

Subthalamic oscillations correlate with motor impairment in patients with Parkinson's disease

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Subthalamic synchronized oscillatory activity correlates with motor impairment in patients with Parkinson’s disease

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Abstract

Objective: Beta band oscillations in the subthalamic nucleus (STN) have been proposed as a pathophysiological signature in patients with Parkinson's disease (PD). The aim of this study was to investigate the potential association between oscillatory activity in the STN and symptom severity in PD.

Methods: Subthalamic local field potentials were recorded from 63 PD patients in a dopaminergic OFF state. Power-spectra were analyzed over the frequency range from 5-95 Hz, and correlated with individual UPDRS-III motor scores in the OFF state.

Results: A correlation between total UPDRS-III scores and 8–35 Hz activity was revealed across all patients ($p=0.44$, $P<0.0001$). When correlating each frequency bin, a narrow range from 10 – 15 Hz remained significant for the correlation (FDR corrected $p < 0.05$).

Conclusion: Our results show a correlation between local STN 8-35 Hz power and impairment in PD, further supporting the role of subthalamic oscillatory activity as a potential biomarker for PD.

Introduction

Deep brain stimulation is an effective treatment for patients with Parkinson's disease (PD).¹ One of the hypothesized mechanisms of actions of DBS is a suppression of aberrant oscillatory activity in the target structure.² Enhanced subthalamic oscillations at beta frequency have been proposed as a pathophysiological signature for PD³. A multitude of studies have revealed abnormally synchronized activity in the subthalamic nucleus (STN) over a broad range of 8-35 Hz in PD off state^{2, 4, 5}, and this band, or portions of it, is generally referred to as beta activity. Dopaminergic therapy and DBS both lead to a decrease of spectral power in this frequency band at the same time that the patient experiences clinical symptom alleviation.^{6, 7} The relative difference of 8-35 Hz band power between the ON and OFF state has been shown to correlate with the difference in symptom severity as measured

by the Unified Parkinson's Disease Rating Scale (UPDRS III).⁵ Moreover, DBS-induced suppression of beta band activity correlated with motor performance in PD.⁸ This has led to the idea that subthalamic oscillatory activity could serve as an index of symptom severity for adaptive stimulation in a closed loop system.⁹⁻¹³ Using this approach, an individual threshold of LFP activity would serve as a biomarker to trigger DBS. Whether the scale of 8 – 35 Hz activity in the OFF state correlates with motor impairment within the same state is less clear. Such a correlation is more consistently reported with more complex measures like LFP complexity¹⁴ or standard deviation¹⁵. The observation that also dystonia patients exhibit peaks in the beta frequency band has recently questioned the specificity of beta activity as a biomarker in PD.¹⁶ To corroborate previous findings, this study aims to investigate the association between subthalamic oscillatory activity and parkinsonian symptom severity in a large cohort of PD patients in the dopaminergic off state. We hypothesized that oscillations in the 8 – 35 Hz band reflect the clinical symptom severity, but a narrower sub-band could be identified as particularly relevant. To this end, we additionally conducted correlations for each frequency bin of the power spectra to evaluate spectrally distinct contributions to the broad band 8 – 35 Hz group effect.

Materials and Methods

Sixty-three patients with Parkinson's disease (27 female; age: 61 ± 1.2 years, mean ± standard error of the mean; disease duration: 12 ± 0.7 years; preoperative UPDRS III OFF medication: 35 ± 1.6) who underwent bilateral implantation of DBS electrodes in the STN were included in the study. 16/63 patients have previously been reported (7/9 from Kühn et al., 2006⁵ and 9 patients that are additionally reported in Kühn et al., 2009⁴ are also included in the study. UPDRS was assessed by a movement disorder specialist before surgery (1-12 weeks) in the OFF medication condition (at least 12 hours after withdrawal of all dopaminergic medication). Note that in this archival data set only total UPDRS III scores were available. Informed consent was obtained before inclusion in the study, which was approved by the local ethics committee in accordance with the standards set by the Declaration of Helsinki. Surgical details are described in Kühn et al., 2005.¹⁷ The DBS

macroelectrode used was model 3389 (Medtronic). Contacts 0 and 3 were the lowermost and uppermost contacts, respectively. Correct placement of the DBS electrodes was confirmed by intraoperative microelectrode recordings in all patients and post-operative imaging in 57/63 patients (48/63 MRI, 4/63 CT, 5 no imaging). All patients were studied 1-7 days after implantation of the electrodes, while the leads were still externalized. Subthalamic local field potential (LFP) recordings were performed at rest after the patients underwent a 12 hour withdrawal from dopaminergic medication. Dopamine agonist therapy was discontinued at least one week prior to the recording. LFPs were obtained from three adjacent contact pairs (01, 12, and 23), amplified x50.000 (Digitimer D360, Hertfordshire, UK) and digitized at a sampling rate of 1000 Hz through an A-D converter (CED, Cambridge, UK). During recordings, patients were seated comfortably in an armchair. Overall, 378 STN contact pairs were recorded from 126 electrodes in 63 patients. All data were visually inspected for artefacts and analyzed using custom MATLAB code (The Mathworks, Natick, MA, USA) based on SPM12 for magnetoencephalography/ electroencephalography¹⁸ (Wellcome Trust Centre for Neuroimaging, UCL, London, UK; <http://www.fil.ion.ucl.ac.uk/spm/>) and FieldTrip¹⁹ (Donders Center for Cognitive Neuroimaging, University Nijmegen, Nijmegen, the Netherlands; <http://fieldtrip.fcdonders.nl/>). Contact pairs that did not have artefact free episodes were omitted (10/378 contact pairs from 7/63 patients, although not all the data from any single patient were completely excluded). Segments with artefacts from the remaining contact pairs were rejected before further analysis leading to an average artefact free recording length of 255 ± 12 s. The continuous rest recordings were divided into arbitrary epochs of 1.024 s (1024 samples) and transferred into the frequency domain using Fourier transform-based methods. This resulted in a frequency resolution of 0.98 Hz over 512 frequency bins. Power-spectra were normalized to the percentage of total power of 5 - 45 Hz and 55 - 95 Hz and are further expressed as percent of total power (%). The 0 - 5 and 45 - 55 Hz ranges were omitted so as to avoid contamination by movement artefact and mains noise, respectively. Relative rather than absolute power was analyzed to allow comparison across subjects, as absolute

power is more likely to be dependent on the proximity to the LFP source than relative power and to vary with local tissue properties. For visualization purposes power was averaged across all patients. Statistical analysis was conducted using MATLAB's statistics toolbox. 8 – 35 Hz⁵ band power was averaged across all contact pairs for each patient and correlated with individual UPDRS-III scores. In a subsequent analysis the spectral distribution of an association of clinical symptom severity and power was investigated by correlating the averaged power in each frequency bin in the range of 8 – 35 Hz of the power spectrum (again averaged across all contact pairs) and the preoperative UPDRS III score. Finally, the correlation of the most relevant sub-band is shown. Spearman's rank based correlations were used in all analyses and statistical significance of all correlations was determined by Monte Carlo permutation. Therefore, a test statistic was generated by calculating 10,000 replications of Spearman's correlations from averaged spectral power and UPDRS scores with positions of UPDRS values randomly exchanged. P values are reported as the position of the original p value in the distribution of the test statistic. Multiple comparisons were corrected by controlling the false discovery rate for $\alpha = 0.05$.²⁰

Results

Relative power spectra were averaged across all available contact pairs and electrodes for each patient as displayed in Figure 1A. Spectral peaks in the 8 – 35 Hz range that were present in all patients contributed to rises in amplitude in the group spectrum. Mean 8 – 35 Hz spectral power averaged across all available contact pairs in each patient showed a highly significant association with respective UPDRS-III scores as a measure of clinical symptom severity in the medication OFF state across all patients, as revealed by Spearman's correlation (Figure 1B; Spearman's $\rho = 0.44$, $P < 0.0001$). The additional analysis on the spectral focality using repeated Spearman's correlations for each ~1 Hz bin within the 8 – 35 Hz band averaged across available contact pairs for each patient identified a significant sub-band of adjacent frequency bins from 10 – 14 Hz that were again correlated with respective UPDRS-III scores (Figure 2; $P < 0.05$ FDR corrected for multiple comparisons).

Discussion

Here we demonstrate a link between subthalamic 8 – 35 Hz band power and the clinical symptom severity in a large cohort of PD patients. Our results suggest that spectral 8 - 35 Hz power may be used as a surrogate index of motor symptoms in PD patients. Interestingly, correlations of each frequency bin in this range revealed a sub-band (10 – 14 Hz) that is most robustly correlated with the clinical symptom severity in our patients. This sub-band partially includes the low beta range (13-20 Hz) that has previously been shown more sensitive to levodopa-induced reduction as compared to the high beta band (20-35 Hz)²¹. Taken together these findings could hint to varying functional roles for these frequency bands, with the lower frequency range more implicated in the parkinsonian off state. The major limitation of the current study is that it provides only correlative, and no causal, evidence of a link between subthalamic 8 – 35 Hz activity and motor impairment in PD. Furthermore, the preoperative UPDRS-III scores may not represent the current motor state at the timepoint of the recordings that were performed shortly after surgery when a stun effect is evident, which can lead to a reduction in motor symptoms or may influence oscillatory activity in the target area in a differential pattern according to spectral frequency. Long-term recordings with the newly available implantable pulse generator that can record LFP in parallel with stimulation is currently being tested in patients with PD^{22, 23} and will allow to explore the relationship between motor impairment and oscillatory activity in a more standardized condition. Whether the link between local STN oscillations and motor state is mechanistically important or epiphenomenal remains to be established, but meanwhile even the simple correlation means that the local power of synchronized oscillatory activity may provide a potential feedback signal indicative of the patients' symptom severity.

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- 2. Statistical Analysis: A. Design, B. Execution;
- 3. Manuscript Preparation: A. Writing of the first draft;

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Consultancies: NONE	Expert Testimony: NONE
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Partnerships: NONE	Contracts: NONE
Honoraria: NONE	Royalties: NONE
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Figure legends

Figure 1: Averaged spectral power and 8 – 35 Hz correlation. Averaged power spectra (A) are displayed on the left vertical axes represented by solid red lines. The red shaded areas designate the standard error of the mean for each frequency bin across patients. Non-parametric Spearman's correlation between averaged 8 – 35 Hz power and the clinical symptom severity as measured by the UPDRS-III revealed a significant positive association (B).

Figure 2: Frequency specificity of significant correlation. Non-parametric Spearman's correlations were calculated again for each frequency bin in the 8 – 35 Hz range with the UPDRS-III score to identify the most influential sub-band on the correlation. The grey shaded area designates a significant correlation (Frequencies 10 – 14 Hz; $P < 0.05$ FDR corrected).

Figure 1

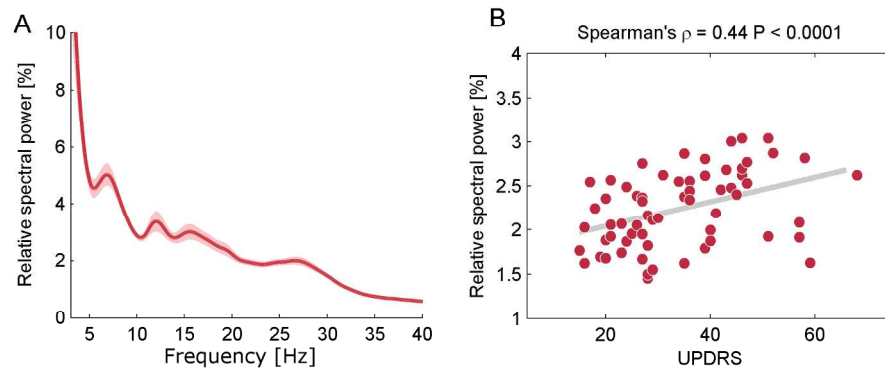


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Figure 1

187x89mm (300 x 300 DPI)

Figure 2

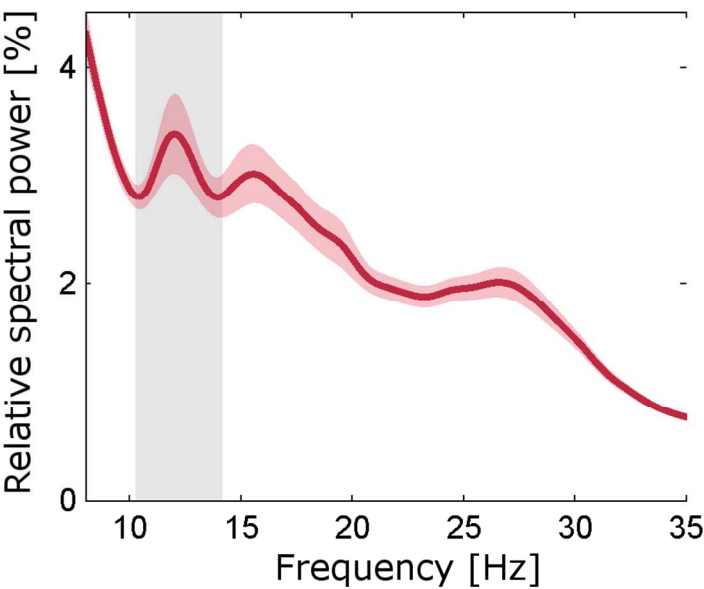


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Figure 2
110x80mm (300 x 300 DPI)

Subthalamic synchronized oscillatory activity correlates with motor impairment in patients with Parkinson's disease

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Objective: Beta band oscillations in the subthalamic nucleus (STN) have been proposed as a pathophysiological signature in patients with Parkinson’s disease (PD). The aim of this study was to investigate the potential association between oscillatory activity in the STN and symptom severity in PD.

Methods: Subthalamic local field potentials were recorded from 63 PD patients in a dopaminergic OFF state. Power-spectra were analyzed over the frequency range from 5-95 Hz, and correlated with individual UPDRS-III motor scores in the OFF state.

Results: A correlation between total UPDRS-III scores and 8–35 Hz activity was revealed across all patients ($p=0.44$, $P<0.0001$). When correlating each frequency bin, a narrow range from 10 – 15 Hz remained significant for the correlation (FDR corrected $p < 0.05$).

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Introduction

Deep brain stimulation is an effective treatment for patients with Parkinson’s disease (PD).¹ One of the hypothesized mechanisms of actions of DBS is a suppression of aberrant oscillatory activity in the target structure.² Enhanced subthalamic oscillations at beta frequency have been proposed as a pathophysiological signature for PD³. A multitude of studies have revealed abnormally synchronized activity in the subthalamic nucleus (STN) over a broad range of 8-35 Hz in PD off state^{2, 4, 5}, and this band, or portions of it, is generally referred to as beta activity. Dopaminergic therapy and DBS both lead to a decrease of spectral power in this frequency band at the same time that the patient experiences clinical symptom alleviation.^{6, 7} The relative difference of 8-35 Hz band power between the ON and OFF state has been shown to correlate with the difference in symptom severity as measured

by the Unified Parkinson's Disease Rating Scale (UPDRS III).⁵ Moreover, DBS-induced suppression of beta band activity correlated with motor performance in PD.⁸ This has led to the idea that subthalamic oscillatory activity could serve as an index of symptom severity for adaptive stimulation in a closed loop system.⁹⁻¹³ Using this approach, an individual threshold of LFP activity would serve as a biomarker to trigger DBS. Whether the scale of 8 – 35 Hz activity in the OFF state correlates with motor impairment within the same state is less clear. Such a correlation is more consistently reported with more complex measures like LFP complexity¹⁴ or standard deviation¹⁵. The observation that also dystonia patients exhibit peaks in the beta frequency band has recently questioned the specificity of beta activity as a biomarker in PD.¹⁶ To corroborate previous findings, this study aims to investigate the association between subthalamic oscillatory activity and parkinsonian symptom severity in a large cohort of PD patients in the dopaminergic off state. We hypothesized that oscillations in the 8 – 35 Hz band reflect the clinical symptom severity, but a narrower sub-band could be identified as particularly relevant. To this end, we additionally conducted correlations for each frequency bin of the power spectra to evaluate spectrally distinct contributions to the broad band 8 – 35 Hz group effect.

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Results

Relative power spectra were averaged across all available contact pairs and electrodes for each patient as displayed in Figure 1A. Spectral peaks in the 8 – 35 Hz range that were present in all patients contributed to rises in amplitude in the group spectrum. Mean 8 – 35 Hz spectral power averaged across all available contact pairs in each patient showed a highly significant association with respective UPDRS-III scores as a measure of clinical symptom severity in the medication OFF state across all patients, as revealed by Spearman's correlation (Figure 1B; Spearman's $\rho = 0.44$, $P < 0.0001$). The additional analysis on the spectral focality using repeated Spearman's correlations for each ~1 Hz bin within the 8 – 35 Hz band averaged across available contact pairs for each patient identified a significant sub-band of adjacent frequency bins from 10 – 14 Hz that were again correlated with respective UPDRS-III scores (Figure 2; $P < 0.05$ FDR corrected for multiple comparisons).

Discussion

Here we demonstrate a link between subthalamic 8 – 35 Hz band power and the clinical symptom severity in a large cohort of PD patients. Our results suggest that spectral 8 - 35 Hz power may be used as a surrogate index of motor symptoms in PD patients. Interestingly, correlations of each frequency bin in this range revealed a sub-band (10 – 14 Hz) that is most robustly correlated with the clinical symptom severity in our patients. This sub-band partially includes the low beta range (13-20 Hz) that has previously been shown more sensitive to levodopa-induced reduction as compared to the high beta band (20-35 Hz)²¹. Taken together these findings could hint to varying functional roles for these frequency bands, with the lower frequency range more implicated in the parkinsonian off state. The major limitation of the current study is that it provides only correlative, and no causal, evidence of a link between subthalamic 8 – 35 Hz activity and motor impairment in PD. Furthermore, the preoperative UPDRS-III scores may not represent the current motor state at the timepoint of the recordings that were performed shortly after surgery when a stun effect is evident, which can lead to a reduction in motor symptoms or may influence oscillatory activity in the target area in a differential pattern according to spectral frequency. Long-term recordings with the newly available implantable pulse generator that can record LFP in parallel with stimulation is currently being tested in patients with PD^{22, 23} and will allow to explore the relationship between motor impairment and oscillatory activity in a more standardized condition. Whether the link between local STN oscillations and motor state is mechanistically important or epiphenomenal remains to be established, but meanwhile even the simple correlation means that the local power of synchronized oscillatory activity may provide a potential feedback signal indicative of the patients' symptom severity.

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Figure legends

Figure 1: Averaged spectral power and 8 – 35 Hz correlation. Averaged power spectra (A) are displayed on the left vertical axes represented by solid red lines. The red shaded areas designate the standard error of the mean for each frequency bin across patients. Non-parametric Spearman's correlation between averaged 8 – 35 Hz power and the clinical

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symptom severity as measured by the UPDRS-III revealed a significant positive association (B).

Figure 2: Frequency specificity of significant correlation. Non-parametric Spearman's correlations were calculated again for each frequency bin in the 8 – 35 Hz range with the UPDRS-III score to identify the most influential sub-band on the correlation. The grey shaded area designates a significant correlation (Frequencies 10 – 14 Hz; $P < 0.05$ FDR corrected).