The Effects of Levodopa and Deep Brain Stimulation on Subthalamic Local Field Low-Frequency Oscillations in Parkinson’s Disease

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LF modulations were related to electrode impedances. LF power increased during DBS, after levodopa intake and under both experimental conditions combined. The LF power increase correlated with the levodopa-induced clinical improvement and the higher the electrode impedance, the greater was the LF power change. These data suggest that the LF band could be useful as a control neurosignal for developing novel adaptive DBS systems for patients with PD.

Key Words
Deep brain stimulation • Levodopa • Local field potentials • Low frequency • Parkinson’s disease • Subthalamic nucleus

Abstract
New adaptive systems for deep brain stimulation (DBS) could in the near future optimize stimulation settings online so as to achieve better control over the clinical fluctuations in Parkinson’s disease (PD). Local field potentials (LFPs) recorded from the subthalamic nucleus (STN) in PD patients show that levodopa and DBS modulate STN oscillations. Because previous research has shown that levodopa and DBS variably influence beta LFP activity (8–20 Hz), we designed this study to find out how they affect low-frequency (LF) oscillations (2–7 Hz). STN LFPs were recorded in 19 patients with PD during DBS, after levodopa medication, and during DBS and levodopa intake combined. We investigated the relationship between LF modulations, DBS duration and levodopa intake. We also studied whether LF power depended on disease severity, the patient’s clinical condition and whether disease progresion.

Introduction
Despite its established effectiveness in treating advanced Parkinson’s disease (PD) \cite{1–6}, deep brain stimulation (DBS) often leaves motor (dyskinesia, dystonia and akinesia) and cognitive dysfunctions uncontrolled. Although DBS improves the motor fluctuations related to fluctuations in levodopa levels, long-term intervention is necessary to achieve clinical stability and control of the disease.

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motor blocks) and nonmotor fluctuations (sweating, akathisia, fatigue, anxiety and mental slowness) only partially controlled. DBS decreases motor fluctuations in only 60% and nonmotor fluctuations in about 50% of patients [7]. A possible explanation for this limitation is that even though PD motor disturbances fluctuate, DBS is delivered with constant settings (reprogrammable only at follow-up visits). One way to improve the clinical results would therefore be to develop neuromodulatory strategies based on a neurosignal that could adapt moment-by-moment (online) to the individual patient’s clinical condition. Previous studies have suggested that STN LF rhythms oscillate in response to levodopa medication and increase with DBS – the subthalamic nucleus (STN) [1]. STN LFP oscillations are specifically modulated during movement, during cognitive and behavioral tasks, and by various treatments [3, 9, 11, 13–26]. Pathophysiological LFP rhythms recorded from the STN in parkinsonian patients oscillate in the low-frequency (LF) band (2–7 Hz) [15], beta band (8–30 Hz) [19, 20], gamma band (60–90 Hz) [27] and high-frequency band (>200 Hz) [28–30]. LFPs remain stable weeks after DBS electrode implantation [9]. For all these reasons, LFPs have been proposed as potential control variables to adjust DBS settings online according to the patient’s clinical condition [8]. The specific LFP bands suitable for use as a control neurosignal for adaptive DBS devices remain to be explored and identified. Candidate rhythms should satisfy several criteria: they should consistently change in all patients during DBS, they should reflect the patient’s clinical condition and they should also persist over time after DBS electrode implantation. The beta frequency band, though decreased by DBS and dopaminergic therapy [3, 13, 18–20], is not invariably present and correlates poorly with the various motor disturbances in PD, including dyskinesias. These limitations prompted the search for additional or alternative LFP rhythms to be used as a control signal. For all these reasons, LFPs have been proposed as potential control variables to adjust DBS settings online according to the patient’s clinical condition, and whether LF power modulations were related to electrode impedances. To do so, we recorded STN LFPs when DBS was turned on, after levodopa intake and when DBS and levodopa intake were combined, in a sample of 19 patients with advanced PD undergoing DBS.

**Patients and Methods**

**Patients**

Nineteen patients (6 women) with advanced idiopathic PD were bilaterally implanted with DBS electrodes (model 3389, Medtronic, Minneapolis, Minn., USA) in the STN at the Functional Neurosurgery Unit of the IRCCS Istituto Galeazzi and at the Neurosurgery Unit at the Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico of Milan, Italy. All patients fulfilled the specific inclusion criteria for DBS treatment and were studied after they had provided informed consent and we had received institutional review board approval [34]. The study conformed to the Declaration of Helsinki. The clinical details of each patient are presented in table 1.

**Surgical Procedures**

STN coordinates were obtained by direct visualization through a computerized tomographic magnetic resonance imaging (CT-MRI) fusion-based technique before surgery. The STN position was estimated by matching the CT-MRI fused images with a digitized stereotactic atlas. During surgery, the implant position was adjusted with microrecordings and by clinically assessing the effects induced by stimulation [12, 35]. The implanted 3389 Medtronic electrode has four cylindrical contacts (1.27 mm in diameter, 1.5 mm in length, placed 2 mm apart, center-to-center) denominated 0–1–2–3, beginning from the more caudal contact. The electrode position details are reported in table 2. To verify the accuracy of the final DBS electrode position, a postoperative MRI scan was acquired in all patients [35].

**Experimental Protocol and LFP Recordings**

LFP activity was recorded in 19 patients with PD 3 days after electrode implantation while the leads were still accessible before being connected to the subcutaneous pulse generator. Each postoperative experimental session lasted approximately 1 h during which patients sat comfortably in an armchair. The experimental session began after overnight withdrawal of antiparkinsonian medication (levodopa).

To verify changes in LFPs induced by levodopa intake and DBS combined in relation to timing, we set up two experimental protocols. In the first protocol DBS preceded levodopa intake (DBS-dopa protocol, 13 patients, 5 men, fig. 1a), in the second, DBS followed levodopa intake (dopa-DBS protocol, 6 patients, 5 men, fig. 1b). The DBS-dopa protocol comprised 4 steps – baseline: a 5-min LFP recording before stimulation and without levodopa (med off-stim off); DBS on: a 10-min LFP recording during DBS and without levodopa (med off-stim on); levodopa intake with DBS turned on: a 10-min LFP recording after patients had reached the levodopa on condition with DBS turned on (med on-stim on), and DBS off and levodopa on: a 5-min LFP recording after DBS.
was turned off and the patients were still on levodopa (med on-stim off) (fig. 1a).

The dopa-DBS protocol comprised the following 3 steps – baseline: a 5-min LFP recording before stimulation and without levodopa (med off-stim off), DBS on and levodopa on: a 10-min LFP recording during DBS and levodopa on (med on-stim on), and levodopa on with DBS turned off: a 10-min LFP recording after DBS was turned off and the patients were still on levodopa (med on-stim off) (fig. 1b). To avoid prolonging the experimental session further we only obtained med off-stim on recordings during the first protocol. This was because patients needed time to recover from the levodopa effect and also because our primary aim, the effect of levodopa and DBS combined on STN LF oscillations, was mainly expressed in the med on-stim on condition.

To distinguish between the clinical effects induced by levodopa and DBS we only stimulated the nucleus contralateral to the most affected body side in each patient. LFPs were recorded unilaterally from the stimulated side. The optimal stimulation intensity was set according to the stimulation threshold represented by the highest stimulation intensity that induced therapeutic effects without side effects. The threshold was established by an experienced neurologist on the most affected side and, in general, resembled that seen in the intraoperative monitoring procedures.

Monopolar STN-DBS was delivered through the electrode contact positioned in the optimal functional target, contact 1, and differential LFP recordings were acquired between contacts 0 and 2 in the stimulated side through the FilterDBS device for artifact-free LFP recordings during ongoing DBS [36]. Impedance in the recording contact pair was evaluated through an impedance meter at 30 Hz (Model EZM 4, Grass Technologies, West Warwick, R.I., USA) before the recording session [37]. For electrical stimulation we used a constant voltage stimulator (Dual Screen, Medtronic) and DBS was delivered with a pulse width of 60 µs, frequency of 130 Hz and intensity previously tested as the optimal stimulation. Levodopa was given at a clinically effective dose according to the individual patient’s therapy (table 1).

### Table 1. Clinical details of patients included in the study

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Years of disease</th>
<th>UPDRS III before surgery</th>
<th>Levodopa equivalent dose before surgery mg/day&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Dopamine agonist before surgery</th>
<th>Enzymatic inhibitor before surgery&lt;sup&gt;2&lt;/sup&gt;</th>
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<tr>
<td>2</td>
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<td>F</td>
<td>8</td>
<td>17</td>
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<td>F</td>
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<tr>
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<td>48</td>
<td>M</td>
<td>8</td>
<td>25</td>
<td>925</td>
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<td>carbidopa</td>
</tr>
<tr>
<td>6</td>
<td>62</td>
<td>M</td>
<td>16</td>
<td>26.5</td>
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<td>–</td>
<td>carbidopa, rasagiline</td>
</tr>
<tr>
<td>7</td>
<td>67</td>
<td>M</td>
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<td>50</td>
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<tr>
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<td>M</td>
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<td>35</td>
<td>960</td>
<td>pramipexole</td>
<td>carbidopa, entacapone</td>
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</table>

**UPDRS** = Unified Parkinson’s Disease Rating Scale.

1 Represents the sum of levodopa and dopamine agonist. Dopamine agonist equivalent doses were calculated with the following equivalences: 100 mg levodopa = 2 mg apomorphine = 1 mg pergolide = 1.5–2 mg cabergoline = 1 mg pramipexole = 10 mg bromocriptine = 5 mg ropinirole [25].

2 Involved in degrading levodopa: catechol-O-methyl transferase inhibitor, monoamine oxidase inhibitor and dopa decarboxylase inhibitor.

Subthalamic LF Oscillations

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Table 2. Electrode position of patients included in the study

<table>
<thead>
<tr>
<th>Patient</th>
<th>Stimulated side</th>
<th>Target coordinates, mm</th>
<th>Voltage stimulation</th>
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<tr>
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<td>right</td>
<td>10.7 2.3 2.6</td>
<td>3.5</td>
</tr>
<tr>
<td>3</td>
<td>left</td>
<td>10.8 2.8 2.7</td>
<td>2.5</td>
</tr>
<tr>
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<td>10.6 2.7 4.2</td>
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<tr>
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<td>4.0</td>
</tr>
<tr>
<td>11</td>
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<td>11.9 3.8 3.2</td>
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<td>10.2 2.8 4.2</td>
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<td>12.6 4.0 3.8</td>
<td>4.0</td>
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<tr>
<td>19</td>
<td>right</td>
<td>12.0 2.1 3.2</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Target coordinates related to the final position of contact 0. Target coordinates were accorded to the anterior commissural-posterior commissural line and midcommissural point. X = Lateral from midline; Y = posterior from midcomissural point; Z = ventral to anterior commissural-posterior commissural line.

electrodes (RedDot, 3M, Maplewood, Minn., USA) placed on the left and right supraclavicular areas were used as recording and stimulation references. The recorded signals were amplified (×50,000) and filtered (0.5–45 Hz) through the FilterDBS system, then digitized through a USB-6251 multifunctional device with 8 inputs (National Instruments Corp., Austin, Tex., USA) at 500 samples/s and 16-bit resolution with a 10-volt range.

Data Analysis

Spectral analysis was run offline with Matlab software (version 7.3, The MathWorks, Natik, Mass., USA). When we analyzed the power data we excluded the 0- to 2-Hz band because it can in part arise from the heartbeat even without stimulation [38]. Hence, signals were preliminarily band passed (2–45 Hz) with a finite impulse response filter and resampled at 125 Hz. The STN oscillatory activity was studied in the frequency domain using the nonparametric approach based on the discrete Fourier transform, using Welch’s averaged modified periodogram method [39]. STN LFP power spectral density (PSD), recorded from DBS-dopa patients (n = 13 nuclei), was estimated on 100-second-long data segments in the three states of interest: baseline (med off-stim off); after turning on DBS with levodopa (med on-stim on), and after turning off DBS (med on-stim off) (fig. 1b).

To account for the intersubject variability the PSD in each nucleus and in each condition (med off-stim off; med off-stim on; med on-stim on; med on-stim off) was normalized by the total spectral power in the 2- to 45-Hz frequency range at baseline (med off-stim off) of each nucleus according to the following formula:

$$PSD_N(f) = \frac{PSD(f)}{\sum_{f_{L,F}} PSD_{med\text{--}off\text{--}stim\text{--}off}(f)}$$

where $PSD_N$ is the normalized PSD, and $f$ is the frequency.

The LF band was analyzed estimating the logarithmic value of the spectral power within the band of interest (2–7 Hz). The spectral power was calculated as:

$$SP_{LF} = \sum_{f_{L,F}} PSD(f)$$

where $SP_{LF}$ is the spectral power.

For patients receiving DBS-dopa and dopa-DBS we also investigated whether levodopa and DBS combined modulated the STN LF peak frequency of the spectral peaks that appeared in the spectrum for the LF range. Peaks were defined as the maximum PSD value within the 2- to 7-Hz band with the null value at the first derivative.

Statistical Analysis

Experimental conditions in patients receiving DBS-dopa were tested with a one-way repeated measures analysis of variance (ANOVA) with ‘condition’ as the factor (four levels: med off-stim off, med off-stim on, med on-stim on and med on-stim off). To exclude LF power differences at baseline (med off-stim off) between patients receiving the DBS-dopa protocol and those receiving dopa-DBS, a one-way ANOVA was run with ‘protocol’ as the factor (two levels: DBS-dopa and dopa-DBS). To study whether the DBS timing, the length of time DBS was turned on before or after levodopa intake, influenced LF activity, a one-way ANOVA was applied to the med on-stim on condition in patients receiving DBS-dopa (with DBS turned on for 40 min before the patients reached the levodopa on condition) and the med on-stim on condition in patients receiving dopa-DBS (with DBS turned on 10 min after patients reached the levodopa on condition) with ‘protocol’ as the factor (two levels: DBS-dopa and dopa-DBS). A one-way ANOVA was also applied to the med on-stim off condition in patients receiving DBS-dopa and those receiving dopa-DBS with ‘protocol’ as the factor (between factor, two levels: DBS-dopa and dopa-DBS). The same statistical analyses were used for STN LF peak frequency in patients receiving DBS-dopa and dopa-DBS. Tukey’s honest significance test was used as required for post hoc analysis (p < 0.05).

To assess whether STN LF power depended on disease severity, Pearson’s coefficient was used to study the correlation between the motor part of the Unified Parkinson’s Disease Rating...
Scale (UPDRS III) in off medication (table 1) and individual STN LF powers at baseline. To assess whether STN LF power depended on the patient's clinical condition, the same analysis was run on UPDRS III on medication scores (table 1) and individual STN LF powers during the med on-stim off condition.

Pearson's linear correlation coefficient was calculated between electrode impedance values and individual STN LF powers at baseline. To assess the influence of electrical impedance on the levodopa and DBS-induced effects, Pearson's coefficient was also used to study the correlation between the electrode impedance values and the percentage changes in STN LF power under all experimental conditions (med on-stim on; med on-stim off; med on-stim off) from baseline (med off-stim off). Differences were considered significant at \( p < 0.05 \). Data are expressed as mean ± 95% confidence interval.

**Results**

Considering the individual patients, LF power increased (more than 5% from baseline) in 91% of the samples during DBS without levodopa, 83% during DBS

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**Table 1**

<table>
<thead>
<tr>
<th>Condition</th>
<th>LF Power Increase</th>
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<tbody>
<tr>
<td>Off-stim off</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>On-stim on</td>
<td>&gt;5%</td>
</tr>
<tr>
<td>On-stim off</td>
<td>&gt;5%</td>
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</tbody>
</table>

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**Fig. 1.** Experimental protocol. **a** DBS-dopa protocol. DBS was turned on for about 40 min before the patients reached the levodopa (dopa)-on condition. The boxes represent the four LFP recording conditions (100 s LFP recording each): baseline (med off-stim off); without levodopa with DBS on (med off-stim on); with levodopa with DBS on (med on-stim on), and with levodopa with DBS off (med on-stim off). **b** Dopa-DBS protocol. Patients reached the levodopa-on condition for about 10 min before DBS was turned on. The LFP recording conditions are the same as in a except for the med off-stim on condition. The arrows indicate time (minutes) and highlight DBS turning on and off, levodopa intake and the approximate time when the levodopa effect begins.
with levodopa and 50% during levodopa alone. One patient in the DBS-dopa group was excluded from the analysis owing to recording artifacts throughout the whole recording session (n = 12 nuclei analyzed). During DBS-dopa, LF power changed significantly (ANOVA, factor ‘condition’, p = 0.003). Post hoc analysis showed that LF power at baseline (med off-stim off: 1.16 ± 0.12 arbitrary units, AU) was significantly lower than power during DBS without levodopa (med off-stim on: 1.29 ± 0.14 AU, p = 0.022), during DBS on with levodopa (med on-stim on: 1.32 ± 0.14 AU, p = 0.003) and after turning DBS off with levodopa on (med on-stim on: 1.26 ± 0.13 AU, p = 0.041). In addition, PSD also showed levodopa-induced changes in the beta band (med off-stim off vs. med on-stim off, p = 0.04) whereas, in the whole population, DBS failed to induce beta band modulations (fig. 2).

No significant differences were found between the two groups of patients undergoing the DBS-dopa and dopa-DBS experimental protocols. ANOVA failed to reveal differences at baseline between patients undergoing the DBS-dopa and dopa-DBS experimental protocols (factor ‘protocol’, p = 0.10). No significant changes were found between the med on-stim on or med on-stim off conditions in the two groups (factor ‘protocol’, p = 0.24 and 0.42, respectively). Because no significant differences were found between the two groups of patients for experimental conditions, data for the whole population were used for further analysis (n = 18 nuclei) except for the med off-stim on condition, which was only used in the DBS-dopa protocol (n = 12 nuclei).

The LF peak frequency was similar in all experimental conditions within the DBS-dopa group (factor ‘condition’, p = 0.54). LF peak frequency in patients receiving DBS-dopa remained unchanged from those in patients receiving dopa-DBS under both med off-stim off, med on-stim on and med on-stim off conditions (factor protocol, p = 0.67, 0.66 and 0.28, respectively).

No correlation was found between UPDRS III in off medication and LF power at baseline ($R^2 = 0.137, p = 0.13$). Conversely, UPDRS III in on medication correlated significantly with LF power in the med on-stim off condition ($R^2 = 0.262, p = 0.026$).

Finally, electrode impedance correlated with LF power at baseline ($R^2 = 0.650, p < 0.0001$), with percentage changes in LF DRO power from baseline values for each experimental condition (med on-stim on: $R^2 = 0.604, p < 0.005$; med on-stim off: $R^2 = 0.481, p = 0.012$; med on-stim off: $R^2 = 0.290, p = 0.021$) (fig. 3).

**Discussion**

Our study was designed to investigate the relationship between LF modulations, DBS duration and levodopa intake in patients with PD undergoing DBS. The results provide reliable data suggesting that the LF band is suitable as a neurosignal for use as a control variable in adap-
tive DBS systems. Our experiments recording STN LFPs show that LF power depends on the patient’s clinical condition and that changes in LF power are related to electrode impedances.

Under all three experimental conditions tested (during DBS, levodopa, and DBS and levodopa combined) LF power values increased, regardless of the order. The DBS- and levodopa-induced increase in LF oscillations agrees with previous reports [24,36] as does the slight LF power decrease after DBS offset [15,40]. Although exactly how DBS modulates STN LF activity remains open to conjecture, electrical polarization around the DBS electrode could modulate activity in STN neurons and, given that we recorded similar STN LF power in patients on medication and on DBS, suggests that polarization could act similarly to levodopa. Some studies have highlighted the striatal dopamine release during high-frequency DBS [41–44]. Hence, again given the similar STN LF power changes recorded on medication and during DBS, the DBS-induced striatal dopamine release and levodopa medication could correspond to the LF power increase in a similar manner [18,24]. Because patients receive levodopa during DBS, the slight LF decrease after DBS offset could depend on the levodopa-induced STN LF saturation contrasting the LF increase during DBS [18,45].

LF oscillations behave the same regardless of the order in which levodopa and DBS are applied. In particular, STN LFPs recorded in patients undergoing the DBS-dopa experimental protocol (who received DBS for 40 min before they reached the levodopa-on condition) and STN LFPs recorded from patients undergoing the dopa-DBS protocol (who reached the levodopa-on condition 10 min

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**Fig. 3.** Correlation analysis. Single plots represent the linear correlation between electrode impedance and LF power: med off-stim off (a), med on-stim on (b), med off-stim on (c) and med on-stim off (d). Dots represent the values obtained in single nuclei. The black line represents the estimated linear fit for values showing a significant correlation (* p < 0.05). Of note, impedances are directly correlated with LF power and with percentage changes in the LF power from med off-stim off in each experimental condition.
before we turned DBS on) remained unchanged in the med on-stim on and med on-stim off conditions, thus suggesting that they act through independent mechanisms.

As a neurosignal for developing an adaptive DBS system, the changes we identified in STN LF activity have several advantages. For example, they could overcome beta activity’s limitation of being present only in a subgroup of parkinsonian patients [3, 9, 18]. Among its drawbacks, beta LFP power decreased significantly for the whole population only after levodopa intake and not when patients received DBS alone [18]. Another drawback of the beta band as a control signal is its spatial specificity, which can prevent it being recorded from all contact pairs. Conversely, LF oscillations are recordable from all the contact pairs [46]. Considering that in individual patients the stimulating contact can be changed to optimize the clinical efficacy of DBS [47], being able to record LF power from multiple contacts is an obvious advantage because it reduces the risk of losing the control variable.

In all the patients with advanced PD we studied, the increase in STN LF band power correlated with patients’ clinical improvement after pharmacological intake. Because we found no correlation between STN LF power at baseline and UPDRS III in patients off medication, STN LF activity could be considered as an index of patient’s clinical condition rather than of disease severity. Another important point favoring the use of LF as a control signal is that LF power correlates with dyskinesias [31].

A useful finding was that the higher the electrode impedance, the higher the LF power change was during DBS, during levodopa intake, and under DBS and levodopa intake combined. Electrode impedance increases 30 days after surgery linearly correlating with LF power increases [37]. Hence, in the chronic condition, the LF modulations would be even more pronounced and, in turn, as the time elapsing after DBS surgery lengthens, LF power could be even more pronounced and useful as a control signal.

A further major open question is whether an adaptive DBS system might rely on more than one control LFP signal. Excessive desynchronization in the beta range could be responsible for levodopa-induced dyskinesias [22, 48]. Hence, levodopa’s ‘destructive’ action on the beta band, together with its over-boosting action on LF power, might shift the oscillatory pattern and cause hyperkinesia to develop [31]. A further approach to control signals for adaptive DBS could therefore entail detecting the ratio between beta and LF power to drive stimulation to rebalance the beta/LF power ratio [18]. Thus, the new adaptive approach might turn power off when beta power is too weak and LF power is too strong, thereby reducing dyskinesias and dystonia.

Finally, although whether or not an adaptive DBS system could improve motor fluctuations remains open to question, the same reasoning could apply to nonmotor fluctuations by detecting the related abnormal LFP patterns [23]. LFP studies investigating cognitive and emotional functions in the STN have found a specific LF modulation [14, 17, 49]. An LFP study recording STN LFPs in PD patients with and without depressive symptoms found a direct correlation between the STN LF band and emotions [50]. Another study found specific oscillatory activity in the theta-alpha band (4–7.5 Hz) in patients with impulse control disorders [33]. This observation might help in modulating the abnormal oscillatory activity to obtain the maximum benefit with the minimum undesirable side effects in patients with PD [33].

In conclusion, the STN LF band seems suitable as a neurosignal for use as a control variable in an adaptive DBS system for patients with PD.

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