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Subthalamic oscillations and phase amplitude coupling are greater in the more affected hemisphere in Parkinson's disease

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HIGHLIGHTS

- Parkinson's neural oscillations and coupling were greater in the more affected STN and were evident in 98% cases.
- Positive correlation between frequencies of beta and HFO at maximum PAC strength.
- Alpha/beta band power was lower in the tremor dominant phenotype and was attenuated by emergent tremor.

ABSTRACT

Objective: Determine the incidence of resting state oscillations in alpha/beta, high frequency (HFO) bands, and their phase amplitude coupling (PAC) in a large cohort in Parkinson's disease (PD).
Methods: Intra-operative local field potentials (LFPs) from subthalamic nucleus (STN) were recorded from 100 PD subjects, data from 74 subjects were included in the analysis.
Results: Alpha/beta oscillations were evident in >99%, HFO in 87% and PAC in 98% of cases. Alpha/beta oscillations ($P < 0.01$) and PAC were stronger in the more affected (MA) hemisphere ($P = 0.03$). Alpha/beta oscillations were primarily found in 13–20 Hz (low beta). Beta and HFO frequencies with the greatest coupling, were positively correlated ($P = 0.001$). Tremor attenuated alpha ($P = 0.002$) and beta band oscillations ($P < 0.001$).
Conclusions: STN alpha/beta band oscillations and PAC were evident in ⩾98% cases and were greater in MA hemisphere. Resting tremor attenuated underlying alpha/beta band oscillations.
Significance: Beta band LFP power may be used to drive adaptive deep brain stimulation (aDBS), augmented by a kinematic classifier in tremor dominant PD.

1. Introduction

Recent advances in neurostimulator technology allow for real-time recording of neural activity directly from the implanted neurostimulator and have made it feasible to treat motor signs of Parkinson's disease (PD) with closed-loop adaptive deep brain stimulation (aDBS) (Little et al., 2016, 2013; Malekmohammadi et al., 2016; Rosa et al., 2015). This has highlighted a critical need to determine reliable neural markers that may be used as feedback signals to monitor, control, and optimize therapeutic aDBS (Hebb et al., 2014; Little and Brown, 2012; Priori et al., 2013).

Neural oscillations reflect periodic rhythmic activity and appear as peaks above the broadband 1/f power spectrum or 'scale-free' brain activity (He, 2014). Resting state alpha/beta (8–35 Hz) oscillations have been observed in the subthalamic nucleus (STN) in the off medication state in PD by many groups (Bronte-Stewart et al., 2009; Brown, 2003; Eusebio et al., 2011; Foffani et al., 2003;

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Giannicola et al., 2010; Kuhn et al., 2008, 2006; Levy et al., 2002; Lopez-Azcarate et al., 2010; Moshel et al., 2013; Ozkurt et al., 2011; Ray et al., 2008; Tan et al., 2013; Wang et al., 2014; Weinberger et al., 2006; Whitmer et al., 2012; Wingeier et al., 2006; Yang et al., 2014). However, the reported incidence of beta band oscillations in the STN of human subjects with PD has ranged from in 54% to 100% of peri-operative recordings, (Rosa et al., 2011; Little and Brown, 2012). There has also been some debate as to whether alpha/beta band oscillations in the subthalamic region are normal or pathological. Several animal studies did not observe basal ganglia beta band oscillatory activity above the 1/f spectrum in healthy non-human primate basal ganglia (Bergman et al., 1998; Nini et al., 1995; Raz et al., 2001; Sharott et al., 2005) while others found evidence of beta oscillations within both motor cortex and basal ganglia of normal primates and have suggested that these oscillations serve an important role in motor program selection (Courtemanche et al., 2003; Feingold et al., 2015).

PD motor signs usually start on one side of the body, which generally remains the more affected (MA) side. Post mortem pathological studies have demonstrated greater neuronal loss in the substantia nigra contralateral to the initially affected side (Kempster et al., 1989), and this was supported by positron emission tomography (PET) studies in live PD subjects, which demonstrated that putaminal uptake of ^{18}F-fluorodopa was more impaired contralateral to the MA side (Leenders et al., 1990). To date, it is unknown whether the degree of subthalamic alpha/beta oscillations and synchrony is related to the clinically more affected side in human subjects with PD.

Recently, it has been reported that beta phase- gamma (50–200 Hz) amplitude coupling is present in the motor cortex in PD and is attenuated during high frequency DBS (de Hemptinne et al., 2013, 2015). However, in subcortical structures such as the STN, high frequency oscillations (HFO) have been more commonly reported in the 200–400 Hz range along with beta phase-HFO amplitude coupling (PAC) (Ozkurt et al., 2011; Yang et al., 2014), and their incidence and functional role in PD are under debate (Foffani et al., 2003; Lopez-Azcarate et al., 2010).

In this study of the largest cohort of well characterized PD subjects to date, we provide evidence that intra-operative resting state alpha/beta band neuronal oscillations and PAC were present in >98% of cases, were stronger in the hemisphere contralateral to the clinically more affected side and were lower in the tremor dominant PD phenotype. These findings have important implications for neural signals that may be used to drive aDBS in PD.

2. Methods

2.1. Human subjects and clinical assessment

One hundred subjects with idiopathic PD, who had been approved for bilateral implantation of deep brain stimulating (DBS) leads (Medtronic Inc, Minneapolis MN) in the STN consented to participate in the study, which was approved by the Stanford Institutional Review Board. Six subjects were excluded due to previous brain surgery, two due a history of stroke or brain hemorrhage, two due to anesthesia at the time of recording, and three due to concurrent mental illness or history of drug abuse or seizure disorder. All subjects had a detailed pre-operative clinical evaluation, which included the Unified Parkinson's Disease Rating Scale (UPDRS) motor (III) performed in both the challenged on and practically defined off medication states, described previously (Bronte-Stewart et al., 2010). The UPDRS III was performed within one year prior to the surgical date, with the exception of five subjects whose pre-operative UPDRS III evaluations were done over one year prior to the surgical procedure. The more affected (MA) and less affected (LA) sides were determined for each subject as the side with the greater lateralized UPDRS III pre-operative off medication score in conjunction with each subject's own report of the side on which the symptoms started. Lateralized UPDRS III sub-scores utilized were rest tremor, postural/action tremor, rigidity, and limb bradykinesia (finger tapping, hand movement, pronation-supination, and leg agility). If lateralized UPDRS III scores were equal for both sides, the MA side was determined using the historical data of disease onset side. If the onset symptom was axial, the first lateralized symptom was used.

2.2. Surgical procedure and experimental protocol

All patients underwent the surgical procedure in the off medication state: all long-acting and short-acting medications were withdrawn at least 24 h and 12 h prior to the surgical procedure, respectively. The STN DBS leads were implanted using the frameless stereotactic neurosurgical technique (Bronte-Stewart et al., 2010) and microelectrode recording (MER) as previously described (Romanelli et al., 2004). Subjects underwent pre-operative contrast enhanced volumetric T1 and T2-weighted magnetic resonance imaging (MRI) of the brain. The day before surgery, NexFrame Unibody bone fiducial markers (Medtronic, Inc., Minneapolis, MN) were applied to the skull, and a full head computed tomography (CT) scan was obtained using 1-mm slice thickness. CT and MRI images were fused using Medtronic StealthStation FrameLink software and the STN was targeted via T2 MRI imaging along with scalable Schaltenbrand atlas overlaid to aid in identification of nuclear boundaries. Prior to the surgical procedure, the subject was secured into position via a head cradle, and both non-sterile and sterile reference arcs were used to obtain passive planner registration for each fiducial marker. Dorsal and ventral borders of the STN and sensorimotor responses of neuronal units were determined from single and multiunit recordings from an Axon Guideline 3000 system as the microelectrode (FHC Crop, Bowdoinham, Maine) was advanced along the dorsoventral extent of the STN, as described in detail previously (Bronte-Stewart et al., 2010). Prior to implantation of the DBS lead, a combination of therapeutic and adverse effects of neurostimulation was tested using the guide tube surrounding the microelectrode. The depth of the DBS lead was advanced so that the base of electrode 0 would lie at the MER identified depth of the ventral base of STN. Once the DBS lead was implanted, intra-operative neurostimulation using a temporary external pulse generator assessed the therapeutic and adverse clinical effects of DBS through each electrode on the leads. Each subject was implanted with bilateral DBS leads (model 3389, Medtronic, Inc., Minneapolis MN, USA), with the exception of one subject who was implanted with lead model 3387.

Local field potentials (LFPs) were recorded from bipolar electrode pairs 0–1, 1–2, and 2–3 immediately after placement of the DBS lead in the operating room while subjects were awake and at rest without anesthesia. No subsequent change in lead placement occurred based on the LFP recordings. Fifteen subjects (30 sides) underwent simultaneous recording of two electrode pairs (0–1 and 1–2) from both STNs immediately after the placement of the second lead.

Subjects were instructed to remain as still as possible throughout the recording while keeping their eyes open. One recording was taken per STN, and recording durations varied from 30 s to two minutes. The presence of voluntary or involuntary movements was monitored using concurrent synchronized kinematic and videographic data. These included angular velocity sensors (Motus Bioengineering, Inc., Benicia, CA) attached to the contralateral limbs (arm and leg), accelerometer recordings from the head, surface electromyography (EMGs, Delsys, Inc., Boston, MA) on the flexor and extensor muscles of the contralateral forearm, continu-