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Subthalamic local field potentials in Parkinson's disease and isolated dystonia: An evaluation of potential biomarkers☆,☆☆

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ABSTRACT

Local field potentials (LFP) recorded from the subthalamic nucleus in patients with Parkinson's disease (PD) demonstrate prominent oscillations in the beta (13–30 Hz) frequency range, and reduction of beta band spectral power by levodopa and deep brain stimulation (DBS) is correlated with motor symptom improvement. Several features of beta activity have been theorized to be specific biomarkers of the parkinsonian state, though these have rarely been studied in non-parkinsonian conditions. To compare resting state LFP features in PD and isolated dystonia and evaluate disease-specific biomarkers, we recorded subthalamic LFPs from 28 akinetic-rigid PD and 12 isolated dystonia patients during awake DBS implantation. Spectral power and phase-amplitude coupling characteristics were analyzed. In 26/28 PD and 11/12 isolated dystonia patients, the LFP power spectrum had a peak in the beta frequency range, with similar amplitudes between groups. Resting state power did not differ between groups in the theta (5–8 Hz), alpha (8–12 Hz), beta (13–30 Hz), broadband gamma (50–200 Hz), or high frequency oscillation (HFO, 250–350 Hz) bands. Analysis of phase-amplitude coupling between low frequency phase and HFO amplitude revealed significant interactions in 19/28 PD and 6/12 dystonia recordings without significant differences in maximal coupling or preferred phase. Two features of subthalamic LFPs that have been proposed as specific parkinsonian biomarkers, beta power and coupling of beta phase to HFO amplitude, were also present in isolated dystonia, including focal dystonias. This casts doubt on the utility of these metrics as disease-specific diagnostic biomarkers.

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1. Introduction

Excessive oscillatory activity in the basal ganglia-thalamocortical circuit may be a major component of the pathophysiology of parkinsonian motor signs. Manifestations of excessive oscillatory activity may include theta (5–8 Hz), alpha (8–12 Hz), or beta (13–30 Hz) band oscillations in single unit discharge (Bergman et al., 1994; Moran et al., 2008), oscillatory synchronization between simultaneously recorded neurons (Hanson et al., 2012; Levy et al., 2002; Nini et al., 1995), and exaggerated spike field synchrony (Moran et al., 2008; Shimamoto et al., 2013; Weinberger et al., 2006). One way to study oscillatory activity in Parkinson's disease (PD) is to record the local field potential (LFP) from implanted basal ganglia electrodes intraoperatively or during a brief postoperative period when leads may be temporarily externalized (Galvan et al., 2015; Hammond et al., 2007). Local field potentials are thought to represent summed, synchronized subthreshold activity from pools of neurons near the recording electrodes. Subthalamic nucleus (STN) LFPs in PD patients show prominent beta oscillatory activity, whose amplitude is suppressed by levodopa and by STN deep brain stimulation (DBS) in a manner that correlates with symptom improvement (Bronte-Stewart et al., 2009; Chen et al., 2007; Kuhn et al., 2008; Little et al., 2012; Wingeier et al., 2006). This has led to the hypothesis that STN beta band oscillations may contain biomarkers diagnostic of the parkinsonian state, and that these features could be used for potential control signals for closed-loop DBS (Little et al., 2013; Stanslaski et al., 2012).

Specific features of the STN LFP that have been proposed as potential diagnostic parkinsonian biomarkers include beta band power (Little et al., 2013) and coupling of beta phase to the amplitude of high frequency oscillations (HFOs, 250–350 Hz), one form of phase-amplitude coupling (Lopez-Azcarate et al., 2010). If true, then these metrics should

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differ between patients with PD and those with non-parkinsonian conditions. However, STN LFP characteristics in non-parkinsonian conditions have rarely been studied (Bastin et al., 2014; Danish et al., 2007) and never compared directly to those of PD patients. Here, we report the first large series (N = 12 patients) of STN LFP recordings in isolated dystonia, and compare them to similar recordings in 28 patients with akinetic-rigid PD. We found that both PD and dystonia patients had STN LFPs whose power spectra had a peak in the beta range, without significant differences in amplitude or the frequency of peak power. Coupling between STN LFP beta phase and the amplitude of HFOs was found in both PD and isolated dystonia patients. Our findings suggest that neither beta power nor phase-amplitude coupling within the STN is a diagnostic biomarker for the parkinsonian state. Our study does not refute the potential utility of these oscillatory features of the STN LFP as markers of response to therapy in PD.

2. Methods

2.1. Patients

Patients with Parkinson's disease and isolated dystonia were recruited from the movement disorders surgery clinics at the University of California San Francisco or the San Francisco Veteran Affairs Medical Center. All patients were scheduled to undergo implantation of deep brain stimulator electrodes into the STN, and underwent evaluation for motor impairments within 30 days prior to surgery using the Unified Parkinson's Disease Rating Scale motor subscale (UPDRS-III) in the off- and on- medication states (for PD patients), or the Toronto Western Spasmodic Torticollis Rating Scale and Burke–Fahn–Marsden Dystonia Rating Scale (for dystonia patients). Inclusion criteria were the following: for PD patients, akinesia and rigidity as the most prominent symptoms with UPDRS-III > 20 in the off state and absent or minimal observed tremor during intraoperative recording; for isolated dystonia patients, those with focal cervical dystonia, segmental craniocervical dystonia or generalized dystonia without evidence for acquired etiology. Dystonia patients in this physiology study were also participating in a prospective clinical trial of the efficacy of STN DBS for isolated dystonia (Ostrem et al., 2011). Informed consent was obtained prior to surgery under a protocol approved by the Institutional Review Board. Data from a subset of these patients has been published previously (de Hemptinne et al., 2013).

2.2. DBS electrode implantation in PD and dystonia patients

Surgical planning and placement of DBS electrodes in the subthalamic nucleus (STN) were performed using methods previously described (Ostrem et al., 2011; Starr, 2002). Briefly, the intended STN target location was identified as a T2 hypointense area immediately lateral to the anterior margin of the red nucleus and superior to the lateral region of the substantia nigra pars reticulata (approximately 12 mm lateral, 3 mm posterior, and 4 mm inferior to the mid commissural point, which is the midpoint of the line connecting the anterior and posterior commissures) (Fig. 1A). All surgeries were performed in the awake resting state after discontinuation of propofol for at least 30 min. Microelectrode recordings (MER) were performed to map movement-related single cells, and borders of the STN were defined based on the MER map. A DBS lead (Medtronic model 3389 for all patients except PD patient #2, who had a 3387 lead) was then placed. All DBS electrodes were placed with contact 0 in ventral STN, contact 3 above the dorsal border and contacts 1 and 2 in the motor territory. LFPs were recorded from the motor territory in the bipolar configuration with contact 1 as the active electrode and contact 2 as reference. Targeting was confirmed by electrical stimulation-induced symptom improvement and side effect thresholds obtained by DBS stimulation. Intraoperative computed tomography (iCT) scans computationally fused to the preoperative MRI were used to confirm correct lead location, as well as a postoperative MRI.

2.3. STN LFP recordings

All LFP recordings were performed intraoperatively after DBS electrode implantation. All anti-Parkinsonian and anti-dystonic medications were stopped at least 12 h before the start of surgery. Patients were instructed to keep their eyes open and refrain from any voluntary movements. An accelerometer was attached to the contralateral wrist to detect tremors during recording, and those with significant tremor on either review of the intraoperative video or accelerometry data were excluded from the study. The LFPs were recorded using either the Guideline 4000 system (FHC Inc., Bowdoin, ME) (n = 26, 21 PD and 5 dystonia patients) or the Alpha Omega Microguide Pro (Alpha Omega, Inc., Nazareth, Israel) (n = 14, 7 PD and 7 dystonia patients) and sampled at 1000 and 1500–3000 Hz, respectively. Bipolar STN LFPs were recorded from the physiologically identified motor territory between contacts 1 (active) and 2 (reference) of the DBS electrode. Signals were bandpass-filtered at 1–500 Hz and amplified ×7000.

2.4. Signal processing and data analysis

LFP data were processed and analyzed offline in MATLAB (Mathworks, Inc). Data were down sampled to 1 KHz and notch filtered for power line noise (60 Hz) and its harmonics (at 120, 180, 240 Hz) using a Butterworth filter. For each recording, the first 30 s free of obvious electrical noise were used for analysis. Root mean square (RMS) values were calculated.

2.5. Spectral power

Power spectral density (PSD) was calculated using the Welch periodogram method (Matlab function pwelch). For PSD calculations, we used a fast Fourier transform of 257 points (for a frequency resolution of 1.95 Hz) and 50% overlap using a Hanning window to reduce edge effects. Power of the resulting spectrogram was averaged across the following frequency bands: theta (5–8 Hz), alpha (8–12 Hz), low beta (13–20 Hz), high beta (20–30 Hz), beta (13–30 Hz), broadband gamma (50–200 Hz), and high frequency oscillations (HFO, 250-350 Hz).

2.6. Coefficient of variation

To calculate the coefficient of variation (CV) for specific spectral bands, LFP signals were bandpass filtered in the following frequency ranges: theta (5–8 Hz), alpha (8–12 Hz), low beta (13–20 Hz), high beta (20–30 Hz), beta (13–30 Hz), broadband gamma (50–200 Hz), and high frequency oscillations (HFO, 250-350 Hz). A Hilbert transform of the filtered signaled was applied and an amplitude envelope was extracted. The CV of the amplitude envelope was calculated using the following formula: CV = standard deviation (amplitude envelope)/mean (amplitude envelope).

2.7. Alpha-beta peak

Absolute measures of spectral power may differ greatly between subjects for trivial reasons, such as proximity of the recording electrode to the signal source. As a method of normalizing the properties of the alpha-beta spectral peak across subjects, spectral power in the 8–30 Hz range was normalized by “baseline” power at frequencies outside of this range. To create the “baseline” polynomial, a 5th order polynomial function was used to fit the log PSD data using the local minimum at the low frequency side of the alpha-beta peak, and values above 40 Hz and under 250 Hz (excluding noise areas around the 60 Hz harmonics). Thus, points around the alpha-beta peak areas were omitted from the