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Deep brain recordings using an implanted pulse generator in Parkinson's disease

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Abstract

Objectives—Recent studies suggest that oscillatory beta activity could be used as a state biomarker in patients with Parkinson's disease for subthalamic closed-loop stimulation with the intention of improving clinical benefit. Here we investigate the feasibility of subthalamic recordings via a novel chronically implanted pulse generator.

Methods—Subthalamic local field potential recordings were obtained from eight patients before and during deep brain stimulation (DBS). All data were analyzed in the frequency domain using Fourier transform based methods and compared between ON and OFF stimulation conditions.

Results—Distinct peaks of oscillatory beta band activity were found in 12 of 15 electrodes. DBS induced a significant frequency specific suppression of oscillatory beta activity ($p = 0.002$).

Conclusion—The results of the study suggest that oscillatory beta band synchronization and its modulation by DBS is recordable with a system suitable for chronic implantation and may serve as a biomarker for subthalamic closed-loop stimulation in patients with Parkinson's disease.

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Keywords

deep brain stimulation; basal ganglia; local field potentials; beta oscillations; subthalamic nucleus

Introduction

Deep brain stimulation (DBS) in the subthalamic nucleus (STN) is an effective treatment for patients with Parkinson's disease (PD). (1) While continuous stimulation is still the standard clinical procedure, its use is limited by side-effects and battery consumption, which results in periodic implanted pulse generator (IPG) exchanges that increase the risk of complications related to surgery. These limitations have inspired a search for innovative stimulation protocols, like temporally irregular (2) and adaptive closed-loop stimulation (3). The latter showed promising results with improved motor outcome, reduction in energy requirements when compared to continuous DBS (3), and reduced side effects such as dyskinesia (4). This was achieved by using beta band (13-30 Hz) oscillatory activity recorded from the DBS electrodes as a biomarker to trigger stimulation. Local field potential (LFP) recordings from STN-DBS electrodes have previously revealed exaggerated beta band synchronization in PD patients that is reduced by levodopa and STN-DBS. Furthermore, the relative DBS induced beta suppression correlates significantly with motor improvement (5). Hence, beta activity is a putative biomarker for adaptive closed-loop stimulation in PD (5). However, due to technical constraints the reported results have been obtained using laboratory hardware connected to externalized DBS leads before IPG implantation. The aim of this study was to evaluate the feasibility of post-implantation LFP recordings from a fully implantable new generation IPG in PD patients ON and OFF DBS.

Materials and Methods

Eight patients with Parkinson's disease who underwent bilateral implantation of DBS electrodes in the STN were included in the study. Further clinical details are given in the table.

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. The macroelectrode used was model 3389 (Medtronic, Minneapolis, MN, USA). Surgical details are described in Kühn et al., 2005 (6). 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 MR or CT in 7/8 patients (except case 5).

All patients were studied 1-4 days after implantation of the new Activa PC+S (Medtronic) pulse generator (7) that has previously been tested in non-human primates (8). Recordings were performed after the patients underwent a 12 hour withdrawal from dopaminergic medication. Dopamine agonist therapy was discontinued one week prior to the recording. The sessions always started OFF DBS, followed by a 15 min break during which the stimulator was already switched ON before the ON DBS recording. DBS was performed bilaterally with standardized monopolar stimulation on contact 1 at 140 Hz, pulse-width of

60 microseconds and a constant voltage of 2 V (except for case 1, who was stimulated at 1.8 V on the left and 2.6 V on the right) with simultaneous bipolar LFP recordings from adjacent contact pairs 0-2 to reduce stimulation-induced artefacts. Stimulation amplitudes were selected as they achieved clinical responses whilst sparing the patients any uncomfortable side-effects. LFPs were amplified (x2000), filtered at 1-100 Hz and recorded at a sampling Rate (SR) of 422 Hz (optimized SR for simultaneous DBS) onto the IPG. During recordings, patients were seated comfortably in an armchair. LFP recordings of one minute length were obtained in OFF and ON DBS conditions in the same session.

All data were downloaded to a personal computer for offline analysis using telemetry. Short recording lengths were chosen to keep battery discharge related to telemetric data transfer minimal. The sampled data traces were interpolated to 300 Hz, visually inspected for artefacts and saturation. Remaining data were analyzed using custom MATLAB code. All continuous rest recordings were divided into epochs of 3.4133 s (1024 samples) and transferred to the frequency domain using fast Fourier-transform-based methods. Power-spectra were normalized to the percentage of total power over the 7-32 Hz, 38-45 Hz, 55-87 Hz and 73-95 Hz ranges for each contact-pair. Relative rather than absolute power was analyzed to allow comparison across subjects, as absolute power is more likely to be dependent on proximity to the LFP source and the local electrical properties of the surrounding tissue. The 0-7 Hz, 46-54 Hz, 33-37 Hz and 68-72 Hz ranges, were omitted so as to avoid contamination by movement artefacts, mains noise and artefacts in the sub-harmonic range of 140 Hz DBS, respectively. Spectral power below 7 Hz was omitted from the analysis, because the combination of a 422 Hz sampling rate and 140 Hz stimulation frequency can lead to folded artefacts in the low-frequency range (2-6 Hz). Recordings from one contact-pair (case 1, right electrode) were contaminated by cardiac pulse artefacts and excluded from further analysis, leaving a total of 15 contact-pairs in 8 patients. All individual OFF DBS power spectra were visually inspected for peaks in the beta range (13-30 Hz). To visualize the beta peaks across patients, an average of all spectra realigned to the individual peak frequency (range -5 Hz to +10 Hz) was plotted (Figure 1G).

Power spectra were averaged across alpha (7-12 Hz) and beta frequency bands (13-30 Hz). Data were not normally distributed (Kolmogorov Smirnov test), so that band averages OFF DBS were compared to ON-DBS using the non-parametric Wilcoxon's signed rank tests. Results are reported as mean $\pm$ standard error of the mean (SEM). Multiple comparisons were corrected using the false discovery rate (FDR) (9).

Results

The stimulators' sensing function allowed recording of local field potential activity ON and OFF DBS without the need for external recording equipment. An example of raw LFP data traces is shown in figure 1A with the corresponding power-spectra demonstrating a distinct beta peak that is reduced during stimulation (figure 1B). Comparison of the group average relative power revealed a frequency band-specific reduction in the beta band (Figure 1C-E). Averaged beta band power was reduced by $14 \pm 5\%$ ($p=0.002$; median: 17%, range: -41% - -0.42%) from $0.59 \pm 0.04\%$ (median: 0.54%, range: 0.34% - 0.85%) OFF DBS to $0.51 \pm 0.03\%$ ON-DBS (Figure 1D; median: 0.53%, range: 0.29% - 0.81%). No change was

found for the alpha band (Figure 1E). There was no discrete peak in the beta band in the group average illustrated in Figure 1C. Additional analysis using only those contact pairs with beta peaks (12/15) demonstrated a stronger relative reduction in beta activity during DBS ($18 \pm 4\%$, median: -16% , range: $-41\% - -3\%$, $p < 0.001$ Figure 1F). However, again there was no discrete peak in the subgroup ($n=12$) average. Accordingly, we tested whether the lack of a discrete peak in group average data was due to jitter in the frequency of beta band peaks in individual spectra. To this end we aligned the individual peaks ($n=12$) in relative power before averaging. This recovered a discrete peak in the group average data. Moreover, this revealed a significant difference between ON and OFF DBS over the frequency range from -1.4 Hz to $+5.8$ Hz surrounding the re-aligned and averaged peak (Figure 1G).

Discussion

Here we demonstrate for the first time recordings of human deep brain activity from a technically advanced implanted pulse generator with recording capabilities and that is suitable for chronic DBS in PD patients. Discrete peaks in beta activity could be recorded from the subthalamic area from 12 (80%) out of 15 electrodes when patients were OFF medication. This incidence is arguably slightly lower than generally seen (5), and may relate to the recording from a single fixed dipole (contact 02) or post-operative stun effects.(6) However, it should also be noted that the implantable device used has an amplification of $\times 2\,000$, compared to the $\times 9\,000 - \times 50\,000$ utilized when recording with external amplifying systems. It is therefore possible that the signal-to-noise ratio of the implantable device may be less, although this also depends on the bits of the converter, noise floor and other system characteristics. Therefore, future generations of sensing enabled IPGs should be engineered with low noise floor and high amplification to allow constant and reliable monitoring of oscillatory synchronisation phenomena that are low in amplitude.

Nevertheless, the implanted pulse generator was able to identify significant suppression of beta band activity during DBS, in line with previous reports (5). However, although there is some evidence that beta oscillations in the subthalamic nucleus remain stable over time (10,11), further studies are required to confirm the stability in frequency and amplitude to ensure long-term effectivity of adaptive stimulation. In this regard, previous studies have used fixed thresholding criteria that would need repeated reassessment related to long term beta amplitude fluctuations. Therefore, adaptive thresholds or more flexible and sophisticated classifiers based on multiple LFP features may be advantageous to secure long-term benefit in the use of adaptive stimulation. In conclusion, this study affords further evidence for beta band activity being a useful state biomarker in PD patients and demonstrates that beta can be followed with implantable systems; this paves the way for trials of chronic adaptive DBS of this target.

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Figure 1. Local field potentials ON and OFF subthalamic high frequency stimulation.

Examples of raw data traces (A) and corresponding power spectra (B) showing a broad 13 – 20 Hz peak that is suppressed by deep brain stimulation in case 5. Averaged normalized power spectra (C, colored shaded areas display the 95 % confidence intervals) show a significant reduction of 14 % in beta band activity (D, $p = 0.002$), but no modulation of alpha band activity (E, $p = 0.3$). Averaged frequency bands are highlighted as light and dark grey shaded areas for alpha and beta frequency bands in figures 1B, C, respectively. A stronger effect was found when only contact pairs with distinct beta (13-30Hz) peaks were

included in the analysis (F, 18 % beta band reduction, $p < 0.001$). Direct comparison of peak aligned, then averaged spectra (G, 0 Hz on the x-axis is the individual peak for each contact pair, mean frequency of peak before alignment $17 \text{ Hz} \pm 0.8 \text{ Hz}$) revealed a significant band from -1.4 to $+5.8 \text{ Hz}$ surrounding the peaks (shown as gray shaded area; FDR corrected for multiple comparisons; significant threshold $p = 0.03$).

Table**Clinical details.**

Eight patients with Parkinson's disease (2 female, mean age $66.1 \pm [\text{SEM}] 1.5$ years; disease duration 10.5 ± 1.4 years) were studied 1-4 days after implantation (mean 2.1 ± 0.4 days).

case	age	gender	Main symptoms	disease duration (years)	UPDRS III preop med OFF*/ON	UPDRS III postop DBS** OFF/ON	Beta peaks (r/l; Hz)
1	66	m	Akinetic rigid	13	46/11	***	n.a.# / 15.8 Hz
2	63	m	Akinetic rigid	10	46/26	35/21	18.2 Hz / no peak
3	63	m	Tremor dominant	15	49/35	26/13	14.3 Hz / 14.2 Hz
4	63	f	Tremor dominant	8	56/16	24/10	14.7 Hz / 19 Hz
5	66	m	Akinetic rigid	8	26/17	##20/17	18.4 Hz / no peak
6	73	m	Equivalent	9	35/20	33/20	no peak / 15.5 Hz
7	63	m	Akinetic rigid	16	42/29	29/17	16.3 Hz / 14.6 Hz
8	72	f	Akinetic rigid	5	34/19	24/15	24.5 Hz / 14.6 Hz

* Evaluation OFF medication was performed at least 12 hours after withdrawal from dopaminergic medication. Dopamine agonist therapy was discontinued one week prior to surgery.

** UPDRS at 1-3 months follow up OFF dopaminergic medication.

*** Case1 was unable to withdraw dopaminergic medication at follow up.

The right electrode of case 1 had artefacts and was excluded.

Case 5 had a stroke due to middle cerebral artery occlusion between implantation and follow-up UPDRS assessment OFF/ON DBS.