research on SID in ET. The availability of novel DBS systems outside the experimental setting in the near future (cinicaltrials.gov, NCT04547712) will help enable on-demand DBS for more personalized treatments. If these new approaches prove successful, they could provide maximum therapeutic benefit with minimal adverse effects for improving the quality of life of DBS-patients with neurological disorders.

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Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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