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Deep Brain Stimulation Improves Lower Extremity Coordination and Coordination Variability in Individuals with Parkinson's Disease

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ABSTRACT

Deep Brain Stimulation (DBS) is associated with vast improvements in the motor symptoms of Parkinson's disease. Recent evidence has identified improvements in movement complexity during treadmill walking in response to DBS. However, the effects of DBS on intra-limb coordination during gait have not been well elucidated. This study investigated changes in intra-limb ankle and knee joint coordinative patterns during treadmill walking in response to DBS. Five individuals with PD performed a four-minute treadmill walking task while 3D kinematics were collected over two periods of 30seconds. Participants completed testing in the DBS-ON and DBS-OFF conditions. Mean Absolute Relative Phase (MARP) and Deviation Phase (DP) were used to evaluate intra-limb ankle and knee joint coordination and coordination variability. DBS-ON was associated with increases in MARP and DP compared to DBS-OFF at the ankle and knee joints. DBS allows individuals with Parkinson's disease to perform walking tasks with greater freedom of coordination and coordination variability. Increased availability of coordinative patterns may represent a greater number of potential strategies to optimize mechanical and metabolic efficiency during the treadmill walking task.

INTRODUCTION

Parkinson's Disease (PD) is a progressive neurodegenerative disease associated with the loss of dopamine-producing neurons in the substantia nigra [1]. Gait-related symptoms of PD include reduced gait velocity, shortened step and stride lengths, reduced joint range of motion, reduced stride length and width variability and freezing of gait [2-7]. These PD-related locomotor symptoms result in decreased independence and quality of life [8]. Current anti-PD treatments include dopamine-replacement therapy, though deep brain stimulation (DBS) provides an alternative treatment when dopaminergic medication no longer controls symptoms [9]. Dopaminergic medication improves gait symptoms of PD including walking speed, stride length and stride variability [1-3,6,7] by replacing endogenous dopamine in the striatum [10]. However, some gait parameters are not benefited by dopaminergic medication such as cadence, swing duration and double limb support time [2,11,12].

Unlike dopaminergic therapy, DBS acts to inhibit overactive connections within the basal nuclei rather than restore disturbed pathways resulting in similar improvements in gait parameters [2,3,6]. Despite the similar benefits of dopamine-replacement therapy and DBS, evidence suggests that these treatments operate via separate mechanisms and may be synergistic [2,3]. DBS may enhance adaptability of the motor system in individuals with PD. Movement variability and complexity of motion are suggested to decline in the presence of disease and represent a diminished capacity for the system to adapt to perturbation or stress [13]. Powell et al. [14] revealed that DBS was associated with increased variability of joint motion at the ankle and knee as measured by sample entropy. Further, DBS was also associated with greater movement complexity at the knee and hip [14]. These findings suggest that DBS may improve the neuromuscular system's capacity for adaptation as evidenced by increased movement complexity in addition to temporospatial gait parameters.

Movement coordination is the process by which movement components are organized in time and in sequence to produce a functional outcome or result [15]. While Powell et al. [14] demonstrated DBS-induced changes in gait variability and complexity, limited data exist pertaining to the effect of DBS on gait coordination. Dopaminergic medication has been associated with improvements in bilateral (side-to-side) coordination in individuals with PD, and while individuals with PD-related Freezing of Gait (FOG) experienced greater benefits in bilateral coordination than those without FOG [16]. An investigation of the effects of DBS on bilateral (left-right) coordination during gait revealed DBS-related improvements in coordination [17]. These studies demonstrate that DBS improves bilateral coordination between the most and least affected limbs, however, no previous study has investigated the effects of DBS on intralimb coordination, a factor that may contribute to reduced walking speed and an increased risk of falling in individuals with PD.

A number of methods have been used to quantify intralimb coordination including measures of vector coding and Continuous Relative Phase (CRP). Vector coding quantifies intersegmental coupling within a limb by assessing the relationship of one segment's angular position relative to another segment's angular position. Several studies have used vector coding during gait to assess intralimb coordination and coordination variability in a variety of activities and populations [18,19]. Conversely, CRP seeks to evaluate intralimb coordination with respect to each segment's angular velocity to determine the segment's phase angle and not simply the relationship between the angular position of two oscillating segments. This consideration of a segment's angular velocity is an important distinction as proprioceptive feedback from the muscle spindle includes magnitude and velocity of stretch [20,21]. Further, it has been suggested that individuals with PD exhibit greater long-latency reflex responses in high- compared to low-velocity movements [22]. Two discrete measures of CRP have been used previously to quantify intralimb coordination and coordination variability during walking including: mean Absolute Relative Phase (MARP) and Deviation Phase (DP). These measures provide a simple and direct measure of intralimb coordination and coordination variability over the entire gait cycle.

Given that no previous study has quantified the effect of DBS on intralimb coordination, the purpose of this study is to evaluate the DBS-induced changes in intralimb coordination and coordination variability in individuals with PD during a treadmill walking task. Based on the findings of previous studies investigating gait variability and complexity, it was hypothesized that DBS would be associated with greater MARP and DP values than walking without DBS.

MATERIALS AND METHODS

Participants

Five individuals with idiopathic PD were recruited to participate in this study. Table 1 presents clinical details for each participant. Participants were included if they: (1) were classified as stage 2 to 4 on the Modified Hoehn &Yahr rating scale, (2) had at least 12 months of successful treatment using bilateral deep brain stimulation of the subthalamic nucleus (DBS), (3) were not being currently treated with dopaminergic medications and (4) were capable of treadmill walking without an assistive device. Participants were excluded if they had a Mini-Mental State Exam (MMSE) score of less than 18 indicating that they could not give informed consent. Experimental procedures were thoroughly explained to all participants and each participant provided written informed consent prior to participating in this study in accordance with

the Declaration of Helsinki. The experimental protocol was approved by the University Institutional Review Board.

Table 1: Individual participant characteristics including age, sex, years since diagnosis, Hoehn & Yahr Score and Timed-Up-&-Go.

Subject	Age (yr)	Sex	Years Since Diagnosis	H&Y	TUG (sec)
PD1	76	M	9	3	9.9
PD2	67	M	4	2	7.6
PD3	58	M	9	3	8.5
PD4	71	M	4	2	8.1
PD5	59	F	7	3	7.8

Experimental Protocol

Participants visited the laboratory on two separate days with a minimum of 48 hours between visits. The first session was a familiarization session in which participants were screened for inclusion, provided written informed consent, performed clinical performance testing (Timed Up & Go) and were familiarized with the treadmill walking task. The familiarization session was performed in the DBS-ON condition to minimize the risk of injury and confounding factor of fatigue.

During the testing session, participants performed two 4-minute treadmill walking bouts at a velocity of 1.0 m/s in each of two experimental conditions: with DBS (DBS-ON) and without DBS (DBS-OFF). The 1.0 m/s treadmill velocity was selected to accommodate reduced walking velocities in the DBS-OFF condition. Once participants reported their comfort with the treadmill walking task, two 30-second trials were recorded from the middle of the second and third minutes of the treadmill walking task. To reduce the potentially confounding factor of fatigue, all participants performed experimental testing in the DBS-ON condition first followed by the DBS-OFF condition. Following completion of testing in the DBS-ON condition, participants turned off their DBS and, following a 60-minute period of rest, repeated the experimental protocol in the DBS-OFF condition. A majority of the beneficial effects of DBS have been shown to subside within a 60-minute period following cessation of treatment [23].

A 9-camera motion capture system (120 Hz, Qualisys Inc., Goteburg, Sweden) was used to collect three-dimensional (3D) kinematic data from the most affected leg of each participant. For all participants, the right limb exhibited worse motor symptoms in both the DBS-ON and DBS-OFF conditions. Anatomical markers were placed over the right and left superior iliac crests, anterior superior iliac spines, posterior superior iliac spines, greater trochanters, medial and lateral femoral epicondyles, medial and lateral malleoli, and first and fifth metatarsal heads. A cluster of four retro-reflective markers were used to track the thigh and shank while two clusters of two retro-reflective markers were used to track the right and left side of the pelvis. The foot was tracked using three individual retro-reflective markers placed over the superior, inferiorand lateral heel.

Data Analysis

Kinematic data were filtered using a 4th order, zero-lag, lowpass Butterworth filter with a cutoff frequency of 8 Hz. Visual3D (C-Motion, Bethesda, MD, USA) was used to calculate temporospatial variables across the entirety of the 30-second trial as previously described [24]. Visual3D was also used to calculate segmental angles and velocities relative to the laboratory coordinate system for the pelvis, thigh, shank and foot.

Custom software (MATLAB, Math Works, Natick, MA) was used to calculate continuous relative phase angles as described by Hamill et al. [25] Plots of interest included sagittal plane foot, shank and thigh phase plots. Phase plots were constructed as the segmental angular velocity (y-axis) plotted against the segmental angular position (x-axis) and were normalized using the following equations:

Eq. 1. $$\theta_{i,norm} = 2\left(\frac{\theta_i - \min(\theta)}{\max(\theta) - \min(\theta)}\right)$$

Eq. 2. $$\omega_{i,norm} = \frac{\omega_i}{max[\max(\omega), \max(-\omega)]}$$

where θ is the segmental angle, ω is the segmental angular velocity and the subscript *i* indicates the data point within the stride. As previously described [26], normalization was conducted to account for differences in movement amplitude and frequencies in the time series prior to the calculation of phase angles. Following normalization of angular positions and velocities, phase angles were defined as the angle between the right horizontal axis and a given data point *i* with phase plot coordinates of ($\theta_{i,norm}$, $\omega_{i,norm}$) and were calculated as follows:

Eq. 3. $$\varphi_{segment} = tan^{-1}\left(\frac{\omega_{i,norm}}{\theta_{i,norm}}\right)$$

CRP angles were calculated as the difference between proximal segment φ and distal segment φ.

MARP characterizes the interaction of two segments across a given movement cycle as a single number [27]. Calculated as the mean of the absolute values of the continuous relative phase time-series, the MARP value represents the coordination of two adjacent segments as in-phase or out-of-phase. A low MARP value indicates that the two segments are oscillating with an in-phase relationship while high MARP values indicate that the segments exhibit an out-of-phase relationship. DP is a measure of the variability of the continuous relative phase time-series and is calculated as the average standard deviation of the ensemble continuous relative phase time-series [25,27,28]. DP provides a measure of the stability of the neuromuscular system during a given task. Low DP values represent a highly stable system with limited coordination variability while high DP values represent a less stable system with greater coordination variability.

Statistical analysis

MARP and DP values were averaged across all steps in each 30-second trial of treadmill walking to create a single data point (subject mean) for each variable for each subject in the two experimental conditions. These subject means were used in statistical testing to compare coordination (MARP) and coordination variability (DP) in the DBS-ON versus DBS-OFF conditions. Wilcoxon Signed Rank tests were used to compare mean MARP and DP values for each coordinative structure (i.e. knee joint relative phase) in each experimental condition (DBS-ON vs. DBS-OFF).Due to the small sample size, Cohen's d effect sizes [29] were reported to compare mean differences between the DBS-ON and DBS-OFF conditions. Cohen's d values were interpreted according to previously published recommendations [30]: small: $d < 0.6$, moderate: $0.6 < d < 1.2$; large: $d > 1.2$. The values were selected based on the sample size and within-subjects design implemented in the current study. All statistical analyses were conducted in GraphPad Prism 8.0with an alpha level of 0.05.

RESULTS

Mean participant age, height and mass were: 66.3 (7.7) years, 1.81 (0.09) m and 74.7 (8.1) kg. Temporospatial gait parameters are presented in Table 2. Stride lengths, double support time and relative double support time were smaller in the DBS-ON compared to DBS-OFF condition (Table 2). No differences in stride width were observed between the DBS-ON and DBS-OFF conditions.

Table 2: Mean gait temporospatial characteristics in participants in the DBS-OFF and DBS-ON conditions. Presented as mean (SD).

	Stride Length (m)	Stride Width (m)	Double Support (sec)	Double Support (% Cycle)
DBS-OFF	1.14 ± 0.30	0.15 ± 0.04	0.64 ± 0.20	45.9 ± 2.3
DBS-ON	0.98 ± 0.31	0.15 ± 0.04	0.50 ± 0.18	40.5 ± 3.0
p-value	0.012	0.756	0.004	0.007
Cohen's d	0.52	0.01	0.74	2.02

MARP and DP values for the ankle and knee are presented in Table 3. At the ankle, individuals with PD had greater MARP values in the DBS-ON compared to DBS-OFF condition ($p = 0.031$, $t = 3.26$, $d = 0.90$). DP was also greater in the DBS-ON condition than the DBS-OFF condition ($p = 0.031$, $t = 2.19$, $d = 1.07$). At the knee, MARP was greater in the DBS-ON compared to DBS-OFF condition ($p = 0.042$, $t = 2.94$, $d = 0.62$). DP was also greater in the DBS-ON compared to DBS-OFF condition ($p = 0.042$, $t = 2.22$, $d = 0.80$).

Table 3: Mean Absolute Relative Phase (MARP) and Deviation Phase (DP) values for the ankle and knee joints in individuals with PD in the DBS-ON and DBS-OFF conditions. Presented as mean ± SD.

Variable	Condition	Ankle	Knee
MARP	DBS-ON	3.2 ± 1.5	6.8 ± 2.8
	DBS-OFF	2.1 ± 0.9	5.1 ± 2.8
	p-value	0.031	0.042
	Cohen's d	0.90	0.62
DP	DBS-ON	2.2 ± 1.0	2.9 ± 1.5
	DBS-OFF	1.4 ± 0.4	2.0 ± 0.6
	p-value	0.031	0.042
	Cohen's d	1.07	0.80

DISCUSSION

This study revealed that ankle and knee joint coordination and coordination variability were greater when individuals with PD are treated with DBS. As PD is associated with reduced gait complexity, it was hypothesized that DBS would be associated with improved coordination and greater coordination variability. The current findings support these hypotheses by demonstrating greater out-of-phase behaviors in the DBS-ON

compared to DBS-OFF condition as evidenced by greater MARP values. Further, coordination variability was enhanced in response to DBS treatment as evidenced by greater DP values. Increased MARP and DP values were observed at both the ankle and knee suggesting a systemic effect of DBS on intralimb coordination and coordination variability.

Coordination is described as the successful organization of multiple segments to perform a given task [15]. The current study used MARP to describe the coordination patterns at the ankle and knee joints with respect to the angular displacement and angular velocities of their constituent segments (foot-shank and shank-thigh). MARP is a composite measure of coordination across a given period of interest and provides insight into the in-phase or out-of-phase behavior of two oscillating segments. Previous research has suggested that strong in-phase coordination patterns may be indicative of a simplistic motor control pattern and indicative of a reduced capacity to respond to an external perturbation [15,31,32]. For example, Byrne et al. [15] investigated the effect of age on ankle and knee joint coordination using MARP and revealed that older adults had smaller MARP values at the knee during level walking and that these differences were retained when gait was perturbed. Current data demonstrated that MARP values at the ankle and knee were greater in the DBS-ON than DBS-OFF conditions. Greater MARP values are indicative of a more out-of-phase movement pattern between the two segments [15] suggesting that motion of the ankle and knee were less constrained in DBS-ON compared to DBS-OFF conditions.

Though few studies have investigated intra-limb coordination in PD using continuous relative phase or its derivatives, several studies have investigated the effects of DBS on motor symptoms of PD. These studies have demonstrated that DBS is associated with improved motor scores on the Unified Parkinson's Disease Rating Scale(UPDRS) [33,34] as well as increases in lower extremity joint excursions during gait [2,3,35]. Greater joint excursions such as greater ankle dorsiflexion or knee joint flexion during midstance would result in more out-of-phase movement patterns. Post-hoc assessment of joint ranges of motion (ROM) from the current study revealed significantly greater ankle ($p = 0.001$; DBS-ON: $15.1° \pm 3.6°$; DBS-OFF: $11.7° \pm 3.0°$) and knee joint ROM ($p = 0.022$; DBS-ON: $32.0° \pm 6.4°$; DBS-OFF: $27.6° \pm 2.8°$) in the DBS-ON compared to DBS-OFF conditions. These differences in ROM and joint excursions in the DBS-ON condition likely underlie the greater MARP values and out-of-phase coordination patterns. The greater MARP values and joint excursions observed in the DBS-ON compared to DBS-OFF conditions suggest that DBS improves the capacity of the neuromuscular system resulting in a less constrained motor system. These improvements in neuromuscular organization and the resulting improvements in mechanical capacity are also demonstrated in the reductions in double support time and reductions in relative durations of double support during the stance phase of the gait cycle.

Variability is an inherent characteristic of human movement [13]. PD is associated with reductions in autonomic and somatic variability including heart rate [36], blood pressure [37], muscle activation [38], voluntary motor patterns [39] and gait [14,40]. Recent research has demonstrated that DBS is associated with increases in joint motion variability and complexity during a treadmill walking task [14]. These increases in variability were suggested to indicate that the neuromuscular system was less constrained and had a greater number of strategies available to successfully complete the treadmill walking task. Though Powell et al. [14] demonstrated increases in joint motion variability, they did not investigate coordination variability. Coordination variability can be described as the variability in oscillatory patterns of two segments. Previous research has suggested that low coordination variability values may also be indicative of a constrained neuromuscular system with a reduced number of strategies available to successfully complete a given task [32]. Previous research investigating coordination variability using DP demonstrated that advancing age is associated with reduced DP values suggesting a more constrained, less adaptable neuromuscular system [15]. Further, healthy young adults demonstrated reduced coordination variability (measured using DP) during gait when a cognitive dual task was presented [31] suggesting that neuromuscular systems with less coordinative variability and fewer potential successful strategies may fail in the presence of a perturbation or challenge. In the current study, the DBS-ON condition was associated with greater DP values than the DBS-OFF condition suggesting that DBS not only improved coordinative patterns as evidenced by increased MARP values but also improved

coordinative variability. The greater coordinative variability suggests that individuals with PD have a greater number of successful strategies that may be employed to accomplish the treadmill walking task [41]. Further, these individuals may exhibit a more robust neuromuscular system that is capable of overcoming greater perturbations during the gait task.

Though the current study presents novel findings regarding DBS-induced improvements in ankle and knee joint coordination and coordination variability, we acknowledge several limitations. The small sample size (N=5) limited our statistical power. The small sample size is a reflection of the difficulty to recruite individuals with PD that are treated with DBS yet are ambulatory without their DBS treatment. To address the small sample size, the investigators included not only tests of differences but also estimates of effect sizes (Cohen's d). The congruence of statistically significant findings with moderate and large effect sizes supports the findings of this study. A second limitation of this study was the use of a treadmill for the walking task. Previous literature has suggested that the use of a treadmill may provide a cueing effect for individuals with PD functionally improving gait performance [5,42]. Another limitation of this study was the imposed order of experimental conditions. In all participants, the DBS-ON condition was completed first followed by the DBS-OFF condition. This order of condition presentation was selected due to the result of preliminary testing in which participants (not included in these findings) reported significant fatigue following the completion of the DBS-OFF condition. As a result, participants completed the DBS-ON condition first followed by the DBS-OFF condition. While this order of condition presentation may bias experimental findings, it was a logistical necessity to complete the required testing. Finally, MARP and DP present holistic measures of coordination and coordination variability and do not represent changes in coordination at a given instance or event in the stride cycle. However, these cycle-based measures may provide insight into improved coordination as a whole across the entire stride cycle that may be missed by more instance-based measures such as discrete relative phasing or point estimate relative phase.

CONCLUSIONS

These data demonstrate that DBS of the subthalamic nucleus alters sagittal plane coordination and coordination variability during treadmill walking. The DBS treatment resulted in a more out-of-phase coordinative pattern at the ankle and knee associated with greater ankle and knee joint ranges of motion. Further, DBS was associated with greater coordination variability at the ankle and knee suggesting a greater number of successful strategies were available to the patient when PD was treated with DBS. These changes in coordinative patterns suggest that individuals with PD exhibit improved neuromuscular organization and adaptability which may enhance both mechanical and metabolic efficiency when PD is treated using DBS (compared to untreated). This greater variability and inferred adaptability may be associated with reductions in fall risk while also increasing independence and improving quality of life.

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CONFLICTS OF INTEREST

None

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