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## Supporting Data

Additional Supporting Information may be found in the online version of this article.

## Adaptive Deep Brain Stimulation in a Freely Moving Parkinsonian Patient



The future of deep brain stimulation (DBS) for Parkinson's disease (PD) lies in new closed-loop systems that continuously supply the implanted stimulator with new settings obtained by analyzing a feedback signal related to the patient's current clinical condition.<sup>1</sup> The most suitable feedback for PD is subthalamic local field potential (LFP) activity recorded from the stimulating electrode itself.<sup>2-4</sup> This closed-loop technology known as adaptive DBS (aDBS) recently proved superior to conventional open-loop DBS (cDBS) in patients with PD.<sup>2</sup>

No studies have yet tested aDBS in freely moving humans for a prolonged time. This information is an essential prereq-

uisite for developing new implantable aDBS devices for chronic PD treatment.

In this single-case study, we tested whether a portable DBS device we developed is suitable to compare the clinical benefit in a freely moving PD patient induced by either aDBS or cDBS. To do so, after a first experimental session for extracting patient settings to personalize the aDBS algorithm, we treated a blinded patient (51 y old, male, 8 y PD history) with cDBS and aDBS in two separate experimental sessions each lasting 120 min, 5 and 6 d, respectively, after DBS electrode implant. To ensure reliable results, the patient underwent repeated clinical assessments every 20 min (T1-T5) by two independent blinded neurologists through Unified Parkinson's Disease Rating Scale (UPDRS) III subsections and Rush Dyskinesia Rating Scale (see Supplemental Data for details).

The aDBS portable device we used was equipped with an ad hoc algorithm that analyzed patient's LFP beta band power (13-17 Hz) and adapted voltage stimulation linearly each second (Fig. 1A).

The patient during aDBS experienced a more stable condition than during cDBS, with better control of symptoms and dyskinesias over time (Fig. 1; video 1). In particular, aDBS and cDBS improved patient's axial symptoms to a similar extent (Fig. 1B), but compared with cDBS, aDBS significantly improved his main symptom, bradykinesia (Fig. 1C). aDBS did not elicit side effects and was well tolerated.

Because we evaluated the patient a few days after surgery when he probably manifested a stunning effect,<sup>5</sup> the aDBS- and cDBS-induced improvements were lower than those reported by others in follow-up DBS studies.<sup>6</sup> A major clinical achievement was that compared with cDBS, aDBS greatly reduced the patient's dyskinesias during gait and at rest (Fig. 1B; Fig. 1D). Presumably it did so because we designed the adaptive algorithm to avoid dyskinesias related to hyperstimulation: when L-dopa reduced beta-band LFP activity, the voltage linearly diminished, avoiding hyperstimulation.

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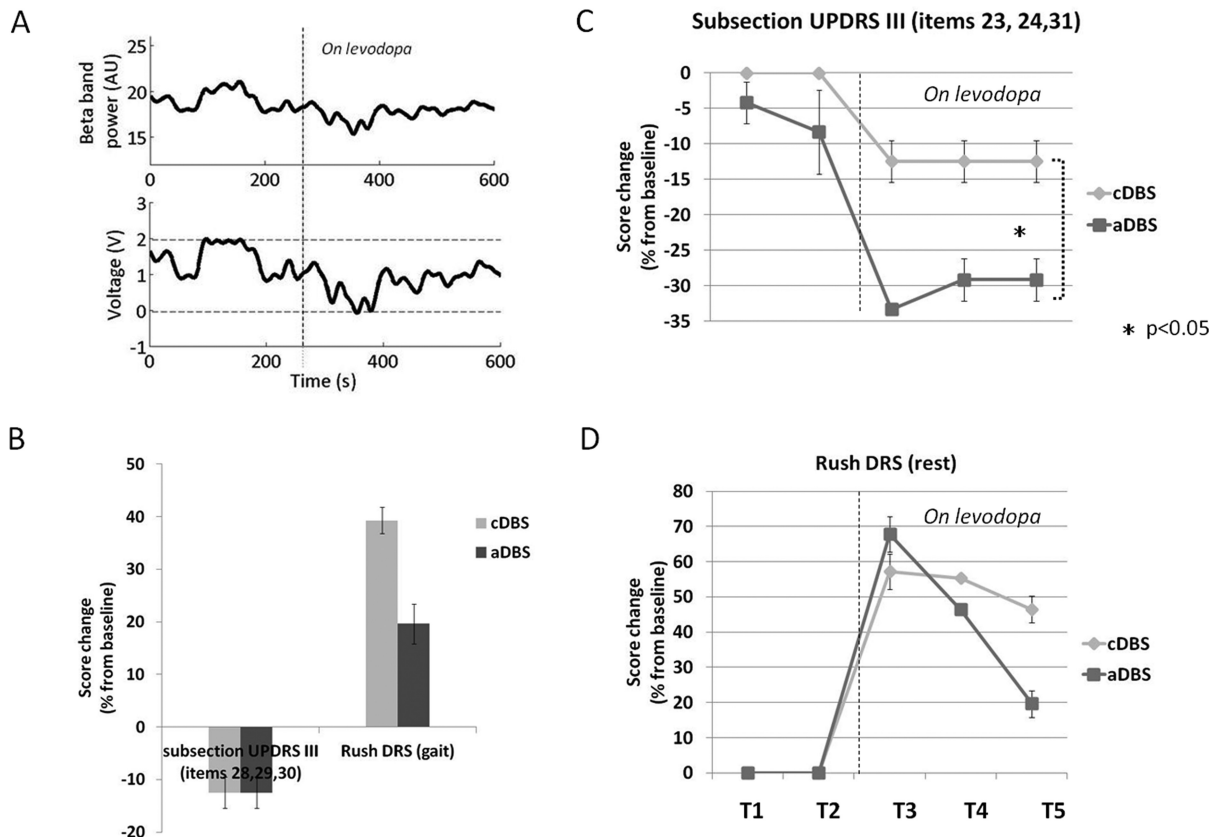
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**FIG. 1.** (A) Sample of aDBS functioning lasting 10 min. Upper panel, the local field potential (LFP) beta band (13-17 Hz) power and below the stimulation voltage. The dotted line represents the time levodopa (L-dopa) took to achieve its clinical effect. The voltage delivered by aDBS followed the beta-band changes: When L-dopa reduced beta-band LFP activity, the voltage linearly diminished. (B) Clinical results for axial symptoms and dyskinesias during gait. Mean Unified Parkinson's Disease Rating Scale (UPDRS) III subsection (items 28, 29, 30) and mean Rush Dyskinesias Rating Scale (DRS) (during gait) percentage score changes from baseline evaluated at T5 (120 min after the experiment began) for cDBS and aDBS. Assessment at T5 showed that the patient's axial symptoms improved to a similar extent after aDBS and cDBS, but dyskinesias during gait reduced more during aDBS than during cDBS. (C) Clinical results for bradykinesia. Mean changes from baseline in the UPDRS III subsection (items 23, 24, 31) percentage score changes from baseline for the upper limb contralateral to the stimulation side for cDBS and aDBS from T1 to T5. The UPDRS III subscore improved significantly more during aDBS than during cDBS (Wilcoxon matched pairs test;  $P < 0.05$ ). (D) Clinical results for dyskinesias at rest. Mean Rush DRS (at rest) percentage score changes from baseline for cDBS and aDBS from T1 to T5. Except at T3, aDBS induced a lower mean Rush DRS increase than cDBS (Wilcoxon matched pairs test;  $P > 0.05$ ) (see Supplemental Data for data analysis details).

Our results, besides corroborating findings reported by Little and colleagues<sup>2</sup> showing that aDBS promises to be more efficient and effective than cDBS, expand them for two important reasons. First, we tested aDBS for a longer observation time than Little et al., and in a more ecological condition (freely moving patient). Second, the personalized algorithm continuously adapts stimulation settings according to LFP beta changes, instead of providing an on-off strategy.

The aDBS device we used here can assess large patient series in real clinical settings, testing different LFP-based adaptive strategies other than those controlled by the beta activity to find the frequency that is more suitable to reflect patient clinical state.<sup>7</sup>

In conclusion, the approach and device we used proved eligible for prolonged use in a freely moving parkinsonian patient and disclosed new opportunities to study aDBS during patients' daily activities, providing new insights into how this novel DBS strategy should improve patients' quality of life. Although we await future studies to confirm our findings and to test other aDBS LFP-based algorithms, our observation is a step toward developing a new

generation of implantable aDBS devices for chronic treatment of PD.

### Video legend

**Video:** The video shows a section of patient clinical assessments performed 120 min after the experiment began (T5) during standard DBS (cDBS) on the left and during adaptive DBS (aDBS) on the right. Standard DBS was delivered at 2 V, 130 Hz, 60  $\mu$ s; aDBS was delivered at a stimulation voltage that automatically changes according to the online LFP beta recording analysis (voltage range, 0-2 V), 130 Hz, 60  $\mu$ s. The video shows the patient during the execution of items 29, 23, 24, and 31 of unified parkinson's disease rating scale (UPDRS) III scale. ■

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## Supporting Data

Additional supporting information may be found in the online version of this article at the publisher's web-site.

## Temporal Processing of Perceived Body Movement in Cervical Dystonia

Patients with idiopathic dystonia exhibit changes in the cognitive processing of movement.<sup>1-3</sup> We showed that patients with writer's cramp are less accurate than normal subjects in temporally predicting perceived handwriting.<sup>4</sup> Whether this is selectively linked to the body area affected by dystonia or is a generalized cognitive feature of dystonia remains unclear. We addressed this issue by applying the same experimental paradigm to patients with focal cervical dystonia (CD).

Fifteen patients with focal CD, aged  $56.2 \pm 13.9$  y and treatment-free for at least 6 mo, and 15 age-matched healthy subjects were recruited in the Department of Neuroscience, University of Genoa. Patients' disease duration was  $9 \pm 6.5$  y, and mean  $\pm$  standard deviation score on the Toronto Western Spasmodic Torticollis Rating Scale was  $14.3 \pm 4.8$ . The experimental paradigm, previously published in Avanzino et al.,<sup>4</sup> consisted of the perception on a screen of two

videos, one showing a right hand writing a sentence (*target* task), and another showing a ball reaching a target (*control* task). After a variable interval from its onset (6, 9, and 12 seconds), videos were darkened. Subjects were asked to indicate when the perceived movement reached its end by clicking on the keyboard space-bar (Supplemental Data). The timing error (Reproduced Interval – Dark Interval), the normalized absolute timing error ( $[(\text{Timing Error}/\text{Dark Interval}) \times 100]$ ), and the coefficient of variability (standard deviation/mean of Reproduced Intervals) were measured and analyzed with a repeated-measures analysis of variance with the factors GROUP, TASK, and DARK INTERVAL.

Repeated-measures analysis of variance showed a significant GROUP\*TASK interaction only for the normalized absolute timing error ( $F[1,28] = 5.85$ ;  $P = 0.022$ ; Fig. 1). On post hoc, this parameter was greater at all dark intervals only in CD patients ( $P = 0.006$ ) and exclusively for the *target* task ( $P = 0.024$ ).

In both groups of subjects, consistently with what was observed in our previous work,<sup>4</sup> the ability to temporally predict the end of the perceived movement was influenced by the duration of the target interval and the type of motion. Shorter dark intervals were associated with a tendency to overestimate the duration of movement ( $F[2,56] = 136.61$ ;  $P < 0.001$ ), greater variability ( $F[2,56] = 50.60$ ,  $P < 0.001$ ), and greater absolute timing error ( $F[2,56] = 26.06$ ;  $P < 0.001$ ). Finally, a tendency to overestimate the duration of movement was observed for the *target* task compared with the *control* task ( $F[1,28] = 6.38$ ,  $P = 0.017$ ). Absolute timing error did not correlate with disease severity (Spearman's  $\rho = -0.161$ ;  $P = 0.58$ ) or duration (Spearman's  $\rho = 0.040$ ;  $P = 0.89$ ).

Our findings suggest that the abnormal timing of visually perceived human body motion is not exclusive to movements topographically related to dystonia. Brain regions relevant to the pathophysiology of dystonia, for example, sensorimotor regions of premotor and parietal cortices and cerebellum, modulate the spatiotemporal prediction of dynamic visual stimuli, and could be involved in the detected abnormality.<sup>5,6</sup> Despite the relatively small sample size, the lack of correlation between timing performance and severity/duration of CD suggests that the observed abnormality may not be a direct expression of the dystonia.

The selectivity of the timing abnormality might depend in part on the difference in complexity between handwriting and the inanimate object motion. However, if motion complexity is the main determinant of implicit timing performance, timing error should decrease at the increase of task complexity also in control subjects, but this was not observed. This notwithstanding, future studies should explore temporal processing of motion in dystonia, using

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