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Short communication

Low-frequency oscillation suppression in dystonia: Implications for adaptive deep brain stimulation

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ABSTRACT

Background: Low-frequency oscillations (LFO) detected in the internal globus pallidus of dystonia patients have been identified as a physiomarker for adaptive Deep Brain Stimulation (aDBS), since LFO correlate with dystonic symptoms and are rapidly suppressed by continuous DBS (cDBS). However, it is as yet unclear how LFO should be incorporated as feedback for aDBS.

Objectives: to test the acute effects of aDBS, using the amplitude of short-lived LFO-bursts to titrate stimulation, to explore the immediate effects of cDBS on LFO-modulation and dystonic symptoms, and to investigate whether a difference in the resting-state LFO is present between DBS-naïve patients and patients with chronic DBS.

Methods: seven patients were assessed during either DBS-implantation (n = 2) or battery replacement surgery (n = 5), and pseudorandomized in three conditions: no stimulation, cDBS, and aDBS. Additionally, resting-state LFP-recordings from patients undergoing battery replacement were compared to those obtained during DBS-implantation; LFP-recordings from a previous cohort of six dystonia patients undergoing DBS-implantation were incorporated into this analysis (total n = 8 newly implanted patients).

Results: we corroborated that a mild LFO-suppression rapidly occurs during cDBS. However, no acute changes in clinical symptoms were observed after cDBS or aDBS. Remarkably, we observed that resting-state LFO were significantly lower in patients who had been effectively treated with chronic cDBS compared to those of newly implanted patients, even when stimulation was suspended.

Conclusions: our results indicate that LFO-suppression in dystonia, similar to symptom response to cDBS, might be gradual, and remain after stimulation is suspended. Therefore, tracking gradual changes in LFO may be required for aDBS implementation.

1. Introduction

Conventional, continuous deep brain stimulation (cDBS) of the internal globus pallidus (GPI) is an advanced treatment for dystonia. Although cDBS is efficacious, it still has some drawbacks. It takes months to find the right programming settings, as dystonia reacts relatively slowly to stimulation [1]. Also, its clinical benefits can be limited, and stimulation-dependent side-effects, such as parkinsonism and dysarthria [1,2], can occur. In order to minimize the impact of stimulation-induced side-effects, while preserving the beneficial effect of stimulation, the development of adaptive DBS (aDBS) for dystonia has been proposed [3]. aDBS aims to reduce the total amount of stimulation by titrating stimulation up or down, according to the presence of dystonic symptoms. In order to predict whether symptoms are present, aDBS requires electrophysiological biomarkers (physiomarkers) that are able to reflect the clinical state of the patients [4]. Up to now, the most promising physiomarker for dystonia is the magnitude of low-frequency oscillations (LFO; 4–12 Hz) embedded in the local field potential (LFP) activity of the GPI. Those oscillations are increased in dystonia [5], and correlate with the severity of dystonic symptoms [4]. However, it is as

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yet unclear how LFO should be incorporated as a feedback signal for aDBS, given that these oscillations present distinctive characteristics at different timescales. On a millisecond timescale, it has been observed that GPI-LFO power gets swiftly suppressed in dystonia patients during cDBS, predominantly in patients with phasic symptoms [6]. However, it is still unclear whether a fast LFO-suppression is synchronous with a reduction in dystonic symptoms during stimulation. On a longer timescale (minutes to hours or more), it has been observed that slow increments in background LFO-power take place in dystonia patients chronically treated with cDBS, after stimulation is suspended [7]. Those increments in LFO are proportional to the return of dystonic symptoms caused by switching off stimulation, which suggests that not only symptoms, but also LFO are chronically suppressed by cDBS. For the aforementioned reasons, aDBS could be programmed to respond either to dynamic changes in LFO-burst amplitude, to fast changes in LFO-power, or to gradual changes in background LFO-power.

In this study, we explore the effects of delivering stimulation at three different timescales in dystonia patients, in order to generate data-driven hypotheses about the incorporation of LFO as feedback signal in aDBS for dystonia. Firstly, we test the immediate effects of burst-based aDBS, in which the amplitude of LFO-bursts is used as feedback signal to dynamically titrate stimulation. Secondly, we explore the acute effects of cDBS, in order to confirm the presence of a LFO-suppression directly after cDBS, and to investigate the relationship between this suppression and dystonic symptoms. Lastly, we estimate the chronic effects of stimulation on LFO-power, by comparing the recordings of DBS-naive patients with those of patients with chronic cDBS.

2. Methods

2.1. No-Stimulation, cDBS and aDBS trials

2.1.1. Patients

Seven dystonia patients who underwent either DBS implantation (n = 2) or battery replacement surgery (n = 5) at the University Medical
Center Groningen, the Netherlands, were included in the study. The protocol was approved by the local ethical committee; all patients provided written informed consent. Patients were operated under local anesthesia, and anti-dystonic medication was suspended at least 12 h before the procedure.

2.1.2. Recordings

LFP-recordings were obtained 20–30 min after intraoperative stimulation testing (DBS-implantation) or 20–30 min after DBS was turned off (battery replacement). The recording procedure lasted approximately 15 min, which has been previously described [6]. In brief, the extension wires that connect to the DBS leads were exposed and attached to a custom-made amplifier (Fig. 1A.2). This amplifier allows for bilateral LFP-recordings, using a bipolar montage from either contacts 0–2 or 1–3, and can simultaneously provide stimulation from either contacts 1 or 2, respectively. Bipolar recordings were obtained at a sampling rate of 2000 Hz, while applying a bandpass filter between 3 and 37 Hz.

Spike2 software (V.8, Cambridge, United Kingdom) was employed for the recordings. For each hemisphere, a baseline recording of approximately one minute was obtained from each bipolar contact (NoStim0) during rest, and periodograms were calculated for each bilateral LFP, in order to identify a low-frequency peak. The contacts selected to further record/stimulate for each hemisphere were chosen based on the contacts that met the most of these conditions: a) contacts that presented the highest low-frequency peak; b) contacts that provided a clear LFP signal; c) contacts that were used in the clinical care (in patients with chronic DBS).

After selecting the contacts, patients were pseudo-randomized into three balanced conditions: no stimulation (NoStim1), cDBS, and aDBS. Conditions were measured sequentially in a crossover fashion and lasted roughly 50% of the maximum amplitude of the smoothed-rectified LFP-aDBS conditions (frequency 135 Hz, pulse width 60 μs). The applied voltage was 9.03 ± 2.4635 V, which has been previously described [9].

2.3. Statistical analysis

A repeated-measures ANOVA was performed using the mean low-frequency power calculated for the NoStim0, NoStim1, cDBS and aDBS conditions. Additionally, due to the exploratory nature of this study and the limited power of our pilot sample to detect differences at a group comparison level, additional pairwise comparisons were performed between conditions using permutation dependent t-tests. Mean low-frequency power between new-implantation and battery-replacement patients was compared using permutation independent t-tests. BFMDRS and TWSTRS scores were compared among conditions using repeated-measures ANOVA and additional explorative pairwise dependent t-tests between conditions were performed. All units are reported in means ± standard error of the mean (SEM).

3. Results

Patient information is presented in Table 1. Two GPI-LFP-recordings, each from a different patient, were discarded due to the presence of cardiac artefacts that interfered with aDBS. The group analysis (n = 12) among stimulation conditions (NoStim0, NoStim1, cDBS and aDBS) did not reach significance [condition: F(3,33) = 2.27; p = 0.097]. Pairwise comparisons between conditions showed a mild but significant mean low-frequency power suppression during cDBS, compared to NoStim0 (Fig. 1B) [mean difference: -0.39 ± 0.17 a.u.; t (11) = -2.2282; p = 0.0477]. The rest of the pairwise comparisons were not significant (Fig. 1C–D, Supplementary Table 1). All patients tolerated aDBS at similar voltages used for cDBS. The total amount of stimulation during aDBS was 43.05 ± 16.8% of that during cDBS. No acute changes in BFMDRS and TWSTRS scores were observed among conditions (Supplementary Table 2-4) [BFMDRS-condition F (2,8) = 2.25; p=0.1678; TWSTRS-condition F (2,6) = 1; p=0.421], and pairwise comparisons were not significant.

Mean low-frequency power in patients with chronic DBS (5.73 ± 10^−3 ±9.24 × 10^−1 z-scores) was significantly lower to that of DBS-naïve patients (9.03 × 10^−3 ±9.24 × 10^−1 z-scores, Fig. 1D) [t (22) = 2.4635, p=0.0221].

4. Discussion

In this study, we explored the effects of delivering stimulation at three different timescales in dystonia patients. Firstly, we observed that aDBS based on LFO-bursts did not lead to an acute change in either LFO-power or dystonic symptoms. Given the delayed response of dystonia to stimulation [1], it is possible that fast LFO-components are not able to directly reflect the clinical dystonic state. However, the long-term effects of targeting LFO-bursts still need to be explored. Secondly, we tested the acute effects of cDBS on LFO-power and dystonic symptoms. We confirmed that cDBS can swiftly suppress aberrant GPI-LFO [7].
Table 1
Clinical details of patients with dystonia included in this pilot study.

| Pt. | Age | Sex | Dystonia type | Disease duration (y) | Years with DBS | Type of operation | Antidystonic Medication | BFMDRS PRE/POST<sup>a</sup> | TWSTRS PRE/POST<sup>b</sup> | DBS parameters<sup>c</sup> | Channels used for recording |
|-----|-----|-----|---------------|---------------------|-----------------|-----------------|----------------------|--------------------------|--------------------------|------------------|-----------------------|
| Dys aDBS-GPi 1 | 65 | F | Blepharospasm and oromandibular dystonia (Meige’s syndrome) | 9 | 5 | Battery replacement | Botulinum toxin every 10 weeks | 22/13.5 | 14/9 | L: 0/C; 1.5 V; 80 Hz; 300 μs | L: 0-2 |
| | | | | | | | | | | R: – 3/C; 2.0 V; 60 Hz; 80 μs | R: 1-3 |
| Dys aDBS-GPi 2<sup>d</sup> | 64 | M | Segmental dystonia + Parkinson’s disease | 4 | 0 | New implantation | Botulinum toxin every 2 months | 8/5 | 19/18 | L: 0/C; 3.5 V; 135 Hz; 90 μs | L: 1-3 |
| | | | | | | | | | | R: – 2/C; 3.5 V; 135 Hz; 90 μs | R: 1-3 |
| Dys aDBS-GPi 3<sup>e</sup> | 55 | M | Segmental dystonia (torticollis) | 5 | 2 | Battery replacement | Clonazepam | 23/14.25 |  | L: 0/C; 3.8 V; 135 Hz; 90 μs | L: 0-2 |
| | | | | | | | | | | R: 0/C; 3.7 V; 135 Hz; 90 μs | R: 0-2 |
| Dys aDBS-GPi 4 | 69 | F | Blepharospasm and oromandibular dystonia (Meige’s syndrome) | 4 | 0 | New implantation | Oxazepam | 24/24 | 17/16 | L: 0/3; 3.0 V; 135 Hz; 60 μs | L: 0-2 |
| | | | | | | | | | | R: 0/3; 3.0 V; 135 Hz; 60 μs | R: 0-2 |
| Dys aDBS-GPi 5 | 83 | F | Segmental dystonia (torticollis) | 28 | 14 | Battery replacement | Clonazepam, Pregabalin | 9/6.5 | 19/16 | L: 0/C; 5.0 V; 130 Hz; 60 μs | L: 1-3 |
| | | | | | | | | | | R: – 2/C; 5.0 V; 130 Hz; 60 μs | R: 1-3 |
| Dys aDBS-GPi 6 | 67 | F | Oromandibular dystonia | 9 | 3 | Battery replacement | Clonazepam | 17/18.25 |  | L: 0/C; 3.5 V; 130 Hz; 90 μs | L: 1-3 |
| | | | | | | | | | | R: – 2/C; 3.5 V; 130 Hz; 90 μs | R: 1-3 |
| Dys aDBS-GPi 7 | 53 | F | Generalized dystonia | 25 | 3 | Battery replacement | Oxazepam, Trihexyphenidyl, Botulinum toxin | 63.75/44.75 |  | L: 0/1; 4.0 V; 130 Hz; 60 μs | L: 1-3 |
| | | | | | | | | | | R: – 0/1; 3.5 V; 130 Hz; 120 μs | R: 0-2 |
| Previous cohort dystonia patients | | | | | | | | | | | | |
| Dys-GPi 1 | 47 | M | Generalized (secondary) + spastic hemiparesis | 11 | 0 | New implantation | Lorazepam | 49/53 |  | L: – 1/C; 2.2 V; 135 Hz; 90 μs | L: 0-2 |
| | | | | | | | | | | R: – 0/C; 2.2 V; 135 Hz; 90 μs | R: 0-2 |
| Dys-GPi 2 | 52 | M | Segmental dystonia (torticollis) | 3 | 0 | New implantation | Clonazepam | 23/14.25 |  | L: 0/C; 3.8 V; 135 Hz; 90 μs | L: 0-2 |
| | | | | | | | | | | R: – 0/C; 3.7 V; 135 Hz; 90 μs | R: 0-2 |
| Dys-GPi 3 | 52 | F | Segmental dystonia (Myoclonus-dystonia) | 33 | 0 | New implantation | Propranolol, zolpidem | 25.25/12 | 22.5/17.5 | L: – 1/C; 3.2 V; 130 Hz; 60 μs | L: 0-2 |
| | | | | | | | | | | R: – 1/C; 3.1 V; 130 Hz; 60 μs | R: 0-2 |
| Dys-GPi 4 | 63 | M | Cervical dystonia | 20 | 0 | New implantation | Clonazepam | 19.5/11.25 | 16.5/13.5 | L: – 0/1; 3.6 V; 130 Hz; 60 μs | L: 0-2 |
| | | | | | | | | | | R: – 0/1; 3.6 V; 130 Hz; 60 μs | R: 0-2 |
| Dys-GPi 5 | 63 | M | Segmental dystonia (torticollis and oromandibular) + Holmes tremor | 63 | 0 | New implantation | Clonazepam | 13.75/5 | 20/8.5 | L: – 1/C; 3.4 V; 180 Hz; 60 μs | L: 0-2 |
| | | | | | | | | | | R: – 3/C; 3.2 V; 130 Hz; 90 μs | R: 1-3 |
| Dys-GPi 6 | 65 | F | Segmental dystonia (torticollis) | 12 | 0 | New implantation | – | 15.25/12 | 22/13 | L: – 0/C; 3.2 V; 135 Hz; 90 μs | L: 0-2 |
| | | | | | | | | | | R: – 0/C; 2.7 V; 135 Hz; 90 μs | R: 0-2 |

<sup>a</sup> Years in which patients have been treated with DBS at the moment of battery replacement.<sup>b</sup> Post-operative scores were obtained one year after DBS treatment.<sup>c</sup> Parameters used for cDBS in the clinical setting at the moment of battery replacement, or one year after implantation for patients measured during DBS-implantation.<sup>d</sup> This patient was included due to the presence of prominent segmental dystonia, which led to choose the internal globus pallidus as the DBS target, instead of the subthalamic nucleus. <sup>e</sup> This patient is the same as Dys-GPi 2.
result supports the hypothesis that DBS modulates pathological low-frequency synchronization in the motor network [5]. However, this acute LFO-suppression is initially subtle and might not be followed by a direct change in symptom severity. Lastly, we observed that the LFO of patients who had been chronically treated with cDBS were considerably lower than those of DBS-naïve patients, even when stimulation was suspended. From all the patients treated with chronic cDBS, most of them (4/5) presented more than the minimal clinically important improvement in dystonic symptoms [11] one year after DBS implantation. Since LFO are correlated with the severity of dystonic symptoms [4], it is possible that the LFO-suppression that takes place during cDBS occurs in a gradual manner, parallel to the gradual reduction in dystonic symptoms observed after cDBS is switched on.

The re-emergence of LFO after cDBS is suspended also occurs in a gradual manner [8]. Barow et al. showed that LFO remain suppressed shortly after stimulation is applied [7]. In our study, we observed that the OFF LFO-power of patients measured after pseudo-randomization (NoStim1) was slightly lower than before pseudo-randomization (NoStim0, Fig. 1C). This can be explained by the fact that in some patients the cDBS condition preceded the NoStim1 condition. This poststimulation effect becomes more apparent when chronic stimulation is suspended, since the LFO of dystonia patients increase only gradually over a period of several hours, if symptoms increase accordingly [8]. Therefore, stimulation algorithms designed to track gradual changes in oscillatory power [12] can be tested in aDBS for dystonia (Supplementary Figure 2).

4.1. Limitations

The results obtained are preliminary, since a small patient sample was included, and only the acute effects of aDBS were explored. Similar to other studies involving LFP-recordings in dystonia, the patient group included is heterogeneous. Nevertheless, dystonic symptoms and prominent LFO were present in all patients. Prospective studies are required to explore the chronic within-subjects effect of both cDBS and aDBS on LFO and dystonic symptoms, in order to corroborate the claims provided here. However, the results obtained in this study are useful to generate data-driven hypotheses regarding the configuration of future aDBS systems for dystonia.

5. Conclusion

LFO-suppression in dystonia, similar to symptom response to DBS, might be gradual, and remain after stimulation is suspended. Therefore, tracking gradual changes in LFO may be required for aDBS implementation. Future sensing aDBS devices will allow to explore the temporal relation between chronic LFO-suppression and dystonic symptoms [12].

Authors’ roles

DPF: 1ABC, 2AB, 3A; MB: 1ABC, 2AC, 3B; JCvZ: 1C, 3B; MEvE: 1C, 3B; DLMo: 1BCE, 3A; JMcvD: 1ABC, 3B; MAJT: 1ABC, 3B.

1) Research project: A. Conception, B. Organization, C. Execution;
2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
3) Manuscript: A. Writing of the first draft, B. Review and Critique.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2020.08.030.

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