Nature Reviews Neurology **8**, 119 (2012); published online 21 February 2012; doi:10.1038/nrneurol.2012.14

PARKINSON DISEASE

Constant-current deep brain stimulation improves symptoms in Parkinson disease

The first controlled trial of constant-current stimulation of the subthalamic nucleus has shown that this approach is relatively safe and improves motor performance in patients with Parkinson disease (PD). Moreover, several novel aspects of the study, including an ethically acceptable control group in a surgical trial, could provide a model for future investigations.

Deep brain stimulation (DBS) has long been recommended for the treatment of patients with PD who do not respond to medication, and usually involves repetitive electrical stimulation at constant voltage. In the new study, Michael Okun and colleagues set out to test a constant-current DBS device, which has the putative benefit of avoiding current fluctuations that are associated with variation in levels of tissue impedance at the target region.

The trial involved 136 patients with advanced PD at 15 clinical sites in the USA. Electrodes were surgically implanted in the brains of all patients but, importantly, stimulation was delayed for 3 months in patients assigned to the control group. This trial design allowed the effect of surgery alone to be studied while avoiding the ethical issues of sham surgery without treatment. As Okun points out, "It had not been demonstrated in a large, carefully conceived trial that the benefits of stimulation exceeded those produced by simply drilling a hole and placing a device in the brain."

Patients and investigators were, however, aware of the treatment group to which the patient had been assigned, raising the possibility that a placebo effect resulting from patients' expectations might have contributed to the observed response to treatment.

Another novel aspect of the study was that the primary outcome was measured from patients' diary data, rather than from the more commonly used unified Parkinson disease rating scale. Specifically, patients were asked to record change in 'on' time—that is, the time the patient spent mobile—without bothersome dyskinesia. "This approach allowed us to examine the most clinically relevant outcome for patients with PD," says Okun.

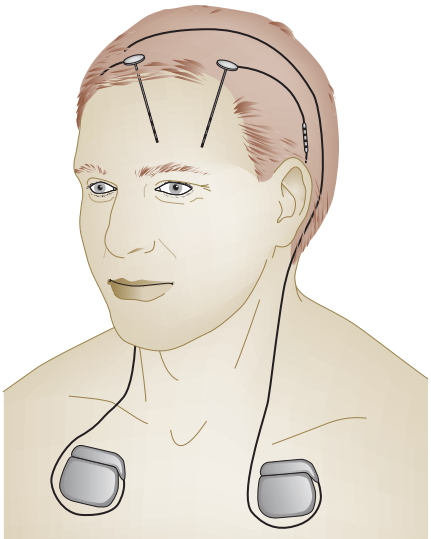
Patients were followed up for 1 year. At 3 months, both groups of patients reported an increased duration of good-quality on time compared with baseline, and this change was significantly greater in the active group compared with controls. "Although the increase was greater in the stimulation group—4.27 h versus 1.77 h—it was important to see the effects of implantation alone," says Okun.

After receiving stimulation for 3 months, the control group showed the same improvements in the primary outcome as was observed in the group that received immediate stimulation, and these benefits were maintained at 1 year.

A well-documented adverse effect of DBS applied to the subthalamic nucleus is impairments in verbal fluency, or "getting words out of the mouth," explains Okun. In the current study, the researchers used the Delis–Kaplin executive function scale to rate verbal fluency, and found similar deficits in the control group and the stimulation group at 6 months. "The worsening of some neuropsychological parameters in the operated patients seems to be an effect of operation and not stimulation," says Günther Deuschl, an expert in DBS for the treatment of PD who was not involved in the study. "Brain structures that are crucial for these functions might be lesioned in the surgical procedure," he suggests.

Given that impairments to verbal fluency were not caused by DBS *per se*, avoidance of such adverse effects might be possible through appropriate refinement of the surgical technique.

Some serious adverse events did occur in this trial, including infections in five patients and intracranial hemorrhage in four patients.



DBS devices have seen little diversification since they entered clinical practice more than 20 years ago. "This study should open the door for the introduction of new and improved stimulation techniques and hardware," says Okun. He adds, "our group plans to better understand the brain's electrical signatures in order to develop scheduled and responsive approaches to stimulation that can be tailored to an individual patient's needs."

"Overall, this is a very useful and careful study for which the authors should be applauded," says Deuschl. "The results should now be analyzed in comparison with existing controlled studies." Optimization of this therapeutic approach will benefit the many patients with PD who respond poorly to drug therapy.

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Original article Okun, M. S. *et al.* Subthalamic deep brain stimulation with a constant-current device in Parkinson's disease: an open-label randomised controlled trial. *Lancet Neurol.* **11**, 140–149 (2012)

Further reading Brodsky, M. A. & Nutt, J. G. Deep brain stimulation versus best medical therapy for PD. *Nat. Rev. Neurol.* **6**, 530–532 (2010)