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Subthalamic beta oscillations are attenuated after withdrawal of chronic high frequency neurostimulation in Parkinson's disease

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ABSTRACT

Subthalamic nucleus (STN) local field potential (LFP) recordings demonstrate beta (13–30 Hz) band oscillations in Parkinson's disease (PD) defined as elevations of spectral power. The amount of attenuation of beta band power on therapeutic levels of high frequency (HF) deep brain stimulation (DBS) and/or dopaminergic medication has been correlated with the degree of improvement in bradykinesia and rigidity from the therapy, which has led to the suggestion that elevated beta band power is a marker of PD motor disability. A fundamental question has not been answered: whether there is a prolonged attenuation of beta band power after withdrawal of chronic HF DBS and whether this is related to a lack of progression or even improvement in the underlying motor disability.

Until now, in human PD subjects, STN LFP recordings were only attainable in the peri-operative period and after short periods of stimulation. For the first time, using an investigational, implanted sensing neurostimulator (Activa® PC + S, Medtronic, Inc.), STN LFPs and motor disability were recorded/assessed after withdrawal of chronic (6 and 12 month) HF DBS in freely moving PD subjects. Beta band power was similar within 14 s and 60 min after stimulation was withdrawn, suggesting that "off therapy" experiments can be conducted almost immediately after stimulation is turned off. After withdrawal of 6 and 12 months of STN DBS, beta band power was significantly lower ($P < 0.05$ at 6 and 12 months) and off therapy UPDRS scores were better ($P < 0.05$ at 12 months) compared to before DBS was started. The attenuation in beta band power was correlated with improvement in motor disability scores ($P < 0.05$). These findings were supported by evidence of a gradual increase in beta band power in two unstimulated STNs after 24 months and could not be explained by changes in lead impedance. This suggests that chronic HF DBS exerts long-term plasticity in the sensorimotor network, which may contribute to a lack of progression in underlying motor disability in PD.

1. Introduction

High frequency[1] (HF) deep brain stimulation[2] (DBS) is a well-established therapy for motor signs and quality of life in Parkinson's disease[3] (PD) (Deuschl et al., 2006; Williams et al., 2010). Subthalamic nucleus[4] (STN) local field potential[5] (LFP) recordings demonstrate oscillatory neuronal activity in the beta (13–30 Hz) band in the resting state in PD, which are attenuated during HF DBS (Kuhn et al., 2006; Wingeier et al., 2006; Kuhn et al., 2008; Ray et al., 2008; Bronte-Stewart et al., 2009; Giannicola et al., 2010; Eusebio et al., 2011; Whitmer et al., 2012; Matzner et al., 2016). An association between the attenuation of resting state STN beta oscillations and the improvement of bradykinesia and rigidity, on therapeutic doses/intensities of medication or DBS, has led to the suggestion that subthalamic beta band oscillations are markers of the Parkinsonian state (Kuhn et al., 2006; Kuhn et al., 2008; Ray et al., 2008). This has been supported by intra-operative findings that the percentage of single units firing at beta frequencies correlated with pre-operative off medication axial and limb rigidity scores (Sharott et al., 2014).

Until now, in human PD subjects, STN LFPs could only be recorded in the intra- or peri-operative period, and any prolonged effect of DBS on neural activity could only be examined for short periods following stimulation (Wingeier et al., 2006; Kuhn et al., 2008; Bronte-Stewart et al., 2009; Abosch et al., 2012; Swan et al., 2014; Oswal et al., 2016). It is now possible to record neural signals from an implanted sensing neurostimulator (Activa® PC + S, Medtronic Inc., FDA IDE approved) in freely moving human PD subjects (Quinn et al., 2015; Rosa et al., 2015; Neumann et al., 2016). These studies have determined that

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[1] High frequency = HF.
[2] Deep brain stimulation = DBS.
[3] Parkinson's disease = PD.
[4] Subthalamic nucleus = STN.
[5] Local field potential = LFP.

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resting state beta oscillations were similar in different resting postures (sitting, lying, standing), and beta oscillations were attenuated during HF DBS, using the implanted clinical neurostimulator, in a voltage dependent fashion (Quinn et al., 2015; Neumann et al., 2016).

One of the most compelling questions regarding the effects of chronic continuous HF neurostimulation is whether it exerts any long-term modulatory effect on underlying neuronal activity and whether this is accompanied by any long-term change in off therapy PD motor disability. Until the availability of an implanted device, that can sense and stimulate over potentially the life of the battery, this question could not be addressed, except by recording LFPs for short periods of time at a neurostimulator battery replacement surgery, when the DBS leads could be accessed (Abosch et al., 2012; Swan et al., 2014).

In this investigation, resting state STN LFPs were recorded from the sensing neurostimulator during a controlled DBS washout experiment, after six and twelve months of HF DBS, in addition to clinical assessments using the Unified Parkinson's Disease Rating Scale[6] (motor, UPDRS III). This study had three aims: 1, to determine whether LFP recordings from the implanted neurostimulator change for up to 60 min after stimulation is withdrawn; 2, to investigate whether the off medication/OFF DBS (off therapy) resting state beta band power and UPDRS III scores, measured before the initiation of DBS, were different after chronic (six and twelve months) HF DBS; and 3, to assess whether there was a relationship between the changes in off therapy beta band power and motor disability scores. The results of this study provide insight into how long it takes for the underlying resting state LFP to stabilize off DBS and reveals for the first time that HF DBS has a prolonged effect on neural activity that may be clinically relevant.

2. Materials and methods

2.1. Human subjects

Twenty PD subjects had bilateral implantation of DBS leads (model 3389, Medtronic, Inc.) in the sensorimotor region of the STN using a standard functional frameless stereotactic technique and multi-pass microelectrode recording[7] (MER) (Bronte-Stewart et al., 2010; Quinn et al., 2015). The leads were connected to the Activa® PC + S neurostimulator (Medtronic, Inc. FDA, IDE-IRB-approved). All subjects signed a written consent for the study, which was approved by the Food and Drug Administration (FDA) and Stanford School of Medicine Institutional Review Board (IRB). The preoperative selection criteria, surgical technique, and assessment of subjects have been previously described (Bronte-Stewart et al., 2010; Quinn et al., 2015). Long-acting dopaminergic medications were withdrawn over 24 h (72 h for extended release dopamine agonists), and short-acting medication was withdrawn over 12 h before surgery and before all study visits. One patient took an extra short-acting carbidopa/levodopa tablet at 3:30 AM on the day of initial programming. Resting state LFP spectra were similar 6.25 h and 8.5 h later, so we included this subject in the study. Three subjects were excluded; one developed electrocardiogram[8] (ECG) artifact after the initial programming visit (Quinn et al., 2015), so the recording contacts were changed and not comparable to initial programming; another was excluded as his DBS was not optimally programmed until the 9 month follow-up visit; and the third was removed from the analysis after statistical testing revealed it was an outlier based on a commonly used metric, Cook's distance. Subjects were classified as akinetic rigid[9] (AR) or tremor dominant[10] (TD), using the following criteria (Quinn et al., 2015): (1) Presence of resting tremor in concurrent angular velocity recordings from limbs and video; (2) The clinical history of a patient's initial and dominant symptoms; (3) UPDRS III scores from the preoperative off-medication visit.

2.2. Experimental protocol

Recordings were collected in the Stanford Human Motor Control and Balance Laboratory, off medication before the initial activation of the DBS system at initial programming[11] (IP), one month after implantation of the DBS leads, and off therapy, after six and twelve months of chronic, continuous HF DBS. During the recording, subjects were instructed to remain seated as still as possible. At the follow-up visits, stimulation was turned off, and seated resting state LFP recordings were collected every 15 min thereafter for at least 60 min. After each recording, data was transferred to a PC and power spectral density diagrams[12] (PSDs) were plotted. Offline analysis was used to determine whether the LFPs recorded at 45 min and 60 min had overlapping 95% confidence intervals over the entire beta band, and this was used as the definition of a "consistent spectrum". If the confidence intervals did not overlap, we performed another recording every 15 min until the spectra were consistent. Two subjects had 75 min recordings at 6 months and two different subjects had 75 min recordings at 12 months. The final recording for all other subjects was performed at the 60 min time point.

Stimulation was turned off once recording had started so that the 0 min time point was immediately captured, Fig. 1. As soon as stimulation was turned off, the patient was asked to remain seated as still as possible for 30 s. Movement was monitored using angular velocity sensors on all four limbs (Motus Bioengineering, Inc., Benicia, CA), a triaxial accelerometer on the forehead, surface EMG (Delsys, Inc., Natick, MA) on the forearm flexor and extensor muscles, and synchronized video recording. The synchronous recordings of kinematic data were used to select periods of at least 10 s of data without transient voluntary or involuntary movements other than resting tremor, Fig. 1. Although both tremor and transient movement may attenuate LFP power, we chose not to exclude resting tremor because this is usually present in the resting state in the TD PD subjects. The mean length of epochs used for the analysis was 28.1 s.

In the 0 min recordings, rest periods were analyzed on average 13.79 ± 4.69 s after stimulation was turned off. In one file, the rest period analyzed was 50.31 s after withdrawal of stimulation because the subject moved partway through the rest period and it had to be restarted. This subject was an outlier and not included in the average.

The UPDRS III was performed pre-operatively (on and off medication), off medication at IP, and at the 6 month and 12 month visits. At the latter two visits DBS had been off for at least 60 min. The off therapy UPDRS at 6 months was completed an average of 134.4 min (range 72 to 233 min), and at 12 months a mean of 131.1 min (range 68 to 188 min) after DBS was turned off. Off medication/ON DBS[13] (off/ON) UPDRS examinations were also performed after the clinical programming at each visit. The lateralized UPDRS III (rigidity, finger taps, hand movements, pronation/supination, toe tapping, leg agility, kinetic tremor, and rest tremor) scores were used for the analysis.

2.3. Data acquisition and analysis

Local field potentials were recorded from electrode pair 0–2 or 1–3 of the DBS lead. The electrode pair, 1–3 was chosen if ECG artifact was present during 0–2 recordings, or if electrode 2 was chosen for clinical programming (Quinn et al., 2015). Pre-amplified LFP signals were high-pass filtered at 0.5 Hz and low-pass filtered at 100 Hz within the device. All LFP data were sampled at 422 Hz (10-bit resolution). Uncompressed LFP data were extracted via telemetry using the Activa® PC + S tablet programmer and transferred to a computer for offline analysis in

[6] Unified Parkinson's Disease Rating Scale III = UPDRS III.
[7] Microelectrode recording = MER.
[8] Electrocardiogram = ECG.
[9] Akinetic rigid = AR.
[10] Tremor dominant = TD.
[11] Initial programming = IP.
[12] Power spectral density diagram = PSD.
[13] off medication/ON deep brain stimulation = off/ON.