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Deep brain stimulation: new techniques

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SUMMARY

The technology of the hardware used in deep brain stimulation (DBS), and the mode of delivering the stimulation have not significantly evolved since the start of the modern era of DBS 25 years ago.
However, new technology is now being developed along several avenues. New features of the implantable pulse generator (IPG) allow fractionation of the electric current into variable proportions between different contacts of the multi-polar lead. Another design consists in leads that allow selective current steering from directionally placed electrode contacts that would deliver the stimulation in a specific direction or even create a directional shaped electric field that would conform to the anatomy of the brain target aimed at, avoiding adjacent structures, and thus avoiding side effects.
Closed loop adaptive stimulation technologies are being developed, allowing a tracking of the pathological local field potential of the brain target, and delivering automatically the stimulation to suppress the pathological activity as soon as it is detected and for as long as needed. This feature may contribute to a DBS therapy "on demand", instead of continuously.
Finally, advances in imaging technology are providing "new" brain targets, and increasingly allowing DBS to be performed accurately while avoiding the risks of microelectrode recording.

1. Introduction

Since the start of the modern era of deep brain stimulation (DBS) more than 25 years ago, not much has happened in terms of new technology that can be readily used in day-to-day practice to deliver the electric current to the brain target. The DBS hardware and the mode and pattern of stimulation have remained essentially the same: a quadripolar lead with 1.5 mm electrodes with an inter-space of 1.5 mm or 0.5 mm, is implanted into a brain target and an implanted pulse generator (IPG) delivers continuous stimulation resulting in a spherical shape of the electric field around the electrodes [1]. Electrical parameters for chronic stimulation (frequency, voltage, pulse width and polarity) are decided based on screening of the four electrode contacts for effect and side effects, which is sometimes a laborious exercise for the programming clinician and the patient, and may need incremental repetitive adjustments after surgery, over periods of weeks and months in some patients. Even surgical targeting has remained essentially the same, relying on a stereotactic frame, conventional MR and/or CT imaging, and in most centres relying also on multiple microelectrode explorations of the brain target. In fact, rather than technological advances, what has taken priority starting at the turn of the century was the expansion of DBS indications beyond Parkinson's disease (PD) and other movement disorders (dystonia, essential tremor), and beyond the classical brain targets (thalamus, pallidum, subthalamic nucleus), towards DBS of "novel" targets for surgical treatment of psychiatric, behavioural, cognitive and other brain disorders [2]. Real technical innovations of the DBS hardware have lagged behind. Most technical "innovations" in DBS that have received American FDA or European CE approval for routine use in the last decade have been mostly marginal and more or less cosmetic, such as a new burrhole anchoring device for the DBS lead, lower profile of connector cables, a double channel IPG, and IPGs that can be recharged and that can deliver a constant current rather than a constant voltage stimulation. The latter feature, that is, the delivery of constant current (milliamp) stimulation rather than the usual constant voltage stimulation, has been reported in one study detailing the clinical results of DBS using the St-Jude constant current DBS device (St Jude Medical, Plano, Texas, USA) in patients with PD [3]. It showed that constant current stimulation was efficacious, and that the clinical outcome was similar to previous studies that have used constant voltage-based stimulation.

It is only in the last couple of years that the field of DBS has been witnessing a surge in true technological innovation. New electrode designs and new patterns of stimulation are being introduced. In parallel, new modalities for brain imaging and new targeting techniques are being developed. Most of these

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innovations, summarised in this paper, are still in the pipeline or at the early stages of proof of concept.

2. Techniques related to new DBS hardware and new patterns of stimulation

DBS is performed in tiny deep subcortical structures that are anatomically, functionally and literally crowded with neurons and axons. These brain structures mediate symptoms that are to be alleviated by the DBS but the therapy entails often more or less unwanted side effects due to propagation of the electric current beyond the specific target aimed at, even if the DBS lead is quite accurately placed. Slurred speech for example is one of the main side effects of stimulation in the subthalamic nucleus almost regardless of how accurate is the location of the electrode in the target [4]. Also, the three-dimensional configuration of the subcortical brain target is not spherical, nor does it have a regular shape, that would match the spherical or ellipsoid shape of the electric field generated by the DBS electrode. Since the relevant brain anatomy is not shaped like a ball, and it is anatomically irregular with a mixture of neurons and axons than can react differently to electrical stimulation, there is a need to shape the electric current in such a way as to maximise the benefit and minimise the unwanted stimulation-induced side effects. Various technical strategies are being explored that would allow a stimulation using an electric field that can be made as conformal as possible to the shape of the structures aimed at, minimizing spill-over of current into adjacent structures, and thus theoretically avoiding side effects while maintaining effect.

2.1. “Interleaving” stimulation mode

This is a novel and readily available feature in the currently used generation of FDA- and CE-approved IPGs, such as Medtronics “PC” or “RC” brands of IPGs (Medtronic, Minneapolis, Minnesota, USA). An interleaving mode allows the independent and alternated stimulation of 2 contacts of the quadripolar DBS lead with different values for voltage and pulse width, but with the same frequency. This mode allows stimulation of adjacent anatomical structures with different energies, and the shape of the resulting electric field will vary accordingly. Interleaved stimulation mode is used when anatomically adjacent targets need to be stimulated at different amplitudes, when classical monopolar, double monopolar of bipolar stimulations fail to provide the desired effect and/or when there are side effects from too high a stimulation amplitude in the vicinity of the area where stimulation at same amplitude is efficient on the symptoms. This technique has been reported to be successful in individual patients stimulated in the subthalamic nucleus (STN) for PD [5], in the globus pallidus internus (GPi) for dystonia [6] and in the STN and the ventrolateral thalamus in a patient with both PD and essential tremor [7]. Some drawbacks of this technique are that it is rather laborious for the clinician programming the stimulation, and it increases the battery drain. Also, the frequency of the stimulating current cannot be adjusted independently for each electrode contact. Additionally, apart for the anecdotic observations reported above, there are no conclusive studies showing its benefit. Finally, the fact that the electric field, even with interleaving stimulation, still cannot be steered in a predetermined direction to avoid side effects, showed that there is a need to develop new electrode designs that permit more focussing and more shaping of the current into the brain target.

2.2. DBS device with multiple source constant current

A newly developed DBS device from Boston Scientific, called “Vercise” (Boston Scientific Corporation, Natick, Massachussets, USA) has recently received European CE approval. This rechargeable device allows delivery of a multiple source constant current with possibility to allocate completely different stimulation parameters independently to each of the eight contacts on the same lead. This would result in an electric field that can theoretically be tailored to the stimulated brain structure, by applying various amplitudes, frequencies and pulse widths to different electrode contacts in the target area. Additionally, this device allows stimulation with pulse widths below what is available with the other established brands of DBS in use today, i.e., below 60 μs. Two multicentre trials with the Vercise device are underway in patients with PD: one aims to evaluate if the therapeutic window of the stimulation can be increased by using shorter pulse widths than the classical 60 μs [8,9]; the other trial will investigate if the flexibilities in variation of stimulation parameters at different electrode contacts allowed by this device would improve outcome while decreasing side effects [10]. Additionally, this device has been used in a patient with phantom limb pain who was successfully stimulated using a trajectory that placed one electrode contact in the parafascicular thalamic nucleus delivering stimulation at 132 Hz and two contacts in the periventricular–periaqueductal grey matter delivering a 10 Hz stimulation [11]. An important drawback of this system is that the electrodes are not MRI-compatible. Also, as with interleaving, the fact remains that the current delivered will still encompass the tissue around the whole circumference of the electrode contact, without possibility for true field shaping and true selective directional steering.

2.3. Current steering and field shaping

The need for true current steering and true electric field shaping arises from the need to conform the electric field to the variable anatomy in the brain target of interest and to circumvent side effects when the electric field affects structures adjacent to the target. For example, if a STN DBS lead is in the STN, but happens to lie close to its lateral border, the electric field around the electrode will be partly into the STN and partly into the internal capsule. Similarly, if the DBS electrode is into the posteroventral GPi but too close to its medial and posterior aspects, the internal capsule will receive the same amount of stimulation as the GPi proper. Motor and other side effects will occur especially at higher stimulation levels that would be eventually needed to control the symptoms that motivated the DBS surgery in the first place. Such side effects may not be readily detectable at surgery, and may mitigate in the long run the benefits of DBS. One way to circumvent this nuisance is to design a lead with electrode contacts that are split in two, three or even four parts along the circumference of the electrode, with each part being able to be stimulated specifically in a selective and predetermined cardinal direction. With this concept, an electrode in the STN or the GPi lying close to the internal capsule, as in the examples above, can be made to deliver the electric current only towards the STN or towards the GPi (like a spotlight) without affecting the internal capsule lying in the opposite direction. This is what is meant by current steering, also called directional electrode design. This concept has been contemplated for some time and has been computer simulated in three cases of ventral intermediate (Vim) thalamic DBS showing the possibility to avoid paresthesias by steering the current anteriorly away from the posteriorly adjacent sensory thalamus and towards the Vim proper [12]. Recently, two designs of directional stimulation electrode have been tried intraoperatively in few patients:

– The “directSTIM” lead, manufactured by Aleva Neurotherapeutics (Lausanne, Switzerland), consists of a lead with four rings, where each ring consists of three independent electrodes with three different orientations allowing independent stimulation in any of the three directions (Fig. 1). Pollo et al. recently presented an