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High beta activity in the subthalamic nucleus and freezing of gait in Parkinson's disease

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ABSTRACT

Objective: Oscillatory activity in the beta band is increased in the subthalamic nucleus (STN) of Parkinson's disease (PD) patients. Rigidity and bradykinesia are associated with the low-beta component (13–20 Hz) but the neurophysiological correlate of freezing of gait in PD has not been ascertained.
Methods: We evaluated the power and coherence of the low- and high-beta bands in the STN and cortex (EEG) of PD patients with (p-FOG) ($n = 14$) or without freezing of gait (n-FOG) ($n = 8$) in whom electrodes for chronic stimulation in the STN had been implanted for treatment with deep brain stimulation.
Results: p-FOG patients showed higher power in the high-beta band ($F = 11.6$, $p = 0.002$) that was significantly reduced after L-dopa administration along with suppression of FOG ($F = 4.6$, $p = 0.042$). High-beta cortico-STN coherence was maximal for midline cortical EEG electrodes, whereas the low-beta band was maximal for lateral electrodes ($\chi^2 = 20.60$, $p < 0.0001$).
Conclusions: The association between freezing of gait, high-beta STN oscillations and cortico-STN coherence suggests that this oscillatory activity might interfere in the frontal cortex–basal ganglia networks, thereby participating in the pathophysiology of FOG in PD.

Introduction

Freezing of gait (FOG) is a common, long-term feature of Parkinson's disease (PD). It is characterized by brief episodes of inability to take a step or by extremely short steps that typically occur on initiating gait or on turning while walking (Giladi et al., 1992; Nutt et al., 2011). FOG can become an important source of disability and its pathophysiology remains elusive (Nieuwboer and Giladi, 2013; Okuma and Yanagisawa, 2008).

The implantation of electrodes for deep brain stimulation (DBS) in patients with PD has allowed recording field potentials, particularly from the subthalamic nucleus (STN), and recognizing specific patterns of activity according to the motor states. Thus, increased oscillatory activity in the beta range (10–35 Hz) features the "off" motor state whereas a marked reduction in this beta activity, frequently associated with an increased gamma activity, marks the "on" motor state (Brown et al., 2001; Levy et al., 2001; Priori et al., 2002). Furthermore, in the "on" associated with levodopa-induced dyskinesias and impulsivity distinct peaks in the theta-alpha bands are also observed (Alonso-Frech et al., 2006; Rodriguez-Oroz et al., 2011).

The beta band has been particularly well studied in numerous studies. A correlation between rigidity and bradykinesia and beta spectral power in the STN, (Lopez-Azcarate et al., 2010) and between motor improvement and a reduction in beta power after L-dopa treatment has

Abbreviations: STN, subthalamic nucleus; PD, Parkinson's disease; FOG, freezing of gait; EEG, electroencephalography; DBS, deep brain stimulation; LFP, local field potential; UPDRS, unified Parkinson's disease rating scale; CT, computerized tomography; MR, magnetic resonance; SMA, supplementary motor area; PPN, pedunculopontine nucleus; SPECT, photon emission tomography; HM-PAO, technetium-99m-hexamethyl-propyleneamine oxime.

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been reported in PD patients (Kuhn et al., 2006; Kühn et al., 2009) although not confirmed in another study (Stein and Bar-Gad, 2013). Recently, it has been proposed that beta band activity can be further sub-divided into low- (13–20 Hz) and high- (21–35 Hz) frequency components where the low-beta band shows a greater decrease in power than the high-beta component in response to dopaminergic treatment (Lopez-Azcarate et al., 2010; Priori et al., 2004). Accordingly, taking into consideration that FOG has a complex and ill-defined pathophysiology (Earhart, 2013; Nieuwboer and Giladi, 2013), and that beta activity promotes tonic activity at the expense of voluntary movements (Jenkinson and Brown, 2011), we investigated if FOG could be associated with enhancement of the higher or the lower frequency component of the beta band in PD patients.

Material and methods

Patients

We studied 22 patients with PD (Hughes et al., 1992) who had STN deep brain stimulation (DBS) electrodes implanted bilaterally (Guridi et al., 2000; Rodriguez-Oroz et al., 2001) (see supplementary material). According to the preoperative presence of FOG in the OFF medication state (without dopaminergic medication), based on direct observation and on the score for item 14 (freezing) of Unified Parkinson's Disease Rating Scale (UPDRS)-II patients were classified as: (i) non-FOG (n-FOG) if they were without episodes of FOG during the motor examination and scored 0 for item 14 of the UPDRS-II; (ii) positive-FOG (p-FOG) if FOG was present during the motor examination, and if they scored $> = 1$ for item 14 of the UPDRS-II. Only those patients in whom there was no doubt about the presence or absence of FOG in the OFF medication state were considered for the study. As a criterion for surgery, FOG was not present during the ON motor examination. Accordingly, only patients with episodes of FOG in OFF and who had no FOG after L-dopa challenge were included in the study. Rigidity, bradykinesia and tremor were scored using UPDRS-III (Table 1). The local Ethics Committee for Medical Research at the Clinica Universidad de Navarra approved the study and all patients provided their written informed consent.

Recording procedure and data acquisition

STN local field potentials (LFPs) were recorded from DBS electrodes 4–5 days after implantation and before internalizing the connector cables and connecting the pulse generator. Activity from five EEG channels (C3, Cz, C4, F3 and F4, referenced to both ear lobes) was obtained simultaneously. Patients were studied seated at rest (awake, relaxed with their eyes open, without voluntary movements) in the OFF and ON motor states (see supplementary material).

Power spectrum analysis

Artifact-free segments (300 s) were selected for each patient in the OFF and ON states. We estimated the Welch periodogram (Halliday et al., 1995) using non-overlapping segments of four second length and a Hanning window, giving a resolution of 0.25 Hz per bin. In these spectra, the mean power was measured for three different frequency bands: theta–alpha (4–12 Hz), low-beta (13–20 Hz) and high-beta (21–35 Hz). A peak of activity was defined as an increase in power of $\geq$2 SD over the baseline spectrum in any band. With these values, the relative peak value in the OFF and ON recordings was calculated relative to the baseline of the spectrum (Valencia et al., 2012). Relative power values in lieu of absolute power values were chosen to reduce inter-subject variability and to facilitate normalization of the data.

Neuroimaging: location of electrode contacts

The position of each electrode contact was obtained by specific analysis of pre and postoperative CT and MR images which were co-registered as previously described (Rodriguez-Oroz et al., 2011) (supplementary material).

Table 1
Clinical characteristics of n-FOG and p-FOG PD patients.

	n-FOG PD n = 8	p-FOG PD n = 14	p-Value
Age (years)	57.3 (11.9)	60.0 (6.4)	0.41
Gender (male %)	75%	57.1%	0.66
Disease duration (years)	12.6 (4.3)	12.9 (4.1)	0.99
MMSE	29.0 (27–30)	28.0 (26–30)	0.66
GDS	4.5 (3.0–5.25)	10.0 (6.7–13.0)	0.11
UPDRS-III OFF	31.6 (9.7)	42.6 (11.6)	0.033
Freezing OFF (item 14 in UPDRS-II) *	100% 0	10 patients (71%): 3 4 patients (29%): 2	<0.0001
UPDRS tremor OFF	4.5 (1.0–7.0)	1.0 (0.0–4.0)	0.15
UPDRS rigidity OFF	6.6 (1.6)	10.5 (3.7)	0.007
UPDRS bradykinesia OFF	10.0 (3.9)	15.0 (6.2)	0.052
UPDRS-III ON	9.3 (5.4)	15.8 (9.4)	0.093
Freezing ON (item 14 in UPDRS-II) *	100% 0	100% 0	–
UPDRS tremor ON	2.0 (1.0–3.0)	0.0 (0.0–0.5)	0.38
UPDRS rigidity ON	1.0 (1.0)	6.0 (3.9)	0.008
UPDRS bradykinesia ON	4.0 (2.0)	6.5 (3.4)	0.27
L-Dopa/day (mg) [a]	807.5 (325.0)	1178.9 (467.3)	0.90
Dopamine agonist (mg) [b]	281.4 (189.2)	163.3 (169.7)	0.25
Total L-dopa equivalent daily dose (mg) [c]	1088.9 (427.7)	1342.2 (525.6)	0.35

Values are stated as mean (SD), except for MMSE, GDS and tremor, stated as median (interquartile range).
Rigidity (item 22 of the UPDRS-III), bradykinesia (items 23–26 of the UPDRS-III) and tremor (items 20–21 of the UPDRS-III).
FOG: Freezing of gait.

* Number and % of patients with each score in the item.

[a] The L-dopa/day dose (mg) was calculated as follows: L-dopa (mg) + L-dopa retard (mg) * 0.77. In case of entacapone/tolcapone co-administration, the L-dopa dose was multiplied by 1.33.

[b] Dopamine agonist = L-dopa equivalents of dopaminergic agonists. The formula used was: [rotigotine (mg) * 5] + [ropinirole (mg) * 20] + [pramipexole (mg) * 67] +[cabergoline (mg) * 67] + [pergolide (mg) * 100].

[c] Total L-dopa equivalent daily dose = dopaminergic agonists + L-dopa.

Topographic analysis of LFPs

To study the distribution of the recorded low- and high-beta activities, we looked for phase reversals in contiguous channels of the STN recordings. The activity observed with opposite polarity in two successive bipolar channels may have its origin around a common electrode (i.e., the activity with opposite polarity in channels 2–3 and 1–2 is probably generated around contact 2) (see supplementary material). The location of the phase reversals, together with the contact coordinates obtained in the image analysis, allowed us to accurately represent the topography of these oscillatory activities in the STN.

Coherence analysis

The coherence between the different STN channels and ipsilateral/midline EEG channels was estimated for the low- and high-beta bands in the OFF state, and for the high-beta band in the ON state as outlined by Halliday et al. (1995) and in previous reports from our group (Alegre et al., 2010; Rodriguez-Oroz et al., 2011) (see supplementary material).

Coherence values were considered significant when p values were below 0.01 in a bandwidth of 5 bins (~1 Hz). The maximal coherence value per side, the frequency at which it occurred, and the channel in which it was observed were used for statistical comparisons.

Statistics

The Student's *t*-test and Mann–Whitney test were used for variables with normal and non-normal distributions (non-transformed demographic values), respectively. Normality of non-normally distributed variables was achieved by applying a square-root or logarithmic transformation. To compare a quantitative outcome in more than two groups, ANOVA or ANCOVA tests were performed based on the absence or presence of covariates. A two factor-mixed design ANOVA, that included age and rigidity and total UPDRS-III as covariates, was applied to test changes in subthalamic power and cortico-subthalamic coherence between the motor states according to the presence or absence of FOG. The distribution of residuals, homoscedasticity and Mauchly's test of sphericity were tested and assumptions were met. Fisher's exact text was applied to test for differences in the localization of maximum coherences. Statistical analysis was performed using R 2.14.2 software.

Results

Eight patients were classified as n-FOG and 14 as p-FOG in the OFF state (Table 1) (supplementary material). The total UPDRS-III and rigidity scores in the OFF state and the rigidity score in the ON state were higher in p-FOG patients. No other differences were observed between groups.

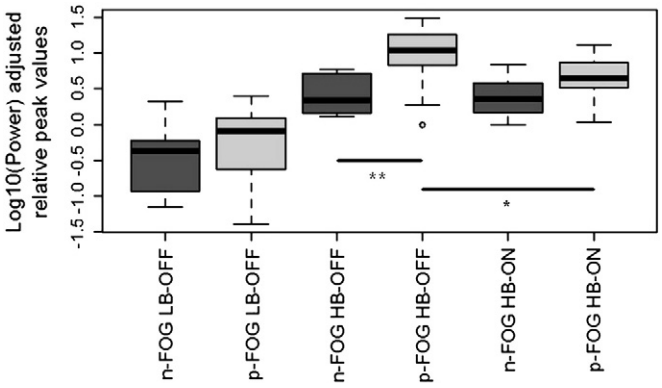

Fig. 2. Relative peak power in the low- beta (LB) and high-beta (HB) bands in p-FOG (light gray) and n-FOG (dark gray) patients in the OFF (left) and ON (right) medication states (multivariate model adjusted for rigidity and UPDRS-III scores). *p < 0.05 **p < 0.005.

Power spectrum of the STN oscillatory activity

In the OFF state, peaks in the theta–alpha, low-beta and high-beta bands were seen in 61.9%, 97.6% and 95.2% of nuclei, respectively. There were no differences between p-FOG and n-FOG patients in the percentage of peaks present in any of the bands (data not shown) (Fig. 1). ANCOVA analyses adjusted for the rigidity ($F = 11.1$, $p = 0.002$) and UPDRS-III scores ($F = 14.8$, $p = 0.0005$) showed that p-FOG patients exhibited a significantly higher high-beta peak relative power than n-FOG patients (Fig. 2). Theta–alpha ($F = 0.53$, $p = 0.48$), and low-beta bands ($F = 1.7$, $p = 0.20$) did not show any difference in relative power peak based on FOG presence.

FOG disappeared after dopaminergic treatment in the p-FOG patients as required by the surgical protocol (Table 1). Changes in the high-beta peak power between the OFF and ON motor states in the two groups of patients were analyzed in a repeated measures model, and a significant interaction between the motor state and FOG group was found ($F = 4.6$, $p = 0.042$). p-FOG patients showed a significant decrease in the high-beta peak after dopaminergic treatment while no differences between motor states were observed in the n-FOG group (Fig. 2). In the ON state, there was no difference between groups with respect to the high-beta power ($F = 3.1$, $p = 0.09$) (Fig. 2).

Cortico-subthalamic coherence in the beta bands

In the OFF state, cortico-STN coherence was significantly higher for the high-beta band than for the low-beta band ($t = 12.5$, $p = 0.0017$).

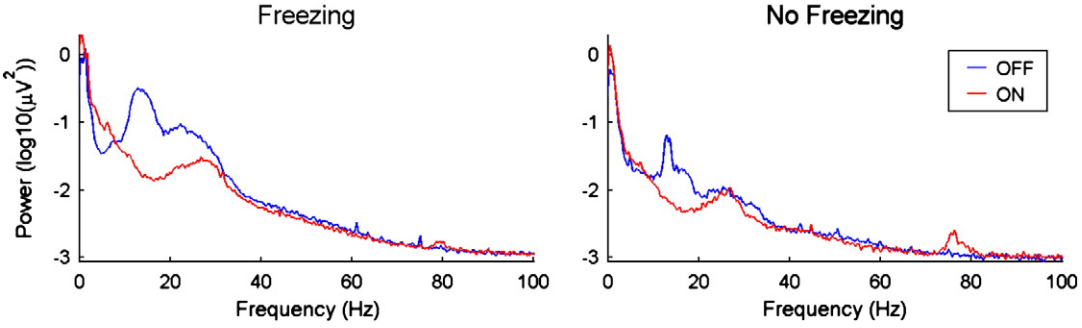

Fig. 1. Mean power spectrum in the 0–100 Hz range (logarithmic scale) at the intermediate contact pairs in the two groups of patients: Parkinson's disease with FOG, n = 27 nuclei (left side); Parkinson's disease without FOG, n = 13 nuclei (right side) in the OFF state (blue line) and in the ON state (red line). The spectrum for the patients with FOG in the OFF state shows two peaks in the low- and high-beta ranges. In the ON state, the low-beta peak is suppressed and the high-beta peak is markedly reduced in this group. In the patients without FOG, the same two peaks are observed in the OFF state, but with lower power, particularly in the high-beta peak. In the ON state, the low-beta peak is suppressed, but the high-beta peak only shows minimal changes.

Table 2
Localization of the generators of activity in the low- and high-beta bands.

	Low-beta OFF	High-beta OFF	High-beta ON	Low-beta OFF vs. High-beta OFF p-Value	High-beta OFF vs. High-beta ON p-Value
X coordinate	10.73 (1.65)	11.01 (1.50)	10.92 (1.52)	0.54	0.73
Y coordinate	−1.28 (1.71)	−1.60 (1.54)	−1.66 (1.62)	0.49	0.87
Z coordinate	−2.70 (1.56)	−2.62 (1.27)	−2.65 (1.26)	0.85	0.90

Mean (standard deviation).
X, Y and Z coordinates represent the position in the mediolateral, anteroposterior and dorsoventral axes. p-Values are not corrected for multiple comparisons.

There were no differences in low-beta (OFF state) or high-beta coherence (in OFF and ON states) between p-FOG and n-FOG patients ($t = 0.20$, $p = 0.85$; $t = 0.40$, $p = 0.70$ and $t = 1.39$, $p = 0.17$, respectively). The high-beta coherence did not change between motor states for the group of patients as a whole, or for the p-FOG and n-FOG groups considered separately ($p > 0.05$ for all comparisons).

Topography of the low- and high-beta activities

Low-beta and high-beta peak phase reversals were similarly located in the dorsal-intermediate region of the STN (Table 2). Accordingly, the subthalamic contacts showing highest cortico-STN coherence values did not differ between bands ($\chi^2 = 5.52$, $p = 0.24$). However, the cortical topography of the coherence in both beta bands was different ($\chi^2 = 20.60$, $p < 0.0001$; Table 3). High-beta coherence was maximal in pairs comprising the cortical midline electrode Cz (73% of STN contact pairs), while low-beta coherence was maximal in more lateral regions of the motor cortex (mainly C3 and C4; 59% of STN contact pairs).

Discussion

FOG frequently improves with dopaminergic and STN-DBS therapies soon after it appears in PD patients. However, this therapeutic response is generally reduced after long-term evolution (Merola et al., 2011; Stolze et al., 2001). In this paper we describe the oscillatory activity of the STN in patients in whom FOG is suppressed after dopaminergic treatment. We have shown that PD patients with FOG have a higher STN high-beta power in the OFF state than patients without FOG, while there was no difference in low-beta power between the groups. The high-beta activity was reduced in p-FOG patients in response to levodopa, which coincided with the disappearance of FOG. Furthermore, maximal coherence in the high-beta activity was located in the midline cortex corresponding to the supplementary motor area (SMA), cingulate cortex and leg area of the primary motor cortex (M1), while low-beta coherence was highest in the lateral M1 region.

FOG and high-beta activity in the STN

Oscillatory activity in the beta band in the STN is typically recorded in PD patients in the OFF motor state in resting state (Brown et al., 2001; Kuhn et al., 2006; Priori et al., 2004). While an association between rigidity and bradykinesia and the low-beta component has been reported (Kühn et al., 2009), no similar study regarding FOG has been conducted before. In this study, we did not observe any difference between p-FOG and n-FOG patients in the low-beta or theta–alpha oscillatory activity recorded in the OFF medication state. However, we found that p-FOG patients exhibited higher high-beta power than n-FOG patients in the OFF state, and that the disappearance of FOG after dopaminergic treatment in p-FOG patients was associated with a decrease in the high-beta peak. Moreover, in the ON state, when no FOG was present in either group, no differences were observed in this oscillatory band. Importantly, these results were maintained after correcting for the UPDRS total score, suggesting that this finding was not due to a greater disease severity and higher global motor disturbance.

Altogether, our results suggest a relationship between FOG and high-beta oscillations in the STN. In keeping with this, increased synchronization of high-beta activity in the substantia nigra pars reticulata during walking has been reported in hemiparkinsonian rats, suggesting that this activity might contribute to gait impairment in the parkinsonian state (Avila et al., 2010). Recently, a small study described a divergent pattern in STN beta band power change in three n-FOG and three p-FOG subjects during normal walking (Singh et al., 2013). n-FOG patients showed a reduction of the oscillatory activity in the whole beta band when walking compared to standing, while p-FOG patients showed no change in the high-beta band (in agreement with our data) and an increase in the low-beta band. In addition, during freezing episodes, progressive step reduction was associated with an increase in the beta band power which reached maximal statistical significance in the high-beta range. While studying FOG during walking is undoubtedly the most direct approach to ascertain this problem, these results are limited by the small number of patients (3 per group). Still, these findings are compatible with the potential role of high-beta oscillations found in our study.

Recently, an association between alpha activity in the pedunculopontine nucleus (PPN) and gait speed in 7 PD patients in the OFF state was described, along with an attenuation of this activity during FOG episodes in a single case (Thevathasan et al., 2012). The apparent discrepancy between our results and those of this last-mentioned study might be due to physiological differences between PPN and STN neuronal activities, by the fact that we considered the low- and high-beta activity components rather the full range of the beta band (Thevathasan et al., 2012), or by the type of PD patients enrolled in the study. Thus, our patients still showed a positive response to dopaminergic treatment unlike the patients typically submitted to DBS in the PPN (Jenkinson and Brown, 2011; Thevathasan et al., 2012). In this regard, it is worth noticing that Singh et al. found changes in the beta activity in the STN in PD patients with levodopa responsive FOG in keeping with our results (Singh et al., 2013).

The findings reported here have some limitations that need to be acknowledged. First, FOG was not evaluated using a specific questionnaire. Instead, patients were readily identified by clinical observation (motor examination in the OFF and ON motor states) and the freezing item of the UPDRS-II, which in this population of patients was probably enough for the simple identification of FOG in the OFF state. Also, STN

Table 3
Cortical electrodes showing maximal coherence for the different beta bands.

	Frontal electrodes (F3, F4) Observed (expected)	Central lateral electrodes (C3, C4) Observed (expected)	Central midline electrode (Cz) Observed (expected)
Low-beta, off state	6 (4.69)	26 (12.98)	12 (26.33)
High-beta, off state	5 (4.69)	7 (12.98)	32 (26.33)
High-beta, on state	2 (3.62)	3 (10.04)	29 (20.34)

studies were made in the resting state and not during episodes of FOG because of practical limitations with the recording set-up. However, abnormal oscillatory power for a given band in the brain may also be interpreted as being indicative of a pathophysiological state, as described previously in PD patients with pathological impulsivity (Rodriguez-Oroz et al., 2011). Thus, a resting difference in the high beta activity between p-FOF and n-FOG patients might be interpreted as a difference in the predisposition to freeze while walking. Accordingly, we may speculate about possible mechanisms whereby pathologically increased high-beta activity in the STN and frontal cortex could be associated with FOG in PD. Enhanced cortical beta band activity has been associated with the facilitation of postural activity, including tonic holding contraction, while inhibiting voluntary movement (Gilbertson et al., 2005). Moreover, beta suppression is critical for the facilitation of continuous movement sequences (Joundi et al., 2013). Thus, it might be that high beta activity interferes with anticipatory postural adjustments in preparation for stepping, thereby facilitating exaggerated postural contraction of the lower limbs associated with FOG (Jacobs et al., 2009). Alternatively, high beta activity might hamper the automatic sequence of walking as suggested by the finding of an increment in high beta activity in the STN coinciding with the progressive reduction of step length that characterizes FOG (Singh et al., 2013). In any case, we acknowledge that definitive corroboration of our findings and hypotheses requires direct testing by recording episodic events of FOG. Importantly, our results cannot be generalized to PD patients in whom FOG is not responsive to dopaminergic treatments. Finally, we need to admit that the findings do not allow establishing firmly a causal relationship between high beta and FOG. However, the same limitation may be applied to most findings regarding neuronal oscillatory activity and PD.

Topography of the low- and high-beta coherence

While both beta bands had a similar topography in the STN, the low-beta component showed maximal coherence with the STN in electrodes located around the lateral primary motor cortex (C3 and C4), which contains the arm representation, while coherence in the high-beta was found in the Cz midline electrode, which mainly records the activity of the SMA, the anterior cingulate cortex and the leg area of M1. In keeping with our data, a magnetoencephalography/LFP in the STN study in PD patients showed that both high-beta coherence and low-beta coherence were maximal over the motor region with a slightly different topography, being high-beta coherence more medial (Litvak et al., 2011). Interestingly, Shine et al. (2013) recently described an increase in the theta frequency band in the EEG (frontal and central cortices) during freezing, which might be related to the presence of conflict-related signals (Alegre et al., 2013), along with increased beta activity in the frontal area. On the other hand, p-FOG patients showed less activation of the SMA than n-FOG patients during motor imagery of walking tasks in an fMRI study (Snijders et al., 2011), and FOG severity was correlated with lower gray matter volume in the frontal and cingulate areas (Kostic et al., 2012). In addition, studies using single photon emission tomography (SPECT) with technetium-99m-hexamethyl-propyleneamine oxime (HM-PAO) in healthy individuals while walking have shown activation of the SMA and of the medial primary sensorimotor and cingulate cortices (Fukuyama et al., 1997; Hanakawa et al., 1999). These data support a putative relationship between the cortical topography (SMA, leg area of M1) of the high-beta band and its involvement in the presence of FOG. An alternative explanation would be that the spectrum of beta activity in PD patients is somatotopically organized and the lower limb representation exhibits higher activity than the upper limb. However, there is no indication as yet either by single cell recording intra-operatively (Zaidel et al., 2009) or by local field potentials and magnetoencephalography (Hirschmann et al., 2011).

Conclusion

In sum, the presence of higher high-beta activity in this group of patients with FOG still responsive to dopaminergic treatments, the fact that this oscillatory activity in p-FOG patients is reduced concomitantly with an improvement in FOG after dopaminergic treatment, and the lack of differences in this band between both patient groups in the ON state when no FOG was present, suggest a link between high beta and FOG. However, the possibility that high beta is actually associated with other general aspects of the disorder, like disease severity, cannot be excluded. Our data suggest that these anomalies are conveyed by physiological dysfunction of the frontal cortex–basal ganglia networks via the motor (SMA, medial primary sensorimotor cortex) and associative (cingulate cortex) STN loops. Further studies of the STN and cortical oscillatory activities during episodic FOG are necessary to corroborate these findings.

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Conflict of interest

Dr. Rodriguez-Oroz served on scientific advisory board for UCB, received honorarium for lectures, travel and accommodation to attend scientific meetings from UCB and Lundbeck and received research support from national and regional government bodies in Spain and Europe (S-PE12BN01, GV-2011111074, EC11-380, PI11/02109, DFG 11/0190 and PIM2010, ERN-00733).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.nbd.2013.12.005.

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