Local Field Potential-Based Programming: 
A Proof-of-Concept Pilot Study

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ABSTRACT

Objectives: Programming deep brain stimulation (DBS) is still based on a trial-and-error approach, often becoming a time-consuming process for both treating physicians and patients. Several strategies have been proposed to streamline DBS programming, most of which are preliminary and mainly address Parkinson’s disease, a condition readily responsive to DBS adjustments. In the present proof-of-principle pilot study, we successfully demonstrate that local field potential (LFP)-based programming can be an effective approach when used for DBS indications that have a delayed temporal onset of benefit.

Materials and Methods: A recently commercialized implantable pulse generator (IPG) with the capability to non-invasively and chronically stream live and/or record LFPs from a DBS electrode after implantation was used to program one pediatric patient with generalized dystonia and an adult with seizures refractory to multiple medications and vagal nerve stimulation.

Results: The IPG survey function detected a peak in the delta range (1.95 Hz) in the left globus pallidus of the first patient. This LFP was detected when recording in the brain area adjacent to contacts 9 and 10 and absent when recording from other areas. The chronic recording of the 1.95 Hz LFP with two sets of stimulation showed a greater power increase with the settings associated with a worsening of dystonia. Broadband LFP home recording of “absence seizure” and “focal/partial seizure” was used in the second patient and reviewer with the IPG “timeline” and “event” functions. The chronic recording of the 2.93 Hz and 8.79 Hz (spit sensing) showed a reduced power with the stimulation setting associated with seizure control.

Conclusions: The approach presented in this pilot proof-of-concept study may inform and streamline the DBS programming for conditions requiring clinicians and patients to wait weeks before appreciating any clinical benefit. Prospective studies on larger samples of patients are warranted.

Keywords: Deep brain stimulation, local field potential, neuromodulation, percept, programming

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[Correction added on September 6, 2021, after first online publication: The copyright line was changed.]
INTRODUCTION

Deep brain stimulation (DBS) is now the standard of care for many neurological and psychiatric conditions. However, to date DBS programming is based on a trial-and-error approach, often becoming a time-consuming process for both treating physicians and patients. Several attempts have been made to streamline DBS programming including but not limited to clinical algorithms, volume of tissue activated (VTA)-based software, functional magnetic resonance imaging (fMRI)-based paradigms, and approaches using the patient’s programmer. Although some have provided promising results, most of these strategies are preliminary and mainly address Parkinson’s disease (PD), a condition in which DBS adjustments mostly target motor symptoms and translate into a clinical effect within a few minutes of changing stimulation parameters. In contrast, for some conditions—particularly dystonia and epilepsy—clinicians and patients need to wait days or weeks before appreciating any clinical benefit, thus causing further challenges with the programming process in terms of complexity and time.

Over the past decade, DBS research has expanded our understanding of the biological meaning of neuronal recording using chronically implanted electrodes. Those signals have been interpreted in terms of local field potentials (LFP), also providing researchers with a framework to use them as immediate biomarkers of particular states. A typical example is represented by oscillations in the beta frequency band recorded in PD patients during the off-L-dopa state, which is now used as a biomarker of bradykinesia and rigidity. Indeed, both L-dopa and DBS have been shown to reduce the beta band; that is, the lower its power the better the motor condition of each individual patient. Recent studies have also clarified that the highest beta power is more represented in the areas within the subthalamic nucleus where DBS will be most effective, as shown by analyzing the LFP distribution in patients implanted with segmented leads for directional stimulation.

In the present proof-of-principle pilot study, we successfully demonstrate that LFP-based programming can be an effective approach when used for indications that have a delayed temporal onset of benefits, such as dystonia and epilepsy. In addition, we show that currently available LFP-based technology can be used to confirm the efficacy of different programming parameters when tested by the patients themselves outside the hospital setting at home.

MATERIALS AND METHODS

This study was made possible by the recent commercialization of an implantable pulse generator (IPG) with the capability to non-invasively and chronically stream live and/or record LFP from DBS electrodes after implantation (Percept by Medtronic, Dublin, IR). The broad spectrum of LFP was recorded in clinic with the “survey” function or at home, triggered by the “event” recording on the patient’s programmer. Each triggered event measures 30 sec of LFP time-domain data (250 Hz sampling rate), although only the average frequency domain content is stored. Specific LFPs of interest were instead chronically recorded (±2.5 Hz) using the “timeline” function. In addition, a JSON file was downloaded for further analysis, which was analyzed on Matlab 2020R, whereby a unitless representation of LFP power of the specified sensing frequency band (“LFP Trend Logs,” averaged value measured over 10-min intervals) was plotted over time. We also localized electrodes and modeled corresponding volumes of tissue activation (VTAs) for each patient. This was performed using Lead-DBS v2.0 software (https://www.lead-dbs.org/) according to our previously published methods. Briefly, electrodes were localized using patients’ post-operative imaging, before being transformed to standard (Montreal Neurological Institute) space. Each patient’s individual stimulation settings were then used for VTA modeling.

RESULTS

The first patient is an 11-year-old girl with generalized dystonia of unknown etiology. In spite of negative whole exome sequencing, her dystonia was considered of probable genetic origin given the absence of perinatal complications and parents’ consanguinity. At the age of six months, she presented with generalized hypotonia and global developmental delay. Dystonia of the trunk, neck, and upper limbs started six months later and progressed over the years, causing failure to thrive (she weighed 12 kg at age 11). Due to the failure of multiple medications (baclofen, chloral hydrate, benzodiazepines, clonidine, tetraabenzine, and trihexyphenidyl), she underwent DBS of the globus pallidus internus (GPi) while in the hospital for a refractory status dystonicus (Fig. 1a). Programming was started within days of implantation as only a marginal lesional effect was noticeable after surgery. The IPG survey function was used to detect any potential LFP peak of interest during the ongoing dystonic state. Particularly on the left GPi a peak in the delta range (1.95 Hz) was shown when recording in the brain area adjacent to contacts 9 and 10 (Fig. 1b).

The initial programming settings were case +1–3.7 mA/60 μsec/160 Hz (0 and 2 were sensing) on the right and case +9–3.7 mA/60 μsec/160 Hz (8 and 10 were sensing) on the left. This setting resulted in a dramatic improvement of the generalized dystonia (Supplementary Data Video S1).

Given the symmetrical placement of the electrodes, we chose contact 1 for the right GPi, which corresponds to contact 9 on the left. Given the presence of a delta peak in areas adjacent to contacts 9 and 10, we also created an additional set of parameters testing contacts 1 and 10 using the same parameters, except that 9 and 11 were now sensing. This new program resulted in a worsening of dystonia (Supplementary Data Video S2), which was also confirmed by the chronic recording of the 1.95 Hz LFP (Fig. 1c). The patient was readily switched back to program A with rapid improvement of dystonia, and she has been on this setting ever since.

The second patient is a 21-year-old man with focal seizures with secondary generalization of unknown etiology that began at the age of 14 years. Prior to consideration for DBS, he underwent an extensive work-up including admission in the epilepsy monitoring unit. Generalized seizures typically began with polymorphic theta activity for 2 sec in both hemispheres simultaneously, followed by a burst of ictal alpha activity, frontally accentuated, lasting a few seconds, after which rhythmic high-amplitude delta waveforms in the 1.5 Hz range appeared bilaterally, more prominently on the left. Then the seizure evolved into a theta/delta combination bilaterally, eventually settling into an ictal theta rhythm in the left hemisphere and an ictal beta rhythm in the right hemisphere, increasing in amplitude and slowing in frequency bilaterally, till the seizure ended a few seconds later. Interictically, the most common epileptiform discharges were in the form of bisynchronous
DISCUSSION

DBS programming for conditions such as dystonia and epilepsy, where the response to stimulation is delayed, provides a unique challenge for both clinicians and patients. For clinicians the delay to identify benefit potentially increases the complexity of programming and the time required to identify optimal programming settings even when employing algorithms as we have described in the past for dystonia and more recently for epilepsy (A. Fasano et al., 2021). In keeping with a method recently proposed (A. Fasano et al., 2021), we created four programs of settings, combining parallel sets of contacts (group A: case +, 2– and 10– for right and left hemisphere respectively; group B: case +, 1– and 9–; group C: case +, 0– and 8–; group D: case +, 3– and 11–). Utilizing parameters from the SANTE trial, we cycled DBS 1 min ON and 5 min OFF using 5 mA/90 μ/145 msec.

Sensing was only possible for group A (1 and 3 sensing at 2.93 Hz, 9 and 11 sensing at 8.79 Hz) and group B (0 and 2 sensing at 2.93 Hz, 8 and 10 sensing at 8.79 Hz). In both cases, we used “split sensing” to detect the course of both absence and focal seizures. Split sensing allows for the recording of different LFPs, one per hemisphere.

The patient was asked to change the program every two weeks and was then re-evaluated two months after. The most effective group was C (reduction of episodes by focal seizures by 90% and absence seizures by 98%), followed by B (reduction of 90% in focal seizures and absence seizures), A, and D. The analysis of the IPG timeline could not be performed for group C but confirmed the superiority of B over A (Fig. 2c). Interestingly, group B was particularly superior for absence control while A was equally effective on focal seizures.

Figure 1. Patient 1—dystonia. a. Electrodes and corresponding VTAs for the GPi-DBS patient for stimulating groups A and B. VTAs (red) are shown in relation to thalamic nuclei: anterior (orange), mediodorsal (light blue), lateral dorsal (green), lateral pulvinar (blue), lateral posterior (purple). b. The IPG survey function detected a peak in the delta range (1.95 Hz) in the left GPi (no ongoing stimulation), which was shown when recording in the brain area adjacent to contacts 9 and 10 (upper row) and absent when recording from other areas (lower row). LFP magnitude (μVp, range: 0.12–4.64) is expressed on the y axis while LFP frequency is on the x axis (Hz). c. Chronic recording (ongoing stimulation) of the 1.95 Hz LFP with groups A and B showing greater power with the latter, also associated with a worsening of dystonia (see text for details). *Representation of the LFP (μVp) range: 0.12–4.64 expressed on the x axis while LFP frequency is on the y axis.

In keeping with a method recently proposed (A. Fasano et al., unpublished data)—and inspired by our algorithm for dystonia programming—we created four programs of settings, combining parallel sets of contacts (group A: case +, 2– and 10– for right and

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unpublished data). For patients this complexity manifests in potential delays to benefit and multiple trips for programming. With limited face time with clinicians, patients may also find it challenging to relate to the team symptomatic improvements that are slow to manifest. Here we propose utilizing objective chronic LFPs from the patient’s IPG to guide programming in conditions that have delayed benefit. In both patients, we were able to record LFPs of different power spectral bands of interest. These LFPs were informed by screening the wide range available and attempting to correlate spectra with examination in the case of dystonia or self-reported events in the case of seizures. Using these LFPs, we were able to identify potential ideal contacts for stimulation and importantly continue to monitor patients for improvement or further events.

The major limitation in our report is that we only report on two cases, and thus further prospective studies will be needed to identify whether this approach results in more efficient programming with the identification of the most optimal contact for stimulation sooner. Similarly, it will be important to assess whether the requirement to actively record events provides an additional burden for patients and their caregivers as this additional autonomy does not always translate into improved quality of life for patients. In addition, patient-driven event capture requires buy-in from the patient, and even with motivated patients this may prove difficult when the patient’s condition may preclude recording important events (eg, a seizure). Technical limitations include the inability of the device to record LFP from all contacts and not all the time. For example, in our first patient we observed the unilateral increase of pathological LFPs from the right GPi during the first survey. Likewise, we could not record any LFP with the most effective settings in our second patient (group C). Lastly, for many conditions that respond in a delayed fashion to DBS adjustments, there is limited data on what the best LFP biomarker should be. This includes not only dystonia and epilepsy, but also psychiatric indications and pain. Interestingly, in our first patient we observed the unilateral increase of pathological LFP in the absence of clinical worsening immediately before changing the DBS setting (Fig. 1c). In addition, we found that some groups modulated the different LFPs in a different manner (eg, group B was particularly superior for absence control while A was equally effective on focal seizures), although the difference was not captured by the patient and his family. The neurobiological meaning of these observations requires further studies.

In spite of all these limitations, the approach presented in this pilot proof-of-concept study may inform and improve DBS programming both for the clinician and the patient. In addition to improving the efficiency for programming DBS for conditions with delayed therapeutic response, this approach may also reveal biomarkers that are amenable to “closing the loop.” Given the less frequent indications that may benefit from the approach outlined in our study, it will be necessary to advocate for multicenter trials to identify the most reliable LFP markers to record for a given condition and work together to optimize programming algorithms. Lastly, it will be most important to understand objectively whether this approach will improve the patient and caregiver experience during programming or add further burden.

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Authorship Statements

Alfonso Fasano was responsible for the study conceptualization, funding acquisition, project administration, and writing the original draft of the manuscript. Suneil K. Kalia was responsible for the study conceptualization and writing, review, and editing of the manuscript. Carolina Gorodetsky and Darcia Paul were responsible for data curation. Carolina Gorodetsky, Han Yan, and Sara Breitbart were responsible for the formal analysis. Andres M. Lozano and George M. Ibrahim supervised the study. Aaron Loh and Jürgen Germann visualized the study. Peter L. Carlen, Andres M. Lozano, and George M. Ibrahim were responsible for the writing, review, and editing of the manuscript. All authors approved the final version of the manuscript.

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REFERENCES

COMMENT
One of issues confronting deep brain stimulation (DBS) is the lack of closed loop neurostimulation utilizing neurophysiological biomarkers. There is scant literature concerning local field potentials as a biomarker and any report is useful.

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