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Long term correlation of subthalamic beta band activity with motor impairment in patients with Parkinson's disease

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HIGHLIGHTS

- Subthalamic beta activity was recorded with an implantable DBS pulse generator over 8 months in 12 patients with Parkinson's disease.
- Dopaminergic medication suppresses subthalamic beta activity at operation, 3 and 8 months after DBS.
- Beta activity correlates with parkinsonian symptom severity over time.

ABSTRACT

Objectives: To investigate the long term association of subthalamic beta activity with parkinsonian motor signs.
Methods: We recruited 15 patients with Parkinson's disease undergoing subthalamic DBS for local field potential recordings after electrode implantation, and at 3 and 8 months post-operatively using the implantable sensing enabled Activa PC + S (Medtronic). Three patients dropped out leaving 12 patients. Recordings were conducted ON and OFF levodopa at rest. Beta (13–35 Hz) peak amplitudes were extracted, compared across time points and correlated with UPDRS-III hemibody scores.
Results: Peaks in the beta frequency band (13–35 Hz) in the OFF medication state were found in all hemispheres. Mean beta activity was significantly suppressed by levodopa at all recorded time points ($P < 0.007$) and individual beta power amplitude correlated with parkinsonian motor impairment across time points and dopaminergic states (pooled data; $\rho = 0.25$, $P < 0.001$).
Conclusions: Our results indicate that beta-activity is correlated with parkinsonian motor signs over a time period of 8 months.
Significance: Beta-activity may be a chronically detectable biomarker of symptom severity in PD that should be further evaluated under ongoing DBS.

1. Introduction

Oscillatory activity in the human motor network is synchronized in the beta frequency band (13–35 Hz) at rest (Pfurtscheller and Lopes da Silva, 1999). Features like movement related desynchronization and post movement rebound synchronisation have led to the suggestion that beta activity serves to promote maintenance of the status quo and is, in these terms, antikinetic (Engel and Fries, 2010). Patients with Parkinson's disease (PD) exhibit exaggerated beta oscillations in the basal ganglia, which have been related to bradykinesia and rigidity in line with the above hypothesis (Brittain and Brown, 2014). Beta activity recorded from implanted deep brain stimulation (DBS) electrodes in the subthalamic nucleus (STN) of PD patients correlates with signs of parkinsonian symptom

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severity (as assessed by UPDRS-III) in the hypodopaminergic state (Neumann et al., 2016a). Both, dopaminergic medication and DBS significantly decrease beta activity in parallel with the clinically apparent symptom alleviation (Brown et al., 2001; Neumann et al., 2016b), and the degree of beta suppression correlates with the change in UPDRS-III scores for either therapeutic procedure (Kühn et al., 2006; Kuhn et al., 2009; Oswal et al., 2016). Thus, beta amplitude may serve as a biomarker for instantaneous monitoring of concurrent therapeutic demand (Little and Brown, 2012). This has led to the trial of adaptive deep brain stimulation algorithms, utilizing a closed loop system that can trigger stimulation according to the level of beta activity in the STN. (Little et al., 2013, 2016a,b; Rosa et al., 2015) Although initial results have been promising, most of the relevant studies have been performed a few days after electrode implantation with DBS leads externalized. Therefore, little is known about the evolution of beta activity after chronic DBS and more importantly its relation to motor impairment over the long term. In the present study we aim to investigate the relation of subthalamic beta activity with parkinsonian motor signs directly after DBS surgery, after three months and eight months of chronic continuous DBS with an implantable sensing enabled pulse generator.

2. Materials and methods

Fifteen patients with Parkinson's disease who underwent bilateral implantation of DBS electrodes in the STN were included in this study. All patients participated with informed consent, which was approved by the local ethics committee. The DBS macroelectrode used was model 3389 (Medtronic). Contacts 0 and 3 were the lowermost and uppermost contacts, respectively. Intraoperative microelectrode recordings were used for target mapping in all patients. Correct placement of the DBS electrodes was confirmed by three-dimensional electrode localization (Horn and Kuhn, 2015) using the in-house LEAD toolbox (LEAD-DBS; www.lead-dbs.org). In brief, preoperative and postoperative MR images are normalized to MNI space and electrode tips are identified and plotted on a three dimensional MNI version of the Morel Atlas (Jakab et al., 2012). All contact pairs included in the analysis had at least one contact inside the subthalamic nucleus. Three patients were excluded from further analysis (two subjects due to refusal of withdrawal from medication at 3 and 8 months, one subject did not complete the 8 months' follow-up). Clinical details for the remaining 12 patients (age 63.16 ± 1.4 MEAN ± S.E.M.) are shown in Table 1. Subthalamic local field potential (LFP) recordings were performed at rest from adjacent contact pairs (01, 12, 23) ON and OFF dopaminergic medication at three time points: first at baseline after implantation of the Activa PC + S (Medtronic) pulse generator (MEAN 2.1 days ± 0.2 S.E.M; on average 7.6 ± 0.4 days after electrode implantation), after three months post-implantation and after 8 months post-implantation. Patients were left on their regular medication. If patients' felt relatively OFF before the ON medication recording, a single dose of a fast-acting levodopa agent was administered (Case 7, 9 and 12 at 3 months and case 1 to 10 at 8 months). Nevertheless, some patients at some timepoints did not show a significant improvement of UPDRS-III scores through medication in the experiment. Notwithstanding this, the decrease of UPDRS-III through medication was highly significant across patients, when assessed with Wilcoxon's signed rank tests ($P < 0.007$ at all timepoints). For OFF medication recordings, patients underwent a 12-h withdrawal from all dopaminergic medication. In three cases pramipexole treatment may have mildly affected the OFF state, as it has a half time of 8–12 h (case 2: 1.05 mg; case 7: 0.35 mg; case 9 1.4 mg). All other cases did not take dopamine agonists. LFPs were amplified (×2000), filtered at 1–100 Hz, and recorded at a sampling rate of either 422 or 800 Hz onto the pulse generator. During recordings, patients were seated comfortably in an armchair. LFP recordings of approximately one-minute length were obtained for each bilateral contact pair in subsequent sessions and cut to exact 60 s segments for analyses. Deep brain stimulation was turned off at least 30 min before the first recording. All data were temporarily stored to the IPG for the time of recording and thereafter downloaded to a personal computer for offline analysis using low frequency proximal (~4 cm) telemetry. Short recording lengths were chosen to keep battery discharge related to telemetric data transfer minimal. All sampled data traces were downsampled to 422 Hz where necessary and visually inspected for artefacts. Cardioelectric pulse artefacts were present in the majority of recordings from contact pairs 01, which led to the exclusion of all 01 contact pairs from the analysis. Segments with artefacts were rejected from the remaining contact pairs, leaving 54.3 ± 1 s (MEAN ± S.E.M.) per recording and data were analyzed using custom MATLAB (The Mathworks, Natick, MA, USA) code based on SPM12 for magnetoencephalography/ electroencephalography (Wellcome Trust Centre for Neuroimaging, UCL, London, UK) and FieldTrip (Donders Center for Cognitive Neuroimaging, University Nijmegen, Nijmegen, the Netherlands). The continuous rest recordings were divided into arbitrary epochs of 1 s (422 samples) and transferred into the frequency domain using Fourier transform-based methods. This resulted in a frequency resolution of 1 Hz over 100 frequency bins. Power-spectra were normalized to the percentage of total power of

Table 1
Patient details.

N	Age at OP	Sex	Disease duration (y)	UPDRS-III preop OFF/ON	UPDRS-III Baseline** mOFF/mON	UPDRS-III 3 months** FU mOFF/ mON	UPDRS-III 8 months** FU mOFF/ mON	Medication (LED) at 8 months FU	DBS effect at 8 months FU (% preop UPDRS)	Stimulation parameters at 8 months FU
1	63	M	10	46/26	43.5/16.5	34.5/25.5	35.5/24	1375 mg	68	L: 2-, 2 V; R: 2-,2.2 V; 60 μs; 130 Hz
2	63	M	15	49/35	25/20.5	26/25	25.5/25	105 mg[a]	56	L: 2-, 3 V; 2-,3-, 3.2 V; 60 μs; 130 Hz
3	63	F	8	56/16	24/15.5	48/31.5	42/24	665 mg	62	L: 3-, 3.2 V; R: 1-, 3.5 V; 60 μs; 130 Hz
4	66	M	8	26/17	28/29	20/18.5	19.5/12.5	1064 mg	48	L: 1-, 1.5 V; R: 1-, 3.3 V; 60 μs; 130 Hz
5	73	M	9	35/20	23/17	33/22.5	27/18.5	1450 mg	56	L: 2-, 3.8 V; R: 2–3.9 V; 60 μs; 130 Hz
6	63	M	16	42/29	36/32	26.5/29	39.5/29	950 mg	57	L: 1-,2-, 3.5 V; R: 1-,2–1.8 V; 60 μs; 130 Hz
7	72	F	5	34/19	31/31	25.5/20	25/14	360 mg[a]	41	L: 2-, 3.8 V; R: 1–3.9 V; 60 μs; 130 Hz
8	61	F	10	20/4	19.5/13	18.5/20	21.5/13.5	500 mg	43	L: 2-, 3 V; R: 2–1 V; 60 μs; 130 Hz
9	58	F	7	34/24	24/16	32.5/27.5	37/23.5	52 mg[a]	43	L: 2-, 3 V; R: 2–1.8 V; 60 μs; 130 Hz
10	56	M	18	41/20	20/16	51.5/33.5	41/17.5	665 mg	45	L: 1-, 2.2 V; R: 1–3.5 V; 60 μs; 130 Hz
11	63	M	9	31/14	19/15.5	18/12	17/13.5	1207 mg	60	L: 1–2.8 V; R: 1–2.7 V; 60 μs; 130 Hz
12	60	M	7	59/32	28.5/10	35/26.5	31.5/20	1325 mg	80	L: 1-, 3 V; R: 1-, 3.2 V; 60 μs; 130 Hz
Mean	63.2	4 F	10.2		27/19	31/24	30/20	817.2 mg	54.9%	

** All UPDRS-III scores were obtained at the time of recording after at least 30 min OFF DBS.
[a] Cases 2/7/9 were on pramipexole treatment (1.05 mg/0.35 mg/1.4 mg); LED = Levodopa Equivalent Dose.