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SUBTHALAMIC DEEP BRAIN STIMULATION AND DOPAMINERGIC MEDICATION IN PARKINSON'S DISEASE: IMPACT ON INTER-LIMB COUPLING

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Abstract—Patients with Parkinson's disease (PD) often present with bimanual coordination deficits whose exact origins remain unclear. One aspect of bimanual coordination is inter-limb coupling. This is characterized by the harmonization of movement parameters between limbs. We assessed different aspects of bimanual coordination in patients with PD, including inter-limb coupling, and determined whether they are altered by subthalamic (STN) deep brain stimulation (DBS) or dopaminergic medication. Twenty PD patients were tested before STN DBS surgery; with and without medication. Post- surgery, patients were tested with their stimulators on and off as well as with and without medication. Patients were asked to perform a unimanual and bimanual rapid repetitive diadochokinesis task. The difference in mean amplitude and mean duration of cycles between hands was computed in order to assess inter-limb coupling. Also, mean angular velocity of both hands and structural coupling were computed for the bimanual task. There was a positive effect of medication and stimulation on mean angular velocity, which relates to clinical improvement. PD patients exhibited temporal inter-limb coupling that was not altered by either medication or STN stimulation. However, PD patients did not exhibit spatial inter-limb coupling. Again, this was not altered by medication or stimulation. Collectively, the results suggest that structures independent of the dopaminergic system and basal ganglia may mediate temporal and spatial inter-limb coupling.

Key words: bimanual, rapid alternating movement, diadochokinesia, Parkinson, STN, DBS.

INTRODUCTION

Deep brain stimulation (DBS) is a recognized therapeutic intervention for the alleviation of drug refractory motor symptoms in Parkinson's disease (PD). While several nuclei can be considered for stimulation, a widely targeted structure is the subthalamic nucleus (STN). Several studies demonstrated the efficacy of STN DBS in the alleviation of PD-related motor symptoms such as rigidity, bradykinesia, tremor and postural instability (Chung et al., 2006; Kleiner-Fisman et al., 2006; Diamond et al., 2007; Gervais-Bernard et al., 2009; Fox et al., 2011). Additionally, STN DBS improves performance during different motor activities such as gait and grasping (Yokoyama et al., 1999; Bastian et al., 2003; Alberts et al., 2004; Johnsen et al., 2009; St George et al., 2010; Bleuse et al., 2011; McNeely and Earhart, 2012). However, little is known about the impact of STN DBS on bimanual movements in PD. Brown et al. (1999) examined the effect of STN DBS on complex movements requiring bimanual coordination. They observed that the time required to perform the bimanual task was significantly improved with DBS. In two other studies, Alberts et al. (2004, 2008) examined the effect of unilateral DBS on bimanual force control. They observed consistent improvements in the control and coordination of grasping forces during those specific bimanual tasks.

Understanding the impact of STN DBS on bimanual coordination could provide information related to its underlying mechanisms as well as important clinical information since most activities of daily living are performed with both hands. PD patients exhibit deficits in several aspects of bimanual control such as accuracy, stability, or pattern switching (Lazarus and Stelmach, 1992; Brown et al., 1993; Johnson et al., 1998; van den Berg et al., 2000; Almeida et al., 2002; Byblow et al., 2002; Joebges et al., 2003; Ponsen et al.,

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Abbreviations: ANOVA, analysis of variance; DBS, deep brain stimulation; PD, Parkinson's disease; STN, subthalamic nucleus; UPDRS, unified Parkinson's disease rating scale.

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2006; Muller and Harati, 2010; Song et al., 2010; Almeida and Brown, 2013). One property associated with bimanual movements is inter-limb coupling. This occurs when the performance of both limbs becomes similar during a bimanual task. Both spatial and temporal aspects of the movement can display coupling (Sherwood, 1991, 1994, 2004, 2006, 2007; Sherwood and Nishimura, 1992, 1999; Heuer et al., 1998; Sherwood and Sullivan, 1999). We recently demonstrated that although PD patients in the advanced stages of the disease do not exhibit deficits in temporal inter-limb coupling during a rapid repetitive diadochokinesis task while off dopaminergic medication, these patients lacked spatial inter-limb coupling (Daneault et al., 2015). Results from this study where motor performance of healthy controls, PD patients and Huntington's disease patients were compared led us to postulate that temporal inter-limb coupling is mediated by structures/networks not primarily affected by pathophysiological changes of PD. On the other hand, we proposed that spatial inter-limb coupling is mediated by structures/networks that are deficient in PD.

The objective of the current study was to compare the impact of therapeutic interventions, namely dopaminergic medication and STN DBS, on spatial and temporal inter-limb coupling during a rapid repetitive diadochokinesis task in PD. A secondary goal was to further circumscribe, using the observed motor output, known pathophysiological characteristics of PD and physiological consequences of the therapeutic interventions, the possible neural networks involved in spatial and temporal inter-limb coupling.

EXPERIMENTAL PROCEDURES

Participants

The results presented here stem from a larger ongoing prospective study on the effect of STN DBS on upper-limb motor performance. Twenty patients (58 years old ± 7 years (SD); mean disease duration of 11 years ± 3 years) diagnosed with idiopathic PD that underwent bilateral STN DBS surgery were prospectively evaluated. All patients exhibited bilateral motor symptoms and Hoehn and Yahr scores ranging from 2.5 to 4. Inclusion criteria were those from the DBS protocol (Defer et al., 1999); and no patients exhibited significant co-morbidities that could affect their motor performance. Unified Parkinson's disease rating scale (UPDRS) (Fahn and Elton, 1987) motor score was significantly reduced from 33.6 ± 11 pre-surgery off medication to 16.4 ± 9 post-surgery off medication/on stimulation ($p < 0.05$). Patients had a levodopa equivalent daily dose of 1405 ± 694 mg preoperatively which was significantly reduced to 747 ± 582 mg postoperatively ($p < 0.05$). There was also a reduction in the UPDRS motor score on medication from 18.5 ± 11 pre-surgery to 12.9 ± 8 post-surgery on medication/on stimulation ($p < 0.05$). Patients signed an informed consent form prior to participation in this study, based on a protocol approved by the institutional research ethics review board.

Procedure

The task and procedure have been described in detail elsewhere (Daneault et al., 2015). Briefly, patients were seated on a chair and asked to hold in each hand a foam handball that was attached to angular displacement sensors. Patients' arms were positioned to their side with the elbows bent at 90 degrees. Patients were first instructed to maintain a "stable" position for 15 s. Patients were then instructed to perform pronation–supination of the dominant hand as fast and with as complete a rotation as possible, for a period of 10 s. Then, patients were asked to return to the stable state for the remaining 15 s. Three trials were recorded with rest periods of 60 s between trials. This was repeated for the non-dominant hand. Patients were then asked to perform the task simultaneously with both hands. For the bimanual task, patients were asked to perform an in-phase movement where both thumbs move simultaneously toward the midline of the body. This was done in order to simplify the task as in-phase movements with respect to the longitudinal axis of the body are more stable and accurate than other phase relationships (Kelso, 1984). Furthermore, this task has relatively large amplitude in displacement and velocity, which reduces the likelihood of biomechanical effect. It is also simple enough to minimize greatly the influence of cognitive deficits known to frequently occur in PD. The order of the conditions was alternated during testing.

Specific for the current study, PD patients were tested while in seven different medication/stimulation states. Before surgery, PD patients were tested off their PD-related medication, after a withdrawal period of at least 10 h (overnight) (off medication). They were then tested again 1 h after taking their usual morning medication dose (on medication). After surgery, PD patients were tested again off medication with their stimulator on (off medication/on stimulation). Patients then took their usual morning medication dose and they were tested after waiting 1 h (on medication/on stimulation) (Day 1). On the following day (Day 2), patients were first tested off medication (again with overnight withdrawal) with their stimulator off. Testing occurred after the stimulator had been off for 1 h (off medication/off stimulation). Next, patients remained off their medication but their stimulator was re-activated on one side; and after a 1-hour wait, patients were tested again (off medication/on stimulation with left DBS lead). Finally, the stimulator that was on was turned off and the stimulator on the opposite side was re-activated; and after a 1-hour wait, patients were tested again (off medication/on stimulation with right DBS lead). Examining the effect of unilateral stimulation was done in order to assess whether introducing a hemispheric imbalance in the basal ganglia network activity would alter inter-limb coupling properties. Note that the post-operative days of testing were consecutive and were counter-balanced between patients such that some performed Day 1 first and then Day 2 while others performed Day 2 first and then Day 1. Also, the off medication/on stimulation with left or