Improving deep brain stimulation: timing makes all the difference

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Today there is an unprecedented wealth of information about the electrophysiology, the brain anatomy and the biochemical pathways relevant to Parkinson's disease (PD). Translating this information into better treatments is a major challenge to academia and industry and requires sophisticated models of how the basal ganglia interact with the remaining motor system. With respect to electrophysiology, early models of basal ganglia function have focused on firing rates (1,2), whereas nowadays most researchers would agree that the exact timing of neuronal activity is crucial to basal ganglia function (3,4).

In a study recently published in Science Translational Medicine, Brocker and colleagues (5) capitalized on this key insight to improve deep brain stimulation (DBS), an effective neuromodulatory therapy of PD motor symptoms (6-9). They present an optimized DBS protocol which is much more energy-efficient than conventional DBS. Using less energy is desirable for several reasons. First, it reduces the amount of battery replacements and thus the amount of surgical interventions in patients treated with DBS. More importantly, the occurrence of stimulation-induced side effects, such as dysarthria or paresthesia, is related to the power applied (10). Hence, reducing stimulation power may increase the therapeutic window, leaving more options to the neurologist adapting the DBS settings. Prospectively, this improvement could increase the therapeutic benefit for a large number of patients.

Apart from its clinical relevance, the study by Bocker *et al*. is appealing due to its systematic approach. The authors first determined the best DBS pattern in a computational model before applying it to an animal model of PD and finally to patients. While this is the pipeline that all medical device developments should follow, it is not always adhered to in the DBS field so far.

In essence, the study by Brocker *et al*. is a comparison of three DBS protocols applied to the subthalamic nucleus (STN): (I) high-frequency DBS (≥130 Hz), which is known to be clinically effective but energy-intensive; (II) 45 Hz DBS, which was expected to be clinically less effective but energy-saving and (III) optimized DBS, which was designed to be both clinically effective and energy-saving. All three protocols were tested in freely moving, hemi-parkinsonian rats and in PD patients undergoing DBS surgery. In rats, clinical effects were assessed using the bar test and a methamphetamine challenge. In PD patients, clinical effects were tested using a finger-tapping paradigm and accelerometer recordings of spontaneous tremor. In addition, the authors investigated the effect of DBS on putatively pathological, neuronal oscillations (11,12). To this end, local field potentials were recorded from the globus pallidus internus (GPi) and motor cortex in rats, and from the STN in humans, while DBS was being applied.

In order to fully appreciate the results of this study, it is crucial to be clear about the difference between regular 45 Hz DBS and optimized DBS. Both had a mean pulse rate of 45 pulses per second, but in the former the DBS pulses were arranged with regular inter-pulse-interval whereas in the latter the interval was variable. In fact, the intervals

were the result of an optimization process that selected those pulse sequences that were most effective in regulating basal ganglia activity in a computational model. Selection was performed using a genetic algorithm, a computational approach that mimics natural selection (13).

Interestingly, the optimized pattern of DBS pulses had quite a different effect on behavioral and electrophysiological measures than its frequency-matched, regular counterpart (45 Hz DBS). It reduced akinesia and neuronal oscillations more strongly than 45 Hz DBS in rats and humans, despite a similar rate of stimulation—an impressive proof of the relevance of timing. The difference was most evident when considering oscillations (7–10 Hz for rats, 20–33 Hz for humans), which were unaffected by regular 45 Hz DBS but strongly suppressed by optimized DBS. With respect to clinical effectiveness, optimized DBS generally performed better than 45 Hz DBS, but it did not quite reach the effect of high-frequency DBS. In particular, optimized DBS failed to suppress rest tremor when tremor was strong. This aspect raises the question whether it is possible to draw level with high-frequency DBS while maintaining the energy advantage. A reasonable strategy for further improvement suggested by the authors is to use a computational model that better represents the tremor circuitry, which has distinct electrophysiological properties (14-17).

Of course, there are limitations which need to be considered. Most importantly, the number of patients was quite low. Only four patients contributed to the results on akinesia and another four contributed to the results on tremor. Second, the time constraints during surgery limited the assessment of motor symptoms and stimulation duration. And finally, the computational model simulated neuronal activity but not motor symptoms. Hence, the authors needed to use an electrophysiological proxy for motor symptoms (fidelity of the thalamic response to a cortical input) to optimize the stimulation pattern.

Despite its limitations, the work by Brocker and colleagues is important to current DBS research. It showcases a promising alternative to closed-loop DBS, which likewise seeks to minimize stimulation energy. In closed-loop DBS, symptoms are continuously monitored and stimulation is only applied when needed. Some studies reported increased clinical benefit compared to continuous DBS (18-20), and it has been shown for a particular closed-loop system that energy costs are substantially lower despite the need for online control (21). While energy expenditure for online control is not necessary when optimizing the pulse train a priori, as Brocker *et al*. have done, it affords continuous adaptation of DBS settings to a continuously changing motor system in the process of degeneration. Only time can tell which advantage—low energy consumption or the ability to adapt—will prove more valuable in clinical practice. For the time being, it is re-assuring to know that neurophysiological insights keep driving clinical innovations in movement disorders, and it will be the responsibility of the field to assure that these innovations eventually reach the patients.

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Footnote

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