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Beta-band oscillations in the supplementary motor cortex are modulated by levodopa and associated with functional activity in the basal ganglia

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ABSTRACT

We investigated the effect of acute levodopa administration on movement-related cortical oscillations and movement velocity in Parkinson's disease (PD). Patients with PD on and off medication and age- and sex-matched healthy controls performed a ballistic upper limb flexion movement as fast and accurately as possible while cortical oscillations were recorded with high-density electroencephalography. Patients off medication were also studied using task-based functional magnetic resonance imaging (fMRI) using a force control paradigm. Percent signal change of functional activity during the force control task was calculated for the putamen and subthalamic nucleus (STN) contralateral to the hand tested. We found that patients with PD off medication had an exaggerated movement-related beta-band (13–30 Hz) desynchronization in the supplementary motor area (SMA) compared to controls. In PD, spectral power in the beta-band was correlated with movement velocity. Following an acute dose of levodopa, we observed that the beta-band desynchronization in the SMA was reduced in PD, and was associated with increased movement velocity and increased voltage of agonist muscle activity. Further, using fMRI we found that the functional activity in the putamen and STN in the off medication state, was related to how responsive that cortical oscillations in the SMA of PD were to levodopa. Collectively, these findings provide the first direct evaluation of how movement-related cortical oscillations relate to movement velocity during the ballistic phase of movement in PD and demonstrate that functional brain activity in the basal ganglia pathways relate to the effects of dopaminergic medication on cortical neuronal oscillations during movement.

1. Introduction

Since the time of Woodworth's seminal studies in motor behavior, we have known that the two key phases in the performance of a voluntary movement are the ballistic phase and the corrective phase (Woodworth, 1899). The initial ballistic phase consists of a fast preprogrammed movement that occurs without feedback (referred to as an "open-loop" movement) while the subsequent corrective phase utilizes proprioceptive and visual feedback to increase movement accuracy. Later studies established the characteristic triphasic pattern of agonist and antagonist electromyography (EMG) activity during ballistic movements, in which an initial agonist EMG burst accelerates the limb toward the target and is followed by an antagonist EMG burst that decelerates the limb as it approaches the target and a final stabilizing burst of agonist EMG activity (Hallett et al., 1975). The acceleration and magnitude of the initial EMG burst has been shown to scale with movement velocity (Gottlieb et al., 1989).

In Parkinson's disease (PD) movements are performed at a reduced

Abbreviations: BOLD, blood oxygen level dependent; DBS, deep brain stimulation; ECoG, electrocorticography; EEG, electroencephalography; EMG, electromyography; ERSP, event-related power spectral perturbation; FDR, false discovery rate; fMRI, functional magnetic resonance imaging; HC, healthy control; ICA, independent component analysis; iEMG, integrated electromyography; LFP, local field potential; M1, primary motor cortex; MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; MEG, magnetoencephalography; MoCA, Montreal Cognitive Assessment; MPA, measure projection analysis; MVC, maximum voluntary contraction; PET, positron emission tomography; PD, Parkinson's disease; PD-OFF, off medication (levodopa) day; PD-ON, on medication (levodopa) day; rCBF, regional cerebral blood flow; ROI, regions of interest; S1, primary somatosensory cortex; SMA, supplementary motor area; SNc, substantia nigra pars compacta; STN, subthalamic nucleus

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velocity, referred to as bradykinesia. The onset of bradykinesia is associated with a selective loss of dopaminergic cells in the substantia nigra pars compacta (SNc) (Fearnley and Lees, 1991; Stocchi and Olanow, 2003). In patients with PD who perform a ballistic movement, the typical triphasic pattern is altered, with fractionated agonist EMG bursts that are marked by reduced agonist burst duration and magnitude, and an increase in the number of triphasic burst cycles. Dopaminergic medication and deep brain stimulation (DBS) of the subthalamic nucleus (STN) have been shown to increase the voltage of the first agonist burst and reduce fractionation of agonist activity (Hallett et al., 1975; Pfann et al., 2001; Vaillancourt et al., 2004). While there has been considerable focus on EMG activity during a ballistic movement, we know far less about how brain activity changes during a ballistic movement in patients with PD.

When using electrophysiological recording methods in the basal ganglia and motor cortex, a consistent observation is that beta-band (13–30 Hz) oscillations decrease in power during a movement (Brown and Marsden, 1999; Kühn et al., 2004; Heinrichs-Graham et al., 2017). In healthy controls, beta-band cortical oscillatory activity is known to be associated with motor control and learning (Pfurtscheller and Lopes da Silva, 1999; Engel and Fries, 2010; Kilavik et al., 2013), and reduced power during movement is often referred to as desynchronization. Desynchronized beta-band power has also been observed during motor planning prior to movement onset (Kaiser et al., 2001; Alegre et al., 2003; Kilner et al., 2005; Tzagarakis et al., 2010), and during both executed and imagined movement (Pfurtscheller and Lopes da Silva, 1999; Engel and Fries, 2010; Kilavik et al., 2013; Brinkman et al., 2014; Nakayashiki et al., 2014; Meirovitch et al., 2015; Ofori et al., 2015). Clinically, patients with PD who have bradykinesia exhibit abnormal movement-related beta-band cortical oscillations when using either electroencephalography (EEG) or magnetoencephalography (MEG) (Brown and Marsden, 1999; Heinrichs-Graham et al., 2014b; Stegemöller et al., 2016). However, it is not known how beta-oscillations in the cortex change during a ballistic movement, and if the level of desynchronization of cortical neurons relates directly to movement velocity in patients with PD off and on levodopa therapy.

Another key question that is not clear in the literature is how beta-band oscillations in the cortex relate to functional activity in the basal ganglia. This is a difficult question to address as it requires an in vivo approach. A key study found that levodopa reduced beta-band power in the local field potentials (LFP) in the STN, which was associated with the improvement of bradykinesia and rigidity (Kühn et al., 2006). However, this approach does not allow for assaying the relation between basal ganglia and cortical oscillations. The approach taken in the current study uses measures of functional activity in nuclei of the basal ganglia from functional magnetic resonance imaging (fMRI) in relation to how cortical oscillations change with levodopa therapy in patients with PD. It is well established that levodopa is an effective therapy for patients with PD (Jankovic and Aguilar, 2008), and levodopa improves movement velocity of both upper and lower limbs (Baroni et al., 1984; Vaillancourt et al., 2004, 2006). We use this prior knowledge to examine how levodopa affects cortical oscillations during an upper limb movement. Next, we use a well-established fMRI motor task to measure functional activity in the basal ganglia to compare with the cortical oscillations from EEG. The fMRI motor task has previously shown reduced fMRI activity in the basal ganglia in patients with PD that correlates negatively with motor deficits (Prodoehl et al., 2010), and the fMRI activity in basal ganglia progressively decreases longitudinally in PD (Burciu et al., 2016). Using a multimodal approach with fMRI and EEG allows the examination of functional activity in the basal ganglia and changes in cortical oscillations with levodopa.

A consensus of studies examining STN LFP in patients with PD during DBS have established that both levodopa and high frequency DBS reduce beta-band spectral power in a manner that scales with clinical improvement. This set of findings have led researchers to hypothesize that hypersynchrony of beta-oscillations and pathological oscillations in the basal ganglia may play a prominent role in the pathogenesis of parkinsonism (Little and Brown, 2014). On the other hand, studies of beta-oscillatory activity in the motor cortex have shown variable and sometimes contradictory results regarding the abnormalities that are present in PD, which may be due to heterogeneous modalities and research methods used (Brown and Marsden, 1999; Stoffers et al., 2007; Pollok et al., 2012; Heinrichs-Graham et al., 2014a, 2014b; Little and Brown, 2014; Moisello et al., 2015; Stegemöller et al., 2016). Here, to examine an association between anti-parkinsonian medication and cortical and subcortical activity in the basal ganglia-thalamo-cortical pathway we used multimodal non-invasive brain imaging techniques to compare patients with PD to healthy controls, and to understand how anti-parkinsonian medication affects brain activity in patients with PD. First, we focused on the initial phase of an isolated ballistic flexion movement of the upper limb in order to evaluate (i) how cortical oscillations are affected by PD during a ballistic movement, (ii) how these oscillations relate to movement velocity, and (iii) the effect of levodopa on cortical oscillatory activity and movement kinematics. Further, we tested the relation between fMRI activity in the basal ganglia and the changes in cortical oscillations to levodopa therapy. To address this question, we used task-based fMRI because this technique has the ability to measure functional activity in the direct and indirect pathway of the basal ganglia nuclei (Spraker et al., 2010). We tested two main hypotheses in this study. The first hypothesis was that an acute dose of levodopa would increase upper limb ballistic movement velocity and voltage of the agonist burst, and modulate beta-band motor cortical oscillations. The second hypothesis was that fMRI activity measured within the putamen and STN during a force control task would predict the modulation of beta-band cortical oscillations by an acute dose of levodopa.

2. Materials and methods

2.1. Subjects

We studied 15 patients (mean age: 62.00 ± SD 10.87 years; 6 females) and all had a positive response to levodopa as measured by a reduction in the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS-III) ($p < 0.001$) (Table 1). Patients with PD were diagnosed by a movement disorder specialist using established criteria (Hughes et al., 2001), and were recruited from University of Florida Center for Movement Disorders and Neurorestoration. 15 age-and sex matched healthy controls (HC; mean age: 62.53 ± SD 8.44 years; 6 females) were also tested. A two-tailed independent *t*-test showed no significant age differences between groups (i.e. PD and HC) ($p > 0.05$) (Table 1). All subjects were asked to refrain from consuming caffeine and refrain from using any hair products on the day of electroencephalography (EEG) and fMRI testing. The experiment was approved by the Institutional Review Board, and all subjects completed an informed consent prior to participating in the study.

2.2. Experimental design

The experiments for patients with PD were performed on two consecutive days: (i) a functionally off medication day (PD-OFF) and (ii) on dopaminergic medication (levodopa) day (PD-ON). The order of testing (PD-OFF and PD-ON) across days was counter-balanced across patients with PD. PD-OFF testing occurred in the practically defined PD off medication state (Langston et al., 1992), with testing following at least 12-hour withdrawal from dopaminergic medication. PD-ON testing occurred approximately 45 min after taking the usual morning dose of medication, corresponding to the time required for levodopa plasma level to reach its peak (Brooks, 2008). Each patient with PD underwent high-density EEG and assessment of motor symptoms and cognitive status during both PD-OFF and PD-ON. Motor symptoms and cognitive status were assessed using MDS-UPDRS-III and the Montreal Cognitive