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200–300 Hz movement modulated oscillations in the internal globus pallidus of patients with Parkinson's Disease

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ABSTRACT

Symptoms in Parkinson's Disease (PD) have been linked to oscillatory activity within the basal ganglia. In humans, such activity has been detected mainly in the local field potentials (LFPs) recorded from electrode contacts used for deep brain stimulation.

Although most studies have focused on activity within the subthalamic nucleus (STN), the internal part of the globus pallidus (GPi) is considered an equally efficacious site for therapeutic neuromodulation. Moreover, while most investigations have evaluated changes in oscillatory activity in the beta (12–35 Hz) and gamma (35–100 Hz) bands, our preliminary spectral analysis of LFP signals in the GPi suggested distinct activity at higher frequencies as well. We hypothesized there is a unique LFP signature in the GPi that consists of movement modulated spectral power increases above 100 Hz. Using invasive recordings from the GPi of patients undergoing DBS, in addition to confirming increased beta band activity within the GPi of patients with PD, we have identified and characterized a previously undescribed peak between 200 and 300 Hz centered at approximately 235 Hz, whose height and width but not center frequency are movement modulated. An increase in peak height is not transient, but rather persists for the duration of movement. The 200–300 Hz rhythms in the GPi could have a functional role in the basal ganglia reentrant circuits by encoding output information entering the thalamo-cortical network or by organizing downstream activity for the successful execution of tasks.

Introduction

Basal ganglia (BG) dysfunction has been implicated in the motor signs of Parkinson's Disease (PD) in humans (Brown et al., 2001; Dejean et al., 2008; Doyle et al., 2005), animal models (Burkhardt et al., 2007; Cruz et al., 2009) and computational studies (Berns and Sejnowski, 1998; Hadipour 2003; Frank, 2006; Humphries et al., 2006; Kang and Lowery, 2009; Noori and Jäger, 2010). The pathoetiology of the disease is attributed to dopaminergic (DA) denervation of BG due to neuronal loss within the substantia nigra. At the systems level, a mechanistic explanation that links BG functionality to motor behavior remains elusive. While oscillations in the β band in the cortico-basal ganglia thalamo-cortical reentrant circuits correlate with parkinsonian symptoms (Brown, 2007; Dostrovsky and Bergman, 2004), it is not known whether the synchronized bursting of neuronal populations in the BG is the primary cause of motor dysfunction or simply an epiphenomenon of the disease (Eusebio and Brown, 2009).

Recordings from BG structures of patients are afforded by electrode contacts on deep brain stimulation (DBS) leads implanted for therapeutic purposes (Kumar et al., 1998; Lopiano et al., 2001) or the microelectrodes used during stereotactic surgery to confirm the target BG nuclei (Chu Chen et al., 2006). The former provide local field potentials (LFPs) representing ensemble neuronal activity over a volume of tissue, with enhanced oscillatory activity represented as increases in the spectral power of LFP. In the DA depleted state, abnormal oscillations in the BG have primarily been reported as increases in β power (13–30 Hz) (Mallet et al., 2008a,b; Ray et al., 2008). It has been proposed that these synchronized oscillations within and between BG structures might interfere with the basal ganglia's proposed role in selectively activating neuronal processes that are relevant to a proposed task and attenuating others (McAuley, 2003). The DA replete state, conversely, has been associated with increased γ-band power at ~70 Hz (Brown et al., 2001). Specifically, increased γ-band power has been found to be coincident with motor tasks (Brown, 2000; Masimore et al., 2005) and therefore considered "pro-kinetic."

Very high gamma-band activity has also been reported in the subthalamic nucleus (STN) of awake patients with PD and have been shown to be dopamine- and activity-modulated, suggesting these rhythms may be intimately related to the pathophysiology of

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disease (Foffani et al., 2003; López-Azcárate et al., 2010). Such very high gamma-band activity, however, has not previously been described in the internal part of the globus pallidus (GPi). Because GPi is a common target for neuromodulation in the treatment of PD and is the final common output node for both the direct and indirect basal ganglia pathways, we hypothesized that a very high gamma band (>200 Hz) rhythm is also present in GPi and that this rhythm would demonstrate activity-modulation.

We recorded LFPs intra-operatively from the GPi of seven patients with PD after overnight withdrawal from dopaminergic medication and found a previously undescribed band of increased spectral power between 200 and 300 Hz that exhibits activity modulation.

Materials and methods

Subjects

Seven subjects (Table 1) with PD symptoms undergoing DBS implantation on the right GPi participated in the study after having provided informed consent approved by the internal review board at the University of California, Los Angeles.

Recording procedures

LFP recordings from the last 24 mm of the DBS lead trajectory of implantation, which included the GPi, were obtained from the lead's four ring electrode contacts (Medtronic, Model 3387, length 1.5 mm, inter-contact distance 1.5 mm). Signal acquisition was performed using BCI2000 v6.2 through a connection of the DBS lead to an amplifier (g.Tec, g.USBamp 2.0). The recording was performed at a sampling rate of 2400 Hz and online high-pass filtering above 0.1 Hz. Concurrent recordings from a data glove (5DT data glove 5 Ultra) worn by the patient on the hand contralateral to the DBS lead were obtained at a slower effective sampling rate, which was oversampled at 2400 Hz by BCI2000 using stair step interpolation. Scalp ground and reference were used. Amplifier potential equalization was provided by an ECG lead attached to each patient's left shoulder.

Once target coordinates were determined based on standard clinical methods, including indirect and direct (image-guided) targeting, microelectrode recordings, and intraoperative fluoroscopy, the DBS lead was advanced to target (average distance anterior to mid-commissural point: 19.82 mm, and interior to AC–PC plane: 4.61 mm) in four incremental steps, beginning initially at a point 13.5 mm from target with subsequent advances as illustrated in Fig. 1. This provided LFP recordings from a 24 mm span of the trajectory with non-overlapping interleaving recordings. At each position, signals were recorded during 60 s of rest and 60 s of self-paced contralateral hand movement (hand opening and closing, Table 2). Thirty to 60 s was allowed between each recording position to allow advancing of the electrode. In each case, the electrode was advanced using the Alpha Omega microdrive system.

Table 1
Subjects 1 and 6 could not be present for Off UPDRS because they were severely affected by symptoms. Subject 4 could not be tested for On UPDRS due to intolerance to medication.

Subject	Age	Sex	MDS-UPDRS PIII, Off/On	Disease duration (years)
1	62	F	52/27	25
2	69	F	33/9	12
3	64	M	NA/21	12
4	60	M	30/NA	10
5	40	M	56/42	5
6	71	M	NA/23	13
7	72	M	46/9	15

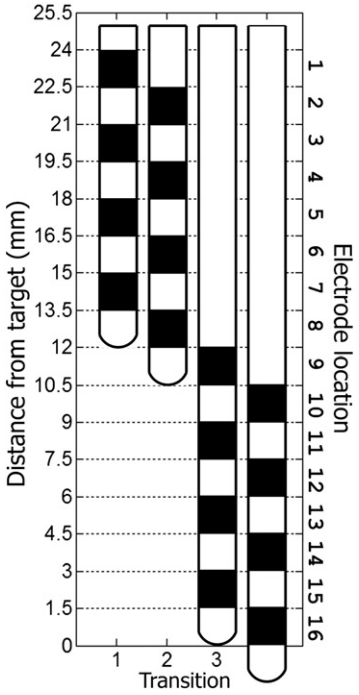

Fig. 1. Advancement of DBS leads to target. The lead was advanced four times such that its most distal electrode contact was 13.5 mm, 12 mm, 1.5 mm and 0 mm away from target. This protocol ensured recordings took place in every part of the last 2.4 cm along the path used to implant the lead. The most dorsal location was named location 1, while the most ventral location 16. Locations 15 and 16 were considered to be in the GPi, the target nucleus for stimulation.

Signal pre-processing

All computational procedures were performed in Matlab v.7.10.0 (www.mathworks.com). The original monopolar signal recordings (MON) were re-referenced offline to generate the equivalent time series for a bipolar (BIP) and a common average referenced (CAR) configuration. Bipolar signals were generated by subtracting signals from adjacent pairs of contacts at each recording position. For CAR, the common average reference of all four electrodes at each recording position was subtracted from the recordings of each contact in that recording position. Because noise characteristics were different among the three configurations, procedures to remove noise were separate.

In the MON configuration data was filtered using a 2 Hz high pass Chebyshev II filter (filter order $n = 18$) implemented as a second order sections direct form II structure using double precision arithmetic.

Table 2
Rest (R1, R2, R3, R4), movement (M1, M2, M3, M4), and lead location transition (T1, T2, T3) phases were alternated in order to obtain recordings for 16 locations evenly spread along a 24 mm trajectory ending at the GPi.

Phase	Duration	DBS location	Hand movement
R1	60 s	1, 3, 5, 7	No
M1	60 s	1, 3, 5, 7	Yes
T1	60 s	(transition)	–
R2	60 s	2, 4, 6, 8	No
M2	60 s	2, 4, 6, 8	Yes
T2	60 s	(transition)	–
R3	60 s	9, 11, 13, 15	No
M3	60 s	9, 11, 13, 15	Yes
T3	60 s	(transition)	–
R4	60 s	10, 12, 14, 16	No
M4	60 s	10, 12, 14, 16	Yes