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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.