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Adaptive DBS in Parkinson's disease: Headlines, perspectives and challenges

With great interest we have read the article by Velisar et al. on adaptive DBS (aDBS) in Parkinson's disease (PD) [1]. The authors report their experience with a novel aDBS system, referred to as Neural Closed loop DBS (NclDBS), that was tested in 13 PD patients with chronically implanted DBS electrodes in the subthalamic nucleus (STN). The key finding of the study is that NclDBS was tolerated for at least 21 minutes, and led to the suppression of tremor and bradykinesia, while less energy was delivered than in conventional DBS (cDBS). A substantial cohort of patients was reported, all implanted with an investigational sensing neurostimulator (Activa PC+S, Medtronic, Inc.). This type of neurostimulator was driven by an external control system (NexusD3, Medtronic, Inc) in the chronically implanted state. The results are an important step forwards in the clinical feasibility of aDBS. The crucial next step for upcoming aDBS trials will be to formally compare the clinical benefits of cDBS versus aDBS. Until now, only one study has shown this superiority in the immediate postoperative phase, using unilateral recordings of 3 of the 33 motor items of the Unified Parkinson's Disease Rating Scale [2]. A subsequent aDBS study in the immediate post-operative phase did not show significant differences between cDBS and aDBS, when tested in more ecological circumstances [3]. A potential confounding factor of such studies is that the measurements have been collected in the presence of the 'stun' or 'microlesion' effect. This effect is often present immediately after implantation of DBS, and causes temporary clinical improvement that cannot be further improved with stimulation.

In 2017, we reported the novel concept of performing aDBS recordings in a patient who already had DBS electrodes implanted for 14 years [4]. Apart from the absence of a stun effect in the chronic phase, another advantage of using this approach is that the response of the patient to DBS has already been verified before inclusion. Velisar et al. took this approach to the next level by using a fully implanted device, opening the possibility of more exhaustive recordings. In their article, a significant clinical improvement was shown with both cDBS and aDBS conditions, compared to no stimulation. Unfortunately, clinical outcomes were measured using different techniques: a clinical rating scale for the former, and kinematic testing with an accelerometer for the latter. Therefore, comparison between aDBS and cDBS using equal rating scales or surrogate markers in both conditions should be a subsequent step to evaluate the clinical benefits of aDBS.

Given the necessity to prove the effectiveness of aDBS in a clinical setting, experimental studies on aDBS in PD, such as the article by Velisar et al., are received with great enthusiasm. The rapidly increasing number of publications on aDBS in PD reached approximately 500 in 2018 [5]. Paradoxically, the number of aDBS-subjects evaluated using clinical outcomes counted only approximately 50, including the paper of Velisar et al.. Such a

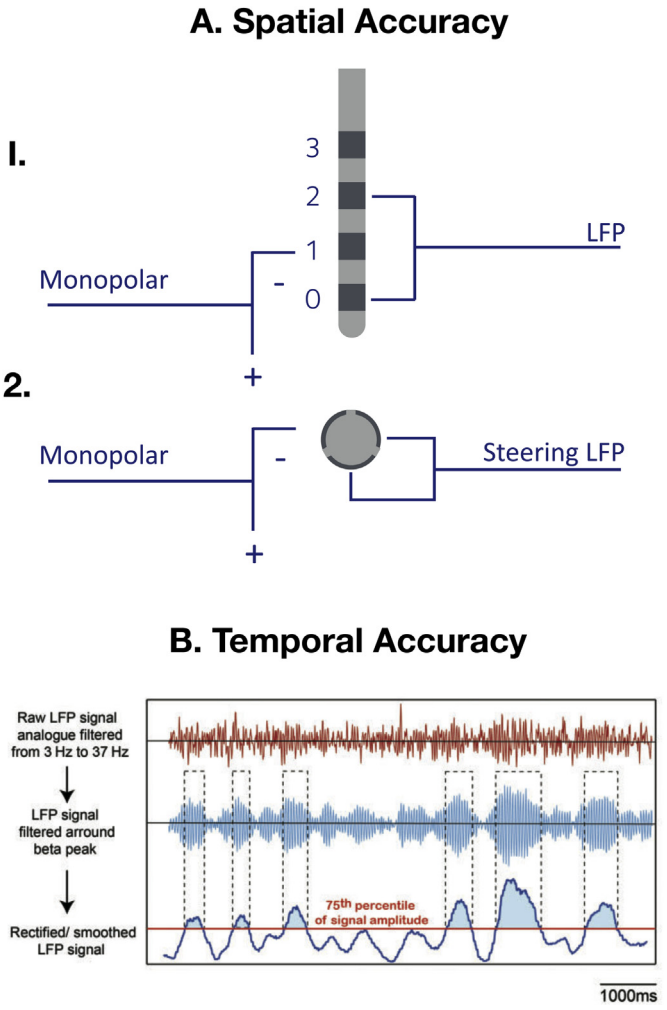

Fig. 1. A.1: schematic representation of the current application of adaptive DBS (aDBS): a bipolar local field potential (LFP) derived from two contact points is used for the recording of beta oscillations. Monopolar stimulation is provided with the electrode in between. A.2: schematic representation of a potentially more refined form of adaptive stimulation by using 'steering' electrodes which would enable aDBS recordings at the sub-millimeter scale. B: illustration of the typical volatility of beta oscillations at the sub-second scale. Figure B Derived with permission from Tinkhauser et al. Brain 2017.

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discrepancy illustrates the technical difficulties to translate conceptual aDBS prototypes into systems that can be tested in patients. Nevertheless, given the strong empirical evidence that indicates the existence of an *optimal* amount of stimulation [6], aDBS has a promising future in clinical practice.

An added challenge to compare the clinical effects of aDBS across studies is that several paradigms to modulate stimulation have been explored [1,2,7]. Also, feedback signals have been obtained from different recording sites [8]. In these studies, the DBS contacts used to obtain bipolar LFP recordings were different from the contacts used for stimulation. This means that the anatomical location where beta oscillations are recorded might be situated more than 2 mm from the stimulation site. For that reason, stimulation might not be provided directly to the source of beta activity. This could be potentially circumvented by directing aDBS to the active DBS contact point used to sense neural oscillations, by means of 'steering' electrodes (Fig. 1A) [9].

Another fundamental question yet to be answered is how fast stimulation needs to be titrated. aDBS systems that titrate stimulation in a staggered way might provide a better control than intermittent ON/OFF systems to fast reacting symptoms, such as tremor. However, as beta bursts longer than 500 ms have been positively associated with clinical impairment [10], the question is whether staggered control algorithms are volatile enough to selectively suppress pathological beta bursts (Fig. 1B). Finally, the applied stimulation algorithms for aDBS are virtually unexplored, which questions whether the same (high frequent) stimulation parameters as in cDBS need to be applied in aDBS.

Given all previous arguments, we consider that the availability of fully implanted DBS devices that are able to simultaneously record and deliver stimulation, will accelerate research in closed-loop systems. By comparing aDBS with cDBS, it will be possible to determine the which candidates are the most suitable and for (a) sensing sites, (b) 'physiomarker' definitions and (c) stimulation algorithms.

Conflicts of interest

All authors declare to have no conflict of interests.

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