

SCIENTIFIC COMMENTARY

Steering technology for deep brain stimulation

Over the last two decades, deep brain stimulation has become widely accepted as a treatment for Parkinson's disease, dystonia and tremor, and its use is increasing in disorders such as obsessive-compulsive disorder, depression and pain. The primary objective is always to achieve symptom suppression with few or no side effects; in other words, to attain as wide a therapeutic window as possible. In the past, efforts to achieve this were focused largely on ensuring accurate electrode placement, be it with the help of imaging and/or with microelectrode recordings. Excellent results can be obtained in this way, but unwanted side effects still occur in ~13% of patients (Deuschl *et al.*, 2006). Today, a number of new technologies are under development to address this problem. In this issue of *Brain*, Pollo *et al.* present data from a randomized clinical trial in which one of these approaches—directional stimulation—produces a wider therapeutic window than traditional methods (Pollo *et al.*, 2014).

To put this result into context, it is worth reviewing, albeit briefly, some of the other strategies that are under development with the aim of maximizing therapeutic benefit while minimizing side effects.

Demand pacemakers

Currently, most pacemakers deliver stimulation continuously at a fixed rate, in what is a rather simple but nevertheless effective therapy. However, constant stimulation can incur unwanted side effects by spreading to other fibre tracts or by disrupting normal brain signals embedded in pathological activity. Alteration of such 'normal' signals may affect emotion or cognition, for example. By targeting stimulation specifically to abnormal oscillations, it may be possible to apply stimulation intermittently and thus allow normal signals to re-emerge. Indeed, there is evidence that symptom suppression may be better with such intermittent stimulation than with continuous stimulation (Little *et al.*, 2013).

Other prospects include a pacemaker with telemetric capabilities, which could aid the identification of pathological markers in various disorders (Medtronic PC-S). Pacemakers that respond to posture could also reduce side effects, as in the case of spinal cord stimulation where lower levels of stimulation may be required in the supine position than in the upright position. Such

pacemakers use directional accelerometers to determine movement and position.

Novel stimulator and electrode arrays

The Boston Scientific Vercise™ implant is capable of providing stimulation at up to two independent frequencies, assigned to any of its 16 contacts. Although stimulation is not directional, it is thought that the use of two frequencies may produce better therapeutic effects with fewer side effects. The implant is under evaluation for the treatment of Parkinson's disease, and simultaneously delivered stimulation at 132 Hz in the thalamus and 10 Hz in the periventricular grey area has been used in a case of phantom limb pain (Sims-Williams *et al.*, 2013).

Imaging

At present, structural MRI is usually used for targeting electrodes. Although not yet fully evaluated, the use of diffusion tensor imaging may improve results by allowing specific parts of a nucleus that are connected to another region or possibly part of a network to be targeted, rather than just the nucleus itself (van Hartevelt *et al.*, 2014). As demonstrated in tumour surgery, diffusion tensor imaging can be used to identify fibre tracts that, if stimulated, would induce side effects, so that these can be avoided. It is also possible to somatotopically identify the best electrode position within homogeneous structures such as the thalamus (Hyam *et al.*, 2012).

Interleaving or shaped stimulation

This technology was introduced by Medtronic and allows for two contacts to vary in amplitude and pulse width but have the same frequency. It does allow for some 'shaping' of the current field and is reported to help in stimulation of the subthalamic nucleus, globus pallidus and thalamus. However, it still produces an omnidirectional pattern of stimulation. The technology drains battery life, but with rechargeable pacemakers this is no longer such an issue. Although advantages of such stimulation have been reported in the literature, the technology has not yet been studied systematically.

Postoperative programming based on images of electrode locations

Traditionally, programming has been based on a physician or specialist nurse using a 'trial and error' method to determine the best parameters. Those with experience will often follow a particular set of principles such as always trying particular contacts first or basing stimulation on intraoperative findings, at least to begin with. However, technology is now emerging that can collate information on electrode positions with clinical effect and provide a visual representation of the electrical field related to the nucleus being stimulated. Such examples include the Boston Scientific Guide DBS™ system and the Medtronic Optivise™ system.

Directional stimulation

A good clinical response is sometimes limited by the proximity of the contacts to structures adjacent to the target. An electrode may be placed in the subthalamic nucleus, for example, but if it is too close to the capsule, stimulation will induce side effects within the therapeutic window. To overcome this problem, technology companies have produced alternative electrode configurations, such as splitting the ring contacts into two or three (an approach under development by various companies), or even arranging 32 contacts in an array resembling a fish-scale (Sapiens). Experimentally, the latter has been shown to offer directionality in the primate (Martens *et al.*, 2011), as well as in a clinical case series (Schuurman *et al.*, 2013) in which it was also possible to record local field potentials from multiple contacts for better localization.

Pollo *et al.* evaluated the simpler split-ring electrode configuration intraoperatively in a series of patients with Parkinson's disease or essential tremor. Essentially, having confirmed the target with microelectrode recordings, they passed a split electrode array (directStim Aleva Neurotherapeutics) to the target and studied patients in which there was no microlesioning effect. Due to the smaller size of the electrodes, the current required to produce a therapeutic effect was significantly smaller than in a standard configuration. Pollo *et al.* have shown clearly that directionality is possible in an intraoperative setting, and that it has the potential to widen the therapeutic window. They should be congratulated for a number of reasons. Firstly, the world of neuromodulation has become swollen over the past decade with companies offering ever-increasing 'advances' in technology that are driven largely by engineers and are aggressively marketed as 'superior' to existing technology. Although these 'advances' are always good to see (and often very clever), there is frequently a lack of objective evidence to support their use, especially with the increased costs that they entail. Such examples include 'burst' technology in spinal cord stimulation, and high frequency stimulation. Pollo *et al.* have bucked the trend in that they have set out to evaluate the therapeutic effects of a new technology at the conceptual stage. This allows the technology to be abandoned if it does not work or for more

refinements to be made to improve it before further development. Secondly, they should be congratulated for the quality of their study. Good quality randomized, blinded trials are difficult and seldom in neurosurgery and this one adds significantly to the literature.

Future directions

In the future it would seem that a combination of all the technologies described above will lead to better outcomes with deep brain stimulation. However, with ever increasing numbers of contacts and electrode combinations, manual programming will become impossible. It may well be that a visual representation incorporating imaging and virtual rendering of tissue activation will be the way forward. Surgical techniques may have to be modified to take into consideration the fact that careful intraoperative alignment of best contacts must be maintained after fixation, as rotation of the electrode could abolish these.

Deep brain stimulation in its current form is beyond the economic resources of most of the world's population. This situation will not be helped by the increased production costs of cutting edge technology, which means that a large proportion of the world's population will probably not benefit from these new advances, at least in the medium term. For financial reasons, therefore, conventional deep brain stimulation will remain the therapy of choice for many patients.

Funding

The authors acknowledge financial support from the UK Medical Research Council, Norman Collisson Foundation, Charles Wolfson Charitable Trust and Oxford NIHR Biomedical Research Centre.

Alexander L. Green and Tipu Z. Aziz
Nuffield Department of Surgical Sciences, University of Oxford,
Oxford, UK

Correspondence to: Professor Tipu Aziz.
E-mail: tipu.aziz@nds.ox.ac.uk

References

- Deuschl G, Schade-Brittinger C, Krack P, Volkmann J, Schäfer H, Bötzel K, et al. A randomized trial of deep-brain stimulation for Parkinson's disease. *N Engl J Med* 2006; 355: 896–908.
- Pollo C, Kaelin-Lang A, Oertel M, Stieglitz L, Taub E, Fuhr P, et al. Directional deep brain stimulation: an intraoperative double-blind pilot study. *Brain* 2014; doi:10.1093/brain/awu102.
- Little S, Pogosyan A, Neal S, Zavala B, Zrinzo L, Hariz M, et al. Adaptive deep brain stimulation in advanced Parkinson disease. *Ann Neurol* 2013; 74: 449–57.
- Sims-Williams HP, Selbi WR, Javed S, Pickering AE, Patel NK. Two birds, one stone: single electrode dual target stimulation for the treatment of phantom limb pain [abstract]. *Stereotact Funct Neurosurg* 2013; 91: 264.
- van Hartevelt TJ, Cabral J, Deco G, Møller A, Green AL, Aziz TZ, et al. Neural Plasticity in Human Brain Connectivity: the effects of long term

- deep brain stimulation of the subthalamic nucleus in Parkinson's disease. *PLoS ONE* 2014; 9: e86496.
- Hyam JA, Owen SL, Kringelbach ML, Phd NJ, Stein JF, Green AL, et al. Contrasting connectivity of the vim and vop nuclei of the motor thalamus demonstrated by probabilistic tractography. *Neurosurgery* 2012; 70: 162–9.
- Martens HC, Toader E, Decré MM, Anderson DJ, Vetter R, Kipke DR, et al. Spatial steering of deep brain stimulation volumes using a novel lead design. *Clin Neurophysiol* 2011; 122: 558–66.
- Schuurman PR, Contarino MF, Bour LJ, de Bie RM, van den Munckhof P. Steering deep brain stimulation: an exploratory study with a new 32-contact lead. *Stereotact Funct Neurosurg* 2013; 91: 86.

NEUROSURGERY

Directional electrodes widen the therapeutic window for deep brain stimulation in movement disorders

Deep brain stimulation (DBS) can dramatically improve the symptoms of Parkinson disease (PD), but typical electrodes can stimulate areas beyond the region of interest, potentially leading to adverse effects. A study recently published in *Brain* presents encouraging results from a new type of electrode that is not only smaller than currently available hardware, but can also deliver stimulation in one of three directions around the lead.

Pollo and colleagues implanted directional electrodes into the subthalamic nucleus of 11 patients with PD, and in the nucleus ventralis intermedius of two patients with essential tremor. After positioning the electrode, the experimenters compared the effects of omnidirectional stimulation—akin to conventional DBS—and stimulation in each of the three directions individually.

As one experimenter adjusted the stimulation parameters, a blinded rater recorded the therapeutic window from

the minimum amount of current required to provide a meaningful improvement in motor symptoms to the maximum current that could be delivered without producing adverse effects, such as dysarthria, focal muscle contractions or paraesthesias.

“This new approach ... might even open doors to unexplored brain regions for DBS”

Although the specific direction varied, each patient had a ‘best’ stimulation direction with a significantly wider therapeutic window than the other two directions. Unidirectional stimulation also yielded wider therapeutic windows than omnidirectional stimulation, and required significantly less current to ameliorate motor symptoms.

“This new approach, allowing a specific orientation and a reduction of the total activated tissue, enhances the accuracy of DBS in commonly used targets,” explains

lead investigator Claudio Pollo. “It should also be useful in small and complex regions such as the the pedunclopontine nucleus in patients with PD, or the medial forebrain bundle for treatment-resistant depression. It might even open doors to unexplored brain regions for DBS.”

At the end of the intraoperative testing, the experimenters removed the directional electrodes—which do not yet have full regulatory approval—and replaced them with conventional implants. Therefore, long-term efficacy and safety data will not be available from this cohort. The authors are currently planning a multicentre study to examine chronic directional stimulation in patients with movement disorders. These data will be crucial to adequately assess this promising new technique.

Alex Chase

Original article Pollo, C. *et al.* Directional deep brain stimulation: an intraoperative double-blind pilot study. *Brain* doi:10.1093/brain/awu102