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The cortical signature of symptom laterality in Parkinson's disease

Elizabeth Heinrichs-Graham[a,b,*], Pamela M. Santamaria[c], Howard E. Gendelman[d], Tony W. Wilson[a,b,d]

[a]Department of Neurological Sciences, University of Nebraska Medical Center (UNMC), Omaha, NE, USA
[b]Center for Magnetoencephalography, UNMC, Omaha, NE, USA
[c]Department of Neurology, Neurology Consultants of Nebraska, Omaha, NE, USA
[d]Department of Pharmacology & Experimental Neuroscience, UNMC, Omaha, NE, USA

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ABSTRACT

Patients with Parkinson's disease (PD) often present with unilateral motor symptoms that eventually spread to the other side. This symptom lateralization is diagnostically important, as it serves to distinguish PD from other motor disorders with overlapping symptom profiles. Further, recent studies have shown that the side of symptom onset is important for prognosis, as there are differences in the rate of disease progression and the incidence of secondary symptoms between right- and left-dominant (RD, LD) patients. Physiologically, previous studies have shown asymmetrical decline in structure and metabolism throughout the basal ganglia, although connecting this directly to motor function has been difficult. To identify the neurophysiological basis of symptom laterality in PD, we recorded magnetoencephalography (MEG) during left- and right-hand movement paradigms in patients with PD who exhibited either RD or LD symptomatology. The beta oscillations serving these movements were then imaged using beamforming methods, and we extracted the time series of the peak voxel in the left and right primary motor cortices for each movement. In addition, each patient's symptom asymmetry was quantitated using the Unified Parkinson's Disease Rating Scale (UPDRS), which allowed the relationship between symptom asymmetry and neural asymmetry to be assessed. We found that LD patients had stronger beta suppression during movement, as well as greater post-movement beta rebound compared to patients with RD symptoms, independent of the hand that was moved. Interestingly, the asymmetry of beta activity during right-hand movement uniquely correlated with symptom asymmetry, such that the more LD the symptom profile, the more left-lateralized (i.e., contralateral to movement) the beta response; conversely, the more RD the symptom profile, the more right-lateralized (i.e., ipsilateral to movement) the beta response. This study is the first to directly probe the relationship between symptom asymmetry and the laterality of neural activity during movement in patients with PD, and suggests that LD patients have a fundamentally different and more "healthy" oscillatory pattern relative to RD patients.

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterized by muscle rigidity, bradykinesia, resting tremor, impaired posture and balance, and speech and writing changes (Jankovic, 2008). PD initially emerges as a unilateral disorder, such that symptoms begin on one side of the body and spread to the other, although symptoms continue to be worse on the initially-affected side throughout the disease process (Djaldetti et al., 2006; Haaxma et al., 2010; Hoehn and Yahr, 2001; Lee et al., 1995; Riederer and Sian-Hulsmann, 2012; Uitti et al., 2005). This lateralization is diagnostically important, as it allows PD to be distinguished from other neurodegenerative disorders including essential tremor (Thenganatt and Louis, 2012), multiple system atrophy, and supranuclear palsy (Suchowersky et al., 2006). Interestingly, the side initially affected in PD has been recently associated with symptom trajectories. Indeed, a large-scale prospective study showed that patients with a right-dominant (RD) symptom profile had significantly more rapid progression of motor symptoms compared to those with a left-dominant (LD) symptom profile (Baumann et al., 2014). Patients with RD symptoms also showed significantly decreased muscle strength on both sides of the body compared to healthy controls, whereas LD patients showed no such differences (Frazzitta et al., 2015). Finally, LD symptomatology has been associated with longer disease duration, indicative of an extended period of survival after diagnosis, as well as delayed ambulatory inhibition compared to RD symptomatology (Munhoz et al., 2013). Taken together, these findings suggest that the side of symptom onset may hold important implications for predicting symptom trajectory in PD, and thus formulating prognoses.

* Corresponding author at: Center for Magnetoencephalography, University of Nebraska Medical Center, 988422 Nebraska Medical Center, Omaha, NE 68198, USA.
E-mail address: Heinrichs.Graham@gmail.com (E. Heinrichs-Graham).

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Nonetheless, the nature of symptom asymmetry in PD, especially the degree of asymmetry (i.e., how unilateral or bilateral symptoms present) and its neurophysiological origin, remains to be characterized.

Various studies have demonstrated asymmetrical subcortical structure and function in patients with PD (Abe et al., 2000; Choe et al., 1998; Eidelberg et al., 1990; Kempster et al., 1989; Morrish et al., 1995; Rinne et al., 1993). Overwhelmingly, researchers have found that the substantia nigra (SN) and putamen contralateral to the more affected side have greater degeneration and reduced dopamine uptake compared to homologous structures on the ipsilateral side. For example, Choe et al. (1998) used ^{1}H-MRS to determine various metabolite levels in the SN and putamen of patients with unilateral PD. They found decreased *N*-acetylaspartate to creatine ratios (NAA/Cr; indicative of neuronal impairment) in both structures contralateral to the affected side, irrespective of whether patients were LD or RD (Choe et al., 1998). Similarly, many PET studies have demonstrated reduced endogenous dopamine, as well as reduced dopamine uptake, in the basal ganglia contralateral to the affected side, and that this asymmetry persists when Parkinson's symptoms become bilateral (Bohnen et al., 2006; Lin et al., 2014; Rinne et al., 1993). Most recently, diffusion tensor imaging in patients with PD has shown reduced fiber integrity throughout the nigrostriatal pathway, but especially contralateral to the more affected side (Wang et al., 2015; Zhang et al., 2015). In contrast to this subcortical work, very few studies have investigated potential neural asymmetries in the neocortex of patients with PD (Hall et al., 2014; Pollok et al., 2012). Overall, these studies show differential resting and movement-related neural activity in the hemisphere contralateral to the more affected side compared to the ipsilateral hemisphere, which suggests that these asymmetries transcend basal ganglia structures. However, these studies did not distinguish between RD and LD patients and thus, did not investigate whether the strength of such asymmetries might differ between these subtypes of patients with PD. Further, no study to date has connected the degree of symptom laterality to neural laterality in subcortical or cortical regions. Given the heterogeneity of symptom expression in PD and the substantial differences between RD and LD patient prognoses, understanding this relationship may provide critical new insight to disease progression.

A widely replicated finding in patients with PD undergoing deep brain stimulation (DBS) surgery is the presence of pathological beta activity (14–30 Hz) throughout the basal ganglia motor circuit (Brown, 2007; Cassidy et al., 2002; Hammond et al., 2007; Little and Brown, 2014; Litvak et al., 2011). Such beta activity is known to be critical for successful movement execution and its inherent time course has been well characterized. Briefly, about 1.0 s prior to movement onset there is a strong decrease in cortical beta activity, which has been termed the beta event-related desynchronization (ERD) response. This response appears to be generated by the bilateral primary motor cortices (stronger contralateral to movement), with weaker activity in the parietal, premotor, and supplementary motor areas (Gaetz et al., 2010; Heinrichs-Graham et al., 2016; Heinrichs-Graham and Wilson, 2016, 2015; Heinrichs-Graham et al., 2014b; Jurkiewicz et al., 2006; Wilson et al., 2014; Wilson et al., 2013; Wilson et al., 2010; Wilson et al., 2011). Approximately 0.5 s after movement offset, there is a strong resynchronization of beta activity that lasts approximately 2.0 s, termed the post-movement beta rebound (PMBR; (Gaetz et al., 2010; Heinrichs-Graham et al., 2014b; Jurkiewicz et al., 2006; Wilson et al., 2010, 2011)). The beta ERD and PMBR have been reliably associated with movement planning/selection and active motor termination operations, respectively (Alegre et al., 2008; Alegre et al., 2004; Doyle et al., 2005; Grent-'t-Jong et al., 2014; Heinrichs-Graham and Wilson, 2015, 2016; Solis-Escalante et al., 2012; Tzagarakis et al., 2010), and are strongly modulated in the healthy aging brain (Heinrichs-Graham and Wilson, 2016; Rossiter et al., 2014). Importantly, recent work from our laboratory using noninvasive magnetoencephalography (MEG) has demonstrated pathologically-reduced beta activity in the motor cortices of patients with PD compared to healthy controls, both at rest and during transient movement (Heinrichs-Graham et al., 2014a, 2014b). Specifically, we found reduced beta ERD (i.e., weaker suppression relative to baseline) and marginally reduced PMBR amplitude (i.e., less increase from baseline) in patients with PD compared to healthy controls. Taken together, these data indicate that beta oscillatory activity is critical to the dysfunction seen in motor circuits, and the overall pathophysiology of PD.

The primary goal of the current study was to determine whether symptom laterality in patients with PD (i.e., LD or RD) is associated with distinct aberrations in motor-related beta activity. To this end, we collected high-density MEG to examine oscillatory activity during two movement tasks in right-handed patients with PD who had either a LD or RD symptom profile. Movement-related beta oscillatory responses were then imaged using beamforming, and the level of symptom asymmetry was quantified using the Unified Parkinson's Disease Rating Scale (UPDRS). These data were then used to evaluate the relationship between neuronal activity and symptom asymmetry. Consistent with recent clinical studies showing differences in LD/RD patients, we hypothesized that patients who were LD would exhibit significantly stronger (i.e., more negative) beta ERD activity, as well as stronger (i.e., more positive) PMBR activity, compared to patients who were RD. The directionality of this hypothesis is in line with prior neurophysiological research showing that patients with PD have reduced motor-related responses compared to healthy controls (Heinrichs-Graham et al., 2014b; Pollok et al., 2012); thus, it is intuitive in this population that stronger motor-related responses are indicative of a "healthier" motor system. Secondly, we hypothesized that the pattern of neural asymmetry would reflect the pattern of symptom asymmetry across the two patient groups.

2. Methods

2.1. Subject selection and behavioral testing

We studied 27 right-handed adults (4 females) with well-documented PD. Four participants were excluded from analysis due to artifacts in their MEG data (2 participants) or no significant movement-related oscillatory response (1 participant). An additional participant was excluded due to the discovery of exclusionary criteria post-enrollment. The mean age of the remaining patients was 64.74 years (range: 52–78 years; see Table 1). All participants had been prescribed a regularly-monitored and unchanged dosage of antiparkinsonian medication for at least 2 months prior to study enrollment, and had showed a satisfactory clinical response to the particular antiparkinsonian medication(s). Exclusionary criteria included any medical illness affecting CNS function, neurological disorder(s) besides PD, history of head trauma, and current substance abuse. After complete description of the study to participants, written informed consent was obtained following the guidelines of the University of Nebraska Medical Center's Institutional Review Board, which approved the study protocol.

Parkinsonism was measured by a certified rater using either the UPDRS (12 patients) or the Movement Disorders Society-sponsored revision of the UPDRS (MDS-UPDRS (Goetz et al., 2007), 11 patients) in the practically-defined "off" state, which means following at least a 12-hour holiday from antiparkinsonian medications. In order to identify left- or right-dominance of symptoms, scores from each item on the (MDS-)UPDRS Part III that contained both a right and a left side component (e.g., right upper limb resting tremor, left upper limb resting tremor) were extracted, which provided left and right motor subscores for each individual. Symptom asymmetry was calculated using each patient's motor subscores by subtracting the total symptom score from the right side from the total symptom score from the left side. Negative values of symptom asymmetry (LI_p) indicated LD of symptoms, while positive values indicated RD. Using this calculation, we divided our patient group by asymmetry of symptoms, such that 12 patients with PD exhibited symptoms that were LD (1 female), and 11 had symptoms