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Local field potentials and motor performances modulation in response to stimulation and levodopa: a study on Parkinson's disease patients on chronic deep brain stimulation

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ABSTRACT

Introduction: Subthalamic (STN) local field potentials (LFP) in the beta band are considered potential biomarkers for closed-loop deep brain stimulation (DBS) in Parkinson's disease (PD). Studies focusing on chronic STN LFP modulation in response to stimulation and treatment are scant. Deepening knowledge on beta modulation during chronic stimulation could aid the development of solid computational algorithm for adaptive DBS.
This study aimed to investigate: 1) the presence of beta peaks in the first 21 patients receiving the Percept PC at our Tertiary Centre; 2) the influence of medications, stimulation, and plasma levodopa levels on beta-peaks magnitude and motor performances.
Methods: Twenty-one (19 males, 2 females) consecutive PD patients who underwent bilateral STN-DBS surgery were prospectively recruited. At 6 months after surgery, an extensive and systematic evaluation of raw LFP, motor performances, and plasma levodopa levels was conducted in the following four conditions: OFF-medications/ON-stimulation; OFF-medications/OFF-stimulation; ON-medications/OFF-stimulation; ON-medications/ON-stimulation.
Results: Analysis of STN LFP revealed that 76.2 % (16/21) of PD patients showed a beta peak. Beta peaks was identified at an average frequency of 21.0 ± 5.4 Hz, with an amplitude of 1.1 ± 0.8 μV/rtHz. A higher significant reduction of beta STN oscillations was observed following stimulation activation ($p < 0.001$) compared to levodopa administration. LFP amplitude patterns reflected motor performance trends across the four treatment conditions.
Conclusion: This study provides a comprehensive and systematic evaluation of LFP behaviour in response to stimulation and medication, conducted during ongoing stimulation and in the chronic state. These findings enhance understanding of beta oscillatory changes related to therapies and stimulation.

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1. Introduction

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is recommended in Parkinson's disease (PD) patients with motor fluctuations or tremor not satisfactorily controlled with medication [1]. Despite its documented clinical efficacy [1], the exact mechanisms through which DBS exerts therapeutic action remain still unclear [2].

Local field potentials (LFP) represent a complex electrical signal incorporating synaptic currents and the firing activity of the neuronal population lying near the electrode [3]. The LFP correlate in phase with time-locked bursts of neuronal spikes and, therefore, reflect synchronous neural oscillations [4]. Elevate synchronization of the subcortical neural oscillations appears in the LFP, resulting in an increase in the power of the spectral components at the frequency of the oscillatios.

Recent studies have highlighted that the clinically relevant frequency range in any given patient might vary, as different oscillatory signatures across the frequency spectrum have been associated with distinct motor symptoms—such as bradykinesia, tremor, freezing of gait, and dyskinesia—as well as non-motor symptoms [5].

Previous studies with LFP of the STN in PD patients without medication showed an excessive oscillatory synchrony in the beta frequency band (15–30 Hz). These peaks in the beta band have been described as an important pathological feature, emerging in the dopamine-depleted state and correlated with the magnitude of PD-related akinetic-rigid symptoms [6,7]. Both the administration of the dopamine precursor, levodopa, and high-frequency DBS of the STN lead to a suppression of resting beta synchrony [8–10]. Some studies have shown correlations between the extent of beta activity suppression by levodopa and clinical improvements in motor performance [11–13].

At present, all DBS devices allow continuous stimulation. However, emerging adaptive DBS (aDBS) could provide symptom-specific and task-dependent stimulation. In fact, the variable nature of PD symptoms calls for a more dynamic and responsive approach that varies according to the individual needs of the subject in everyday life. Beta power has been extensively investigated, and various studies suggest that it could serve as a biomarker of bradykinesia and rigidity for aDBS in PD [9,14–18].

Although aDBS has great potential to become a key tool in the personalized approach to successful management of PD, many challenges (artifacts, different peaks modulations in the STN of the two hemispheres, beta oscillations suppressed by tremor or voluntary movements, feedback signals modulation in some physiological states such as physical activity or sleep) must still be overcome [19]. Studies focusing on the complex behaviour of beta peaks in response to stimulation and levodopa [14,17,20], especially during chronic stimulation [15], are scanty.

Recently developed implantable pulse generators (Medtronic Percept™ PC, Medtronic PLC) allow chronic simultaneous recording and electrical stimulation of basal ganglia [21]. The sensing capabilities of these new implantable devices could allow a better understanding of disease-related brain activity patterns and their modulation in response to therapies, bringing the implementation of adaptive stimulation therapies closer to clinical practice. Deepening the knowledge of beta modulation during chronic stimulation could help the development of solid computational algorithms for aDBS.

This study aimed to investigate: 1) the presence of beta peaks in the first 21 patients receiving the Percept PC at our Tertiary Centre; 2) the influence of medications, stimulation, and plasma levodopa levels on beta-peaks magnitude and motor performances.

2. Methods

2.1. Study protocol

In this study, we analysed clinical and neurophysiological data of the first 21 PD patients receiving the Percept™ PC at our Tertiary Centre. Patients were not selected based on specific characteristics or phenotype, as the implant was performed in the context of clinical practice.

The preoperative inpatient program at our centre [22,23] included: 1) quantification of Levodopa response using the Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS), as follows: [(preoperative "OFF" medication MDS-UPDRS III score − preoperative "ON" medication MDS-UPDRS III score)/preoperative "OFF" medications MDS-UPDRS III score] × 100; 2) the MDS-UPDRS I, II, IV scores along with the Hoehn and Yahr (HY) scale score; 3) the levodopa kinetic-dynamic test along with motor performances analysis; 4) cardiovascular reflex tests [24]; 5) an extensive neuropsychological evaluation; 6) a psychiatric interview; 7) a 3-T MRI.

Patients' eligibility was discussed by a multidisciplinary team, which included neurologists, neurosurgeons, neuropsychologists, neuroradiologists, physiatrists, anesthesiologists, and biomedical engineers.

Electrode leads (Medtronic 3389 or B3300542) were implanted into the STN on both sides [25]. Microelectrode recordings and clinical test (thresholds for motor effect and side effects) were performed during the surgery. In the same session, the pulse generator was implanted (Medtronic Percept™ PC).

DBS programming was performed 1 month after surgery in order to avoid the transient post-operative symptomatic improvement related to the microlesion effect. The initial programming session was performed in the morning after an overnight medication washout to guarantee a stable OFF drug condition to prevent medication effects from interfering with DBS effects.

During DBS programming, the amplitude thresholds for clinical benefits and side effects were tested for each electrode contact. For stimulation electrodes #1, #2, #9 and #10, raw LFP traces were recorded from the electrodes adjacent to the respective stimulation electrode on each side during rest and streamed wirelessly to a tablet computer. The monopolar review was performed at a frequency of 130 Hz in the 3 patients with 3389 electrode leads, according to the basic algorithm for DBS programming, and of 125 Hz in the 18 patients with B3300542 electrode leads to allow simultaneous stimulation and sensing (a pulse width of 60 μs was maintained across all participants).

At the end of the monopolar review, contacts were selected on the basis of clinical benefits and side effects. According to clinical practice, follow-up visits were performed to adjust stimulation settings and medications progressively.

Six months after surgery, a systematic evaluation of raw LFP, plasma levodopa levels, and motor performances was performed in the following four conditions: "OFF" medications and "ON" stimulation (MED-OFF/STIM-ON); "OFF" medications and "OFF" stimulation (MED-OFF/STIM-OFF); "ON" medications and "OFF" stimulation (MED-ON/STIM-OFF); "ON" medications and "ON" stimulation (MED-ON/STIM-ON). This evaluation was performed in the morning, after a 12-h washout of levodopa and any concomitant antiparkinsonian drugs, and included [22,23]: 1) the MDS-UPDRS III score performed in each condition; 2) the MDS-UPDRS I, II, IV scores and the HY scale score; 3) the levodopa kinetic-dynamic test along with motor performances analysis; 4) the raw LFP recorded via the Brainsense™ Streaming and the Brainsense™ Events (see LFP analysis section).

The levodopa kinetic-dynamic test included the simultaneous serial assessments of plasma levodopa concentrations and motor performances in order to assess both pharmacokinetic and pharmacodynamic parameters [22]. During the levodopa kinetic-dynamic test, performed both before and 6 months after surgery, blood venous samples (2 mL) for the measurement of plasma levodopa concentrations were drawn by an indwelling catheter, from medications OFF to medications ON condition, at 15-min intervals for the first 120 min after dosing. The levodopa challenge was performed in the morning, using the patient's regular morning dose of levodopa, after a 12-h washout of antiparkinsonian drugs. Blood specimens were collected and processed for plasma levodopa analysis, as previously reported [22].

Motor performances analysis were performed in each conditions

before surgery (MED-OFF and MED-ON), and 6 months after surgery (MED-OFF/STIM-ON, MED-OFF/STIM-OFF, MED-ON/STIM-OFF and MED-ON/STIM-ON conditions and every 15-min after dosing). The following motor tests were performed in each conditions and at every time point after levodopa administration from MED-OFF/STIM-OFF to MED-ON/STIM-OFF [23]: 1) Alternate index finger tapping test: this test objectively measures the number of times the patient can alternately tap two buttons 20 cm apart in 60 s with the most affected hand, using a computerized touch screen system; 2) Timed Up and Go test (TUG); 3) 18-m (18-m) walking test. During the TUG and the 18-m walking test, the patient wore a set of 3 wearable inertial sensors (mTest3 system, mHealth Technologies, Italy): one sensor was secured to the lower back using an elastic belt, and two sensors were fixed on the shoes with Velcro straps. The wearable system automatically extracted quantitative motor parameters such as TUG total duration and gait speed [26].

The percentage of post-operative motor improvement was calculated as follows: [(preoperative MED-OFF MDS-UPDRS III score − post-operative MED-OFF/STIM-ON MDS-UPDRS III score)/preoperative MED-OFF MDS-UPDRS III score] × 100.

The preoperative and post-operative levodopa equivalent daily dose (LEDD) were calculated, along with the percentage of LEDD change calculated as follows: [(preoperative LEDD – post-operative LEDD)/ preoperative LEDD]x 100 [22,23].

2.2. LFP analysis

For each condition, the raw LFP were sampled at 250 Hz using the implanted leads (one channel from each side) and streamed wirelessly to a dedicated tablet. The raw LFP were recorded via the Brainsense™ Streaming for about 3-min in resting-state condition and during the different tests (finger tapping, TUG, and 18-m walking test). Moreover, Brainsense™ Events were recorded at the beginning of each condition and at 15-min intervals after dosing (simultaneously with blood sample collection).

The power spectral density (PSD) estimate and the spectrogram were computed from the time domain signals recorded while the patient was sitting on a chair in a resting condition, with hands on the armrests, eyes open, and without speaking. Although this represent a stable resting condition, we implemented an automated method to identify a 30-s window (for each 3-min LFP recording) characterised by minimum signal standard deviation in order to mitigate the effect of transient mechanical noise observed in some recordings and which caused transient large-amplitude fluctuations visible as brief bursts spanning multiple frequency bands. In addition, recordings presenting cardiac artifacts were excluded, as they may mask relevant information in the LFP within the 0–40 Hz frequency range, potentially overlapping with the beta band. The PSD was computed for the identified 30-s window using Welch's method with a 1-s Hamming window and an overlap of 60 % [22]. The recorded signals were analysed using Matlab 2021b to compare them in each medication and stimulation condition.

The peaks in the extended beta-band (10–35 Hz) were defined as the maximum of the computed PSD of the raw LFP. A minimum distance of 5 Hz was established to avoid selecting closely spaced peaks. The MED-OFF/STIM-OFF condition served as the reference for peak identification in other conditions, where the same frequency range (±2.5 Hz) was investigated. If no peak was detected in the specific bands, then the PSD value at the peak frequency in the MED-OFF/STIM-OFF condition was considered.

The amplitude distribution of the detected beta-band peaks related to the most-affected body side was analysed. The percentage change in LFP peak amplitude, MDS-UPDRS clinical scores, and motor-related parameters were analysed for each condition compared to the MED-OFF/STIM-OFF condition. For each hemisphere, the corresponding MDS-UPDRS subscore was also considered in relation to the percentage change in LFP peak amplitude.

3. Ethics statement

The study was conducted in agreement with the principles of good clinical practice. The study protocol was approved by the Local Ethics Committee of the local health service of Bologna, Italy (Cod. CE: 21156). All patients gave their written informed consent to participate in the study.

3.1. Statistical analysis

The normality of continuous parameters distribution was checked using the Skewness-Kurtosis test. Variables were expressed as mean ± standard deviation (SD) or median along with interquartile ranges (IQR) when appropriate. Continuous variables were compared using a *t*-test or Wilcoxon rank-sum, as appropriate. Categorical variables were described by their absolute and/or relative frequencies and compared using the Chi-square test.

Repeated measures ANOVA was performed to investigate significant main effects for all patients across time (pre- and post-surgery). The Kruskall-Wallis test was utilized for multiple comparisons across time when appropriate. The LFP peak amplitude, clinical, and motor scores among the four conditions performed 6 months after surgery, were compared using a repeated measure ANOVA or Friedmann non-parametric statistical test. In the case of a significant ANOVA or Friedman test, the Wilcoxon rank-sum test was performed between each possible pair of conditions. A p-value lower than 0.05 (2-sided) was considered significant. Statistical analyses were performed using the statistical software STATA®, version 17.0. Effect sizes for all pairwise comparisons between clinical states (medication ON/OFF; DBS ON/OFF) were computed using paired Cohen's d.

Standardized response mean (SRM) values were calculated to assess the responsiveness of LFP peak amplitude and motor performances to stimulation (MED-OFF/STIM-OFF vs. MED-OFF/STIM-ON) and medication (MED-OFF/STIM-OFF vs. MED-ON/STIM-ON). The mean difference between the various conditions was divided by the standard deviation of the differences. SRM values below 0.20 suggest a weak response, while values between 0.20 and 0.50 indicate a moderate response, and values above 0.80 indicate a large response to medication or stimulation [27].

The Spearman correlation coefficient was computed to investigate potential associations between the variation of LFP peak amplitude, the clinical scores, and the motor parameters against the baseline condition MED-OFF/STIM-OFF.

A correlation analysis examined the relationship between the beta-band peak observed in the MED-ON/STIM-ON condition and the area under the curve (AUC) of the plasma concentration-time curve. The AUC was calculated over the 2-h period following drug intake.

As an exploratory analysis, linear mixed-effects models (LMM) were employed to explore the association between levodopa concentration and beta-peak amplitude recorded via Brainsense™ Events (from MED-OFF/STIM-OFF to MED-ON/STIM-OFF conditions) at 15-min intervals after dosing (simultaneously with blood sample data collection), estimating the beta coefficient (β) and the 95 % confidence interval ($CI_{95\ \%}$) for each hemisphere.

4. Results

Demographic and clinical features of the study sample are shown in Table 1. A total of 21 consecutive PD patients (19 males and 2 females, disease duration at surgery 11.4 ± 4.2 years) were included in the study. The preoperative evaluation showed a mean levodopa response of 48.5 ± 14.8 %. The post-operative motor improvement resulted in 48.1 ± 21.2 %.

Six months after surgery, a remarkable improvement in patients' symptoms and motor fluctuations was observed (Table 1). The MDS-UPDRS II and IV scores and LEDD showed a significant reduction after

Table 1
Demographic and clinical characteristics of the study sample.

	Total PD sample	
	21	
Sex		
Male, *n (%)*	19 (90.5)	
Female, *n (%)*	2 (9.5)	
Age at surgery, *y*	59.1 ± 5.7	
Age at disease onset, *y*	47.7 ± 7.1	
Disease duration at surgery, *y*	11.4 ± 4.2	
Phenotype		
Tremor-dominant, *n (%)*	10 (47.6)	
Akinetic-rigid-dominant, *n (%)*	11 (52.4)	
Side PD onset		
Right, *n (%)*	10 (47.6)	
Left, *n (%)*	11 (52.4)	
Levodopa challenge		
Preoperative OFF MDS-UPDRS III	42.7 ± 10.7	
Preoperative ON MDS-UPDRS III	22.4 ± 9.6	
Preoperative levodopa response, %	48.5 ± 14.8	
Preoperative levodopa test dose, *mg*	171.4 ± 42.8	
Motor Outcome		
Post-operative MED OFF/STIM ON MDS-UPDRS III	22.7 ± 9.8	
Post-operative MED OFF/STIM OFF MDS-UPDRS III	48.7 ± 11.1	
Post-operative MED ON/STIM OFF MDS-UPDRS III	32.6 ± 13.8	
Post-operative MED ON/STIM ON MDS-UPDRS III	15.5 ± 7.6	
Post-operative motor improvement, %	48.1 ± 21.2	
Postoperative levodopa test dose, *mg*	119.1 ± 48.6	
LEDD change	0.41 (0.24–0.55)	
	Preoperative	**Post-operative**
Clinical Features and Scales		
FOG, *n (%)*	9 (42.9)	4 (19.1)
LEDD, *mg*	670 (500–1110)	400 (300–620)[a]
HY	2 (2–2.5)	2 (2–2)
MDS-UPDRS I	8.4 ± 4.2	6.1 ± 4.3
MDS-UPDRS II	11.7 ± 5.0	5.2 ± 2.5[a]
MDS-UPDRS IV	7 (5–10)	1 (0–2)[a]

Data are expressed as mean ± standard deviation or median (interquartile range).
Legend: FOG: Freezing of gait; HY: Hoehn and Yahr scale; LEDD: levodopa equivalent daily dose; MDS-UPDRS: Movement Disorders Society—Unified Parkinson's Disease Rating Scale; *n*: sample size; PD: Parkinson's Disease; *y*: years.
[a] Statistically significant (p value ≤ 0.05) at repeated measures ANOVA or Kruskall-Wallis test.

surgery [MDS-UPDRS II: from 11.7 ± 5.0 to 5.2 ± 2.5, $p < 0.001$; MDS-UPDRS IV: from 7 (5–10) to 1 (0–2), $p < 0.001$; LEDD: from 670 (500–1110) to 400 (300–620), $p = 0.0059$]. Other clinical variables improved without reaching statistical significance. The median percentage of LEDD change was 41 (24–55)%.

Two patients could not perform the 18-m walking test in the MED-OFF/STIM-OFF condition, and another did not perform the TUG test in MED-ON/STIM-OFF condition due to the inability to get up from the chair independently.

On the total sample, 16/21 (76.2 %) patients (9 tremor dominant and 7 akinetic-rigid dominant) showed at least one beta peak: 5 (23.8 %) patients showed one bilateral beta peak; 6 (28.6 %) patients showed a bilateral double beta peak, defined as the presence of two distinct peaks within the beta frequency band; 5 (23.8 %) patients showed one beta peak in one hemisphere and a double beta peak in the other one (Supplementary Table 1). The remaining five patients (1 tremor dominant and 4 akinetic-rigid dominant) exhibited no beta peak in either hemisphere.

Six months after surgery, the beta peak was identified in 32/42 STN at an average frequency of 21.0 ± 5.4 Hz. In MED-OFF/STIM-OFF condition, the beta-peak amplitude was 1.1 ± 0.8 μV/rtHz. The maximum beta peak was found in 25/32 in contact pair #1–3 and 7/32 in #0–2. No significant differences were observed analysing all patients, in the MED-OFF/STIM-OFF condition, between LFP peaks amplitude recorded in STN corresponding to the worst and best body side. Differentiating the patients based on their phenotype, the mean amplitude of the beta peaks was higher in akinetic-rigid dominant patients (1.55 ± 1.24 μV/rtHz) compared to tremor dominant patients (0.96 ± 0.58 μV/rtHz), although the difference was not significant. No difference was observed in the mean frequency of the beta peaks between phenotype subgroups (20.79 Hz and 20.36 Hz for tremor and akinetic-rigid patients, respectively). In 10 STN, no contact pair displayed a beta band.

Concerning the spectra of the LFP related to both STN, a higher significant reduction of beta STN oscillations was observed following stimulation activation (MED-OFF/STIM-OFF vs. MED-OFF/STIM-ON and vs. MED-ON/STIM-ON) compared to levodopa administration (MED-OFF/STIM-OFF vs. MED-ON/STIM-OFF) (Fig. 1A). In particular, significance in LFP amplitude variation was reported between MED-OFF/STIM-OFF vs. MED-OFF/STIM-ON conditions ($p < 0.001$), between MED-OFF/STIM-OFF vs. MED-ON/STIM-ON conditions ($p < 0.001$), between MED-ON/STIM-OFF vs. MED-OFF/STIM-ON conditions ($p < 0.001$), and between MED-ON/STIM-OFF vs. MED-ON/STIM-ON conditions ($p < 0.001$). Instead, between MED-OFF/STIM-OFF and MED-ON/STIM-OFF, the p-value was <0.01, indicating significance. The results remained consistent after excluding the outlier (ID = 13).

The same results were obtained when the analysis was repeated exclusively for the STN corresponding to the best body side (Fig. 1B–Supplementary Table 2), with stimulation-related comparisons showing greater significance than those for medication. Concerning the spectra of the LFP in the STN corresponding to the worst body side (Fig. 1C–Supplementary Table 2), stimulation significantly suppressed beta STN oscillations (MED-OFF/STIM-OFF vs. MED-OFF/STIM-ON and MED-ON/STIM-ON, $p < 0.001$) while levodopa partially decreased them without reaching significance (MED-OFF/STIM-OFF vs. MED-ON/STIM-OFF, $p = 0.09$) but highlighting a weak effect.

By visual inspection, the analysis of variation, in each condition, of MDS-UPDRS III total scores, as well as scores for the more affected and less affected body sides in each condition, revealed a trend similar to the variation in LFP peak amplitude (Fig. 2). Both in MDS-UPDRS III total scores (Fig. 2A) and in MDS-UPDRS III from worst and best body sides (Fig. 2B and C, Supplementary Table 2), a significant reduction ($p < 0.001$) was observed after both stimulation and medication, but a higher improvement was seen following the stimulation activation (MED-OFF/STIM-ON and MED-ON/STIM-ON). Concerning variation of other motor performances, alternate index finger tapping test and 18-m gait speed showed a similar trend of LFP peak amplitude, with significant improvement only in comparisons between conditions related to stimulation (Fig. 3 and Supplementary Table 3). TUG duration showed a significant improvement both after stimulation and medication ($p < 0.001$). Supplementary Table 4 reports the computed effect sizes for all paired treatment comparisons.

Regarding SRM results, high responsiveness to both stimulation and medication was observed in MDS-UPDRS III total score (5.85 and 1.35, respectively) (Fig. 4). Stimulation led to large-moderate responsiveness of tapping score (0.87), LFP peak amplitude reduction (0.66 and 0.88 in STN corresponding to worst and best body side, respectively), TUG duration (0.35), and 18-m gait speed (0.69). After medication, lower responsiveness in tapping score (0.47), LFP peak amplitude (0.45 and 0.28 in STN corresponding to worst and best body side, respectively), and 18-m gait speed (0.33) were reported (Fig. 4).

After levodopa intake, the LFP peak amplitude progressively decreased over time; however, no significant correlation ($r = -0.324$; $p = 0.280$) was observed between the LFP peak amplitude corresponding to the most affected body side and the 2-h AUC (Supplementary Fig. 1).

As an exploratory analysis, resting-state recordings of the LFP in the STN corresponding to the worst body side, performed via Brainsense™

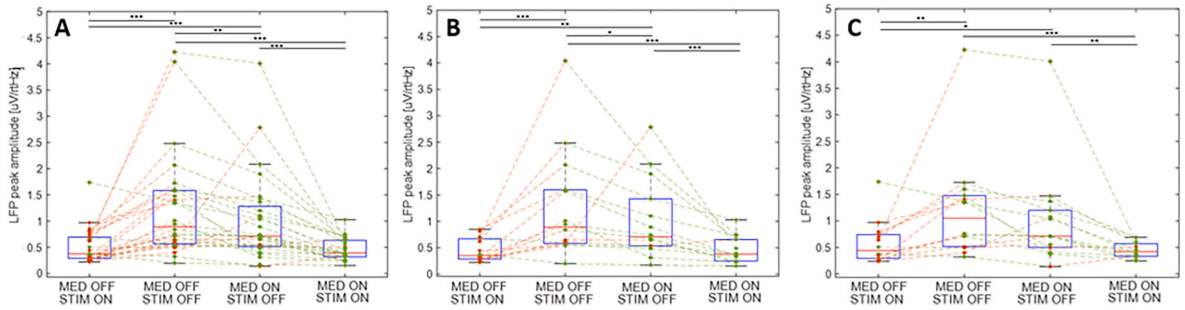

Fig. 1. Boxplot of the LFP peak amplitude recorded in both STN (A) and in hemisphere related to the best (B) and worst (C) body side in the different medication (MED) and stimulation (STIM) conditions. Red and green dashed lines indicate improvement (lower amplitude) and worsening (higher amplitude) from the previous condition, respectively.
Legend: *p < 0.05, **p < 0.01, ***p < 0.001, LFP: Local Field Potentials.

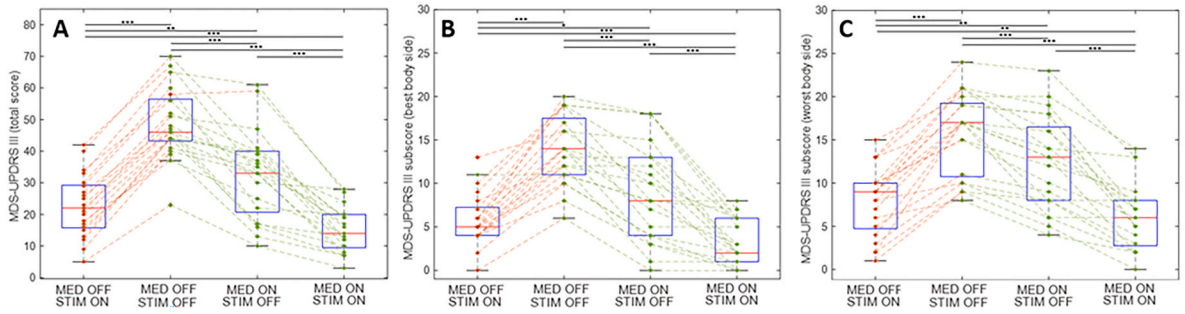

Fig. 2. Boxplot of the MDS-UPDRS total score (A) and MDS-UPDRS motor subscore related to the best (B) and worst (C) body side in the different medication (MED) and stimulation (STIM) conditions. Red and green dashed lines indicate improvement (lower value) and worsening (higher value) from the previous condition, respectively. In subplot B, three outliers in the MED-OFF/STIM-OFF condition were excluded from the figure.
Legend: *p < 0.05, **p < 0.01, ***p < 0.001, MDS-UPDRS: Movement Disorders Society—Unified Parkinson's Disease Rating Scale.

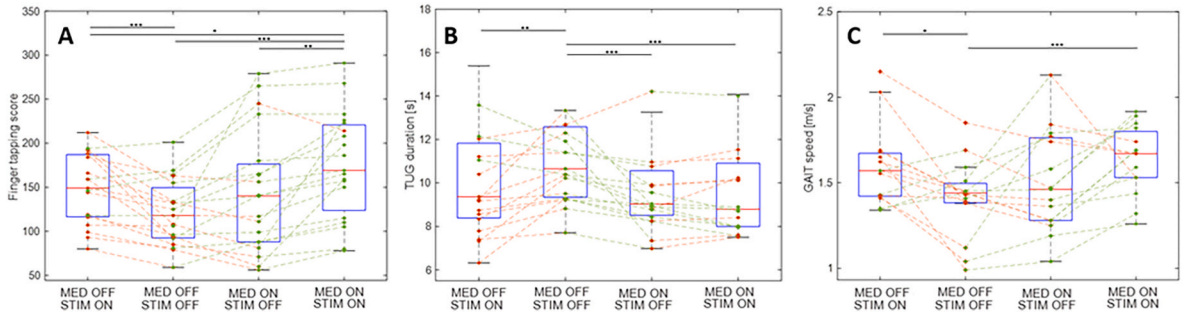

Fig. 3. Boxplot of the sensor-based motor parameters in the different medication (MED) and stimulation (STIM) conditions: Finger tapping score (A), TUG duration (B), 18-m gait speed (C). Red and green dashed lines indicate improvement and worsening from the previous condition, respectively. In subplot B, three outliers in the MED-OFF/STIM-OFF condition were excluded from the figure.
Legend: *p < 0.05, **p < 0.01, ***p < 0.001, TUG: Timed Up and Go test.

Events, from MED-OFF/STIM-OFF to MED-ON/STIM-OFF condition, at 15-min intervals after dosing for the first 60–90 min, showed significative negative association with variation in levodopa concentrations [$\beta = -0.143$; $CI_{95\ \%}$ (−0.272; −0.032); $p = 0.0158$]. No significant association was found in the STN corresponding to the best body side [$\beta = 0.088$; $CI_{95\ \%}$ (0.247; 0.058); $p = 0.2180$].

5. Discussion

This is one of the first studies investigating LFP and motor performances behaviour in response to stimulation and levodopa, in 21 PD patients on chronic DBS. The analysis of STN LFP revealed that 76.2 % (16/21) of PD patients showed a beta peak. Some of these showed a double beta peak in at least one hemisphere. These data are in line with previous studies demonstrating that not all PD patients display a sharp beta peak in the STN LFP [18,21,28–31].

Akinetic-rigid and tremor-dominant phenotypes did not show differences in beta peak frequencies. The first group showed a trend (although not statistically significant) of increased amplitude compared to the tremor-dominant one. No difference in LFP peak amplitude was observed between the STN corresponding to the worst and the best body side.

Concerning LFP behaviour, a higher significant reduction of beta STN oscillations was observed following stimulation activation compared to levodopa administration. Analysing LFP in the STN corresponding to the worst body side, stimulation significantly suppressed beta oscillations while levodopa induced a partial decrease that was not significant.

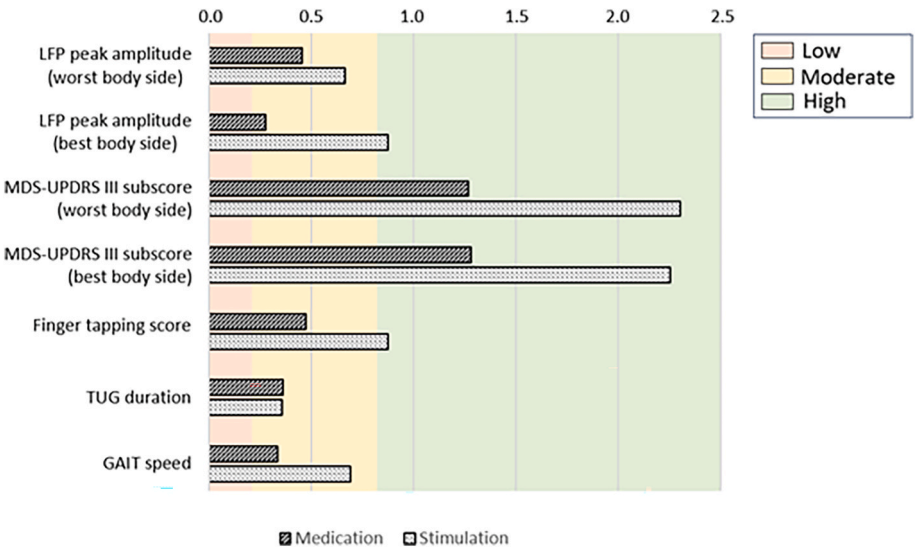

Fig. 4. Responsiveness of Local Field Potentials amplitude and clinical motor outcomes to subthalamic deep brain stimulation (stimulation) and to levodopa (medication). SRM values < 0.20, <0.50, and >0.80 indicate small, moderate and large responsiveness, respectively. Positive values indicate improvement under the respective treatment.
Legend: LFP: Local Field Potentials, MDS-UPDRS: Movement Disorders Society—Unified Parkinson's Disease Rating Scale, TUG: Timed Up and Go test.

Analysis of variation, in each condition, of MDS-UPDRS III total scores, scores for the more and less affected body side, and other motor performances, revealed a trend similar to the variation in LFP peak amplitude, with higher improvement in comparisons between conditions related to stimulation ($p < 0.001$). Changes in alternate index finger tapping and 18-m gait speed followed a trend similar to LFP peak amplitude, with significant improvement only in comparisons between conditions related to stimulation ($p < 0.001$). TUG duration had significant improvement both related to stimulation and medication ($p < 0.001$). Higher responsiveness to stimulation than medication was found in MDS-UPDRS III scores, tapping score, STN LFP peak amplitude, TUG duration, and 18-m gait speed.

As an exploratory analysis, the LFP recorded in the STN corresponding to the worst body side, performed via Brainsense™ Events, showed a significative negative correlation with plasma levodopa levels.

Fully implantable devices have the technical capability to provide chronic adaptive neurostimulation, using real-time detection of neural signals to automatically adjust stimulation amplitude or other parameters in response to patient activities or variations in symptoms severity during daily life [21]. At present, several barriers could limit its clinical implementation, including the limited understanding of neural signatures of specific symptoms in brain disorders treatable by DBS, the technical complexity of sensing brain signals during ongoing electrical stimulation, and the lack of standardized algorithms for optimizing feedback control across a vast parameter space [19,32,33].

Modulation of STN beta power could represent a reliable biomarker for aDBS paradigm, providing better control of symptoms and preventing the add-on effect of continuous DBS in times of levodopa efficacy. Improving the understanding of STN beta peaks during chronic stimulation could be helpful, in view of future aDBS, to define specific LFP patterns and task-related beta modulation. The results of our study deepen the knowledge of beta burst modulation in response to stimulation and levodopa, showing that the LFP amplitude pattern reflects the motor performance trends (MDS-UPDRS IIII score, alternate index finger tapping test, TUG duration, and 18-m gait speed) among the four treatment conditions. Resting-state LFP recordings showed a reduction in beta STN amplitude after levodopa intake (MED-OFF/STIM-OFF to MED-ON/STIM-OFF condition) in nearly all patients, although the magnitude of the decrease was smaller than that observed with stimulation. While stimulation may provide a greater magnitude of LFP suppression and more stable effects throughout the day, levodopa intake may cause LFP fluctuations within a single day, and this aspect should be considered when optimizing stimulation and oral therapy.

To note, in 1/16 patient, high beta peak progressively increased after levodopa intake (Fig. 1), with an amplitude rise concordant (albeit delayed) with the increase of plasma levodopa levels, as previously reported [22]. This behaviour might be assumed as a discordant and tricky feature by aDBS algorithms, potentially being misinterpreted as a need for further stimulation increase.

Therefore, in future aDBS, the LFP in MED-OFF/STIM-OFF and LFP behaviour in response to levodopa should be evaluated in single patients to identify patient-specific individual LFP patterns and program DBS parameters accordingly.

Moreover, based on our analysis, we suggest that, in patients with a double beta peak, the peak with the highest amplitude in the MED-OFF/STIM-OFF condition should be considered in the chronic aDBS algorithm, as the highest beta peak showed a better modulation in response to treatments.

To date, no studies have focused on chronic STN LFP modulation in response to stimulation and treatment. Most studies of this kind have analysed LFP patterns during the post-operative window, when the beta band may be influenced by microlesion effect, and typically for a limited duration. One study investigated changes induced by levodopa and stimulation on STN beta LFP in 9 PD patients across the four treatment conditions [14]. This study identified a significant low beta peak (central frequency from 13.6 to 16.6 Hz) in 6 out of 9 patients. The analysis of STN LFP recorded 3 days after electrode implantation showed that levodopa abolished beta oscillations in all the patients, while DBS decreased beta activity in only 5 of the 9 patients. Additionally, levodopa completely suppressed beta oscillations, whereas DBS merely decreased them [14]. Another study, on 16 patients, analysed 25 STN LFP recorded in the few days between electrode implantation and their connection to the pulse generator, showing progressive suppression of 11–30 Hz beta activity with increasing stimulation intensity [9]. A large dataset of postoperative rest recordings from 106 patients investigated the association between subthalamic beta power and bursts with motor symptoms, as well as their change with dopaminergic medication [20]. A reduction in low beta (13–20 Hz) power following medication administration was observed, and this reduction was paralleled by dopamine-related symptom alleviation [20]. Finally, in a different study

approach, STN LFP were recorded from the DBS lead, using a sensing neurostimulator (Activa PC + S, Medtronic, Inc.) [15], under OFF-medication and OFF-DBS conditions, either before the initial DBS programming or 1–3 months later. LFP recorded from 10 STN during randomized STN stimulation at 0, 1, and 2.5/3 V showed that stimulation at 1 V and 2.5/3 V attenuated beta power when compared to 0 V, with greater attenuation at 2.5/3 V ($p < 0.001$) than at 1 V ($p < 0.003$) [15].

The current study is the first to provide a comprehensive and systematic evaluation of LFP behaviour in response to stimulation and medication, conducted during ongoing stimulation and in the chronic state. A notable strength is the timing of the analysis, which was performed six months after STN-DBS surgery, ensuring stable stimulation parameters and dopaminergic medication state. Furthermore, LFP recordings were carried out in the resting state under each condition, preventing the influence of motor activity on beta burst modulation. Another key strength of our study is that all patients were seen and followed at a single tertiary centre, ensuring consistent and uniform data collection. Additionally, patients were prospectively recruited, and data were systematically gathered.

The study's main limitation is the relatively small sample size, which has prevented stratification for disease duration or phenotype. Another limitation of this study is the gender imbalance related to the higher male prevalence in this sample, primarily caused by the Percept™ PC size, as females preferred smaller rechargeable devices for the lower aesthetic impact. To assess the impact of the four conditions on beta activity and motor response, a subacute study design was chosen and a 12-h levodopa washout was employed to eliminate potential effect of medications, ensuring an accurate evaluation of patients in a true OFF-medication state. Consequently, the chronic effects of levodopa may not have been fully captured in this study design. Finally, despite several studies focused on beta band leading the now well-established acceptance of beta as a biomarker in PD, it is not necessarily implied that subcortical beta will universally be the optimal biomarker for every individual patient. In fact, recent studies have highlighted that the clinically relevant frequency range in any given patient might vary, as different oscillatory signatures across the frequency spectrum have been associated with distinct motor and non-motor symptoms [5].

In conclusion, our findings contribute to understanding physiological changes in beta oscillations related to therapies and stimulation. They also reveal a similar pattern of beta modulation and motor outcomes across the four conditions and in chronic states. Considering that implantable devices with sensing capabilities were recently developed, further multicentric prospective studies, on larger sample, should be conducted to confirm our results and to provide a better understanding of disease-related brain activity patterns and their modulation in response to different input signals (symptoms, motor activity, or other behavioural features), in order to develop real-time sensing algorithms and bring aDBS therapy closer to clinical practice and real-world conditions.

CRediT authorship contribution statement

Giulia Giannini: Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Ilaria D'Ascanio:** Writing – original draft, Formal analysis, Data curation. **Luca Baldelli:** Formal analysis, Data curation. **Ilaria Cani:** Formal analysis, Data curation. **Alfredo Conti:** Writing – review & editing. **Gaetano Leogrande:** Methodology, Formal analysis. **Giovanna Lopane:** Formal analysis, Data curation. **Paolo Mantovani:** Writing – review & editing. **Marianna Pegoli:** Writing – review & editing. **Pietro Cortelli:** Writing – review & editing, Supervision, Methodology. **Lorenzo Chiari:** Writing – review & editing, Supervision, Methodology. **Giovanna Calandra-Buonaura:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Luca Palmerini:** Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships:

- Giulia Giannini reports no competing interests for this work. Outside the present work, Dr. Giannini has received honoraria for speaking engagements or consulting activities from Bial.
- Ilaria D'Ascanio reports no competing interests.
- Luca Baldelli reports no competing interests.
- Ilaria Cani reports no competing interests for this work. Outside the present work, Dr. Cani has received honoraria for speaking engagements or consulting activities from Bial.
- Alfredo Conti reports no competing interests.
- Gaetano Leogrande is an employee and shareholder of Medtronic PLC.
- Giovanna Lopane reports no competing interests.
- Paolo Mantovani reports no competing interests.
- Marianna Pegoli reports no competing interests.
- Pietro Cortelli reports no competing interests for this work. Outside the present work, Prof. Cortelli has received honoraria for speaking engagements or consulting activities from Jazz Pharmaceuticals, Abbvie, Zambon, Lundbeck.
- Lorenzo Chiari is co-founder and owns shares of mHealth Technologies.
- Giovanna Calandra Buonaura reports no competing interests for this work. Outside the present work, Prof. Calandra Buonaura has received honoraria for speaking engagements or consulting activities from Bial.
- Luca Palmerini is co-founder and owns shares of mHealth Technologies.

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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.2025.107942.

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