Back to the future: 30th anniversary of deep brain stimulation for Parkinson's disease

This year, 2017, brings the 30th anniversary of the use of deep brain stimulation (DBS) for the treatment of movement disorders, and it may also mark the beginning of a new DBS era, one in which critical revision of what we have learned in the past will guide our future treatments.

It was in 1987 that Alim-Louis Benabid first published a paper on the application of DBS as a treatment for drug-resistant tremor in Parkinson's disease (PD) (Benabid et al., 1987), thus revolutionizing the treatment of this condition. Unfortunately, that seminal article remained sorely overlooked until Limousin and colleagues reported the efficacy of DBS of the subthalamic nucleus (STN-DBS) at 1-year follow-up in 20 patients with PD (Limousin et al., 1995). Their paper rapidly became a "citation classic" and STN-DBS a mainstay of treatment for advanced PD (Deep-Brain Stimulation for Parkinson's Disease Study Group, 2001).

Since then many things have changed, but DBS treatment has constantly proved its efficacy in ameliorating the complex symptomatology of advanced PD (Toda et al., 2016; Kurtis et al., 2017). STN-DBS, in particular, was shown to improve the severity of PD-related motor symptoms by up to 93%, as assessed by means of the UPDRS-III, when combined with adequate medical treatment (Toda et al., 2016), and dopaminergic replacement therapy could be greatly reduced after surgery, thus also bringing about a benefit in terms of control of levodopa-induced dyskinesia and overall motor fluctuations (Toda et al., 2016). DBS treatment was supported by its safety profile too. Despite initial apprehension over its effect on cognitive performances, extensive evidence in fact proved its lack of impact on the evolution of cognitive decline in PD, with the exception of verbal fluency performances (Zangaglia et al., 2009). Other non-motor aspects, such as sleeping time and anxiety, improved with DBS, thus leading, overall, to a great improvement in patients' quality of life (Toda et al., 2016). These results fostered a rapid increase in the application of this treatment, to the point that it is now used in upwards of hundreds of thousands of patients, and its application is anticipated to become even more frequent. A growing number of studies recently provided robust arguments for modifying the timing of DBS treatment, to include young patients first facing the motor complications of the disease. Specifically, it was shown that STN-DBS is superior to the best medical treatment alone in ameliorating quality of life in PD patients in an early stage of the disease (Schuepbach et al., 2013). However, despite all that has been achieved over the past three decades, some concerns recently emerged, and STN-DBS for the treatment of PD is now undergoing a critical reappraisal (Hariz, 2016, 2012a,b; Galati and Stefani, 2015).

Several studies have reported limits and risks related to STN-DBS treatment for PD, introducing the concept of DBS failure (Hariz, 2016, 2012a,b; Galati and Stefani, 2015). Suboptimal management of motor symptoms and the development of stimulation-related complications are the main aspects of this complex topic. The results of STN-DBS on gait and postural control are inconsistent, with a striking discrepancy found between the described improvement as assessed with standardized outcome variables (e.g. gait kinematic parameters), and patient reports, which instead reveal dissatisfaction, with a worsening of self-perceived performances in up to 40% of cases (Pötter-Nerger and Volkmann, 2013).

On the non-motor side, on the other hand, the behavioral and psychiatric (e.g. impulsivity) side effects of the treatment have raised questions about the moral costs of STN stimulation (Florin et al., 2013; Seymour et al., 2016; Valentino et al., 2014). The relevance of these doubts is further strengthened by the parallel refinement of competitive treatments such as non-invasive stimulation techniques, which are starting to provide interesting results (Valentino et al., 2014).

These highly relevant concerns require careful evaluation; the concept of DBS failure is broad and complex and necessitates critical reasoning. In particular, the determinants of STN-DBS suboptimal benefit on gait and postural instability remain uncertain (Fasano et al., 2015). The STN is a key structure of the supraspinal locomotor network and it is unlikely that its modulation does not influence locomotion (Pötter-Nerger and Volkmann, 2013). The physiological mechanisms of human locomotion and their failure in PD are still largely unclear and their direct assessment will certainly foster treatment possibilities, also by means of STN-DBS (Pötter-Nerger and Volkmann, 2013). Following the recent findings obtained on assessing gait disturbances in patients with STN area stimulation for tremor control (Reich et al., 2016), it is tempting to speculate that PD-related gait abnormalities, too, might be managed with refined simulation paradigms in the near future.

Behavioral and psychiatric issues following STN-DBS should also be critically evaluated. These complex symptoms can devastate patients' lives much more than any motor disability and they have an even more complex pathophysiology, wherein stimulation of the STN might simply be the last straw. In line with this, accurate and individualized assessment of patients' characteristics and expert management of the dopaminergic treatment, able per se to evoke similar symptoms, have been shown to prevent and control these complications (Castrioto et al., 2014; Volkmann et al., 2010).

Altogether this body of evidence highlights the complexity of STN-DBS treatment in subjects with PD and the need for a highly individualized approach. Personalized medicine has become a core concept of patient care that is now

receiving more and more attention (Schork, 2015). It refers to any treatment informed by each person's unique information (i.e. clinical, genetic, and environmental) and it likely represents the future of medical treatment (Schork, 2015). However, one must bear in mind that, if we aim at a genetic or (electro) physiologically based treatment, we must start from a clinically tailored approach. The management of PD patients, above all those receiving STN-DBS, pioneered this strategy and now, thanks to the critical reasoning fueling DBS-related research, it is one that might guide their treatment to a bright, individualized new future.

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