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Does Cycling Cadence Affect Interlimb Symmetry in Pedaling Power in Individuals with Parkinson's Disease?

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By

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Accepted in Partial Completion
of the Requirements for the Degree
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Master's Thesis

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Gary D. Wiley Jr.

November 6, 2018

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A Thesis
Presented to
The Faculty of
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In Partial Fulfillment
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Master of Science

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Abstract

Cycling at faster pedaling rates leads to symptomatic improvement in patients with Parkinson's disease (PD). However, these patients show inter-limb asymmetry in pedaling power when cycling at their slow self-selected cadence. The effects of faster pedaling cadence on symmetry of effort between limbs is unknown. We compared the effect of pedaling cadence on symmetry of crank power output in individuals with PD versus healthy controls. In this case series, two participants with PD and two healthy controls performed 3-minute bouts of stationary cycling at three cadences (50, 65, 80 rpm) at 60W and self-selected workload. Power output contribution of each limb towards total crank power output was computed over 60 crank cycles from the effective component of pedal force, which was perpendicular to the crank arm. Although no statistical analysis was performed for this case series, the data across the experimental conditions showed that individuals with PD demonstrated substantial interlimb asymmetry in power output (35-154%) compared to healthy controls (1-34%). There was no clear trend for the effect of pedaling cadence in participants with PD and healthy controls. Two patients with PD and one healthy control participant showed an increase in asymmetry with increase in pedaling cadence. In conclusion, participants with PD demonstrate large interlimb asymmetries in power output compared to healthy controls and this interlimb asymmetry is not systematically affected by pedaling cadence.

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Chapter I

Introduction

Parkinson's disease (PD) is a common progressive neuromuscular condition affecting more than 10 million individuals worldwide [1-3] and costs the healthcare system in the United States 14 billion dollars annually [4]. In patients with PD, degeneration of the dopaminergic neurons within the substantia nigra leads to substantial reduction in dopamine production [5-6], resulting in symptoms such as resting tremors, bradykinesia or akinesia, rigidity, and postural imbalance [7-11]. These symptoms adversely affect the ability of these patients to perform activities of daily living such as maintaining balance and walking. In addition, these clinical features in patients with PD are generally more pronounced on one side compared to the other, thereby leading to asymmetry in performing motor tasks, such as walking and cycling [12-13].

Cycling is a commonly prescribed mode of neurorehabilitation for patients with PD [9, 13-14]. Generally, patients with PD are prescribed stationary cycling at high cadences (i.e. 80-90 rpm) three times per week with sessions ranging from 30-60 minutes [9, 15-16]. Post-cycling sessions, patients experience immediate and long-term improvements, such as decreases in resting tremor, bradykinesia, and rigidity [9, 17-18], and enhancement in executive function [19]. Cycling cadence is a critical variable for effectiveness of pedaling as an intervention for patients with PD. Several studies have shown that symptomatic improvement is only observed at faster, and not slower or preferred cadences in patients with PD [9, 14, 17, 20]. Researchers have speculated that cycling at faster cadences alleviates symptoms of PD by promoting changes in neural drive by increasing both motor output and sensory input [14, 16]. More specifically, it is suggested that increasing cadence improves the rhythmic pattern generation that is required in lower extremity coordination [13].

Penko et al. [13] found that individuals with PD are asymmetrical when pedaling at their self-selected cadences. Specifically, these individuals exerted lesser power with their more affected leg and compensated by exerting greater power with their less affected side. Generally, self-selected cadences of patients with PD were low (59 ± 13 rpm) [9, 14, 16-17, 21], whereas symptomatic improvements were observed at faster pedaling cadences (80-90 rpm) [9, 14, 16-17, 21]. Previous research in healthy subjects has shown that pedaling at faster cadences reduces asymmetry in power output. However, no previous research has investigated whether asymmetry of power output between lower limbs in cycling changes when pedaling at faster, compared to slower, cadences in patients with PD. As with healthy subjects, pedaling at faster cadences could also reduce interlimb asymmetry in power output for patients with PD. However, this hypothesis has not yet been tested. Interlimb asymmetry in pedaling power would place asymmetrical stresses on the lower extremity joints on each side [22-23]. By reducing interlimb asymmetry in cycling, effectiveness of pedaling could potentially be improved for rehabilitation of patients with PD.

The purpose of this study was to examine the effects of pedaling cadence on interlimb asymmetry in crank power output in patients with PD compared to healthy controls. We hypothesized that: 1) interlimb asymmetry in power output would be greater for patients with PD compared to healthy controls, and; 2) interlimb asymmetry in power output would decrease at faster cadences.

Chapter II

Methods

Study Design

In this cross-sectional, case-controlled study, differences in interlimb asymmetry in crank power outputs at different cadences were assessed during low-intensity stationary cycling between patients with PD and age-and-sex matched control subjects. All experimental data were collected in a single data collection session. The Western Washington University Institutional Review Board approved the study, and all participants gave written informed consent before participating.

Participants

Eight individuals with idiopathic PD and eight age-and-sex matched healthy controls were recruited from the surrounding community. Sample size was calculated using GPower 3.1 software based on index of asymmetry data reported by Penko et al.[13]. A total sample size of 16 participants (8 per group) was needed to achieve a statistical power of 0.8 to detect a large effect size (Cohen's f = 0.53) [24] for group main effects at an alpha level of 0.05.

Participants with PD visited their neurologist to get screened before visiting the lab. These individuals were also assessed by a local neurologist within four weeks of their testing day. The Movement Disorders Society's revision of Unified Parkinson's Disease Rating Scale (UPDRS) was utilized while the participants were "off" anti-parkinsonian medication for at least twelve hours prior to examination, and only individuals with Hoehn and Yahr stage II-III were eligible to participate [13]. UPDRS is a reliable and valid test to assess the severity of Parkinson's disease [25-26]. This scale was used to determine which lower extremity was more affected, based on UPDRS motor examination of tremor, rigidity, and leg agility score on each side. These tests

were scored on a scale from 0-4. A score of 0 indicates a normal, unaffected individual, where a score of 4 indicates a high severity of PD [15]. These data were used to identify the limb that was more affected by PD.

All of the participants completed a health history and physical health questionnaire to screen for exclusion criteria and obtain information about their current physical activity status and exercise experience. Exclusion criteria included any muscular, orthopedic, other neurologic, and/or cardiovascular disorders that limited an individual's ability to pedal on an ergometer at low to moderate intensities for more than thirty minutes. The Western Washington University Institutional Review Board approved the study, and all participants gave written informed consent before participating.

Instrumentation

All pedaling trials were conducted on an electronically braked Velotron Dynafit cycle ergometer (Racer-Mate Inc., Seattle, WA) which is shown to be accurate and reliable for measuring power output during cycling [27-28]. Power output of each leg was determined using an instrumented force pedal system (Sensix, Poitiers, France), which synchronously measures pedal forces in all planes of motion via orthogonal strain gauges, and pedal and crank orientation via optical encoders. Prior to arrival of participants, the calibration of the Velotron ergometer was verified by performing the Accuwatt calibration check test (Racer-Mate Inc., Seattle, WA) and instrumented force pedals were initialized to ensure they were calibrated accurately with respect to manufacturer settings.

Procedures

In a single test session, participants completed six three-minute pedaling trials at cadences of 50, 65, and 80 rpm at an experimentally controlled power output (i.e. 60 W) [13], and

self-selected power output [9, 14, 16] in a random order. These chosen cadences fell within the range of self-selected cadences (i.e. 50-70 rpm) [9, 14, 16] and therapeutically prescribed cadences (i.e. 75-90 rpm) [9, 14, 16, 21] of individuals with PD. Subjects were asked to change into comfortable clothes to cycle in, and shoes provided by the researchers. The subjects' mass and height were measured in kilograms and meters, respectively, using a standard balance beam scale with stadiometer. Subjects then completed a three-minute warm-up at a self-selected resistance and a self-selected cadence on the Velotron cycle ergometer [13, 15]. Three minutes of rest followed the warm-up, during which participants sat on the cycle ergometer. Following this warm-up, participants completed three-minute trials at self-selected resistances for the three cadences (50 rpm, 65 rpm, and 80 rpm). Following the self-selected power output pedaling conditions, participants repeated the three 3-minute trials of the same cadences at a controlled resistance of 60 W in a random order. A rest interval of three minutes separated each condition.

During these six cycling conditions, data were synchronously captured for bilateral pedal forces and orientation, and crank position using instrumented force pedals at a sampling frequency of 240 Hz during the entire three-minute experimental condition. Verbal encouragement was provided along with a visual screen (image below) that participants watched in order to maintain their assigned cadence. Participants finished with a three-minute cool-down at a self-selected resistance and a self-selected cadence [13, 15].

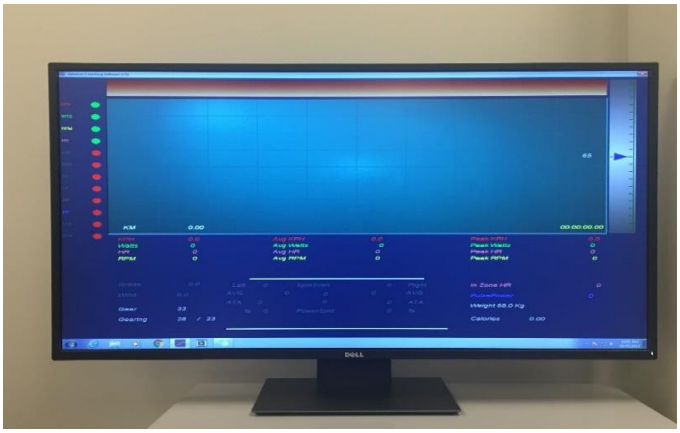

Figure 1. Cadence feedback provided via Velotron CS software

Data Analysis

The crank position, pedal orientation, and pedal force data were low pass filtered at 4 Hz using a fourth order recursive Butterworth filter [22-23, 34]. The pedal forces were transposed to the crank coordinate system using pedal force and orientation, and crank position data using the Sensix I-Crankset software (Poitiers, France). The anterior-posterior and normal components of pedal forces were then used to compute resultant sagittal pedal forces. Effective component of force is the only component of force that creates the angular impulse to rotate the crank. The effective force was computed as the component of the resultant force perpendicular to the crank arm using trigonometric methods described in previous studies [29-30]. Effective crank torque on each side for a complete crank cycle was computed as a product of the component of the effective pedal force and length of crank arm (0.1725 m). The crank power on each side was computed as a product of effective crank torque and crank angular velocity. The data for crank power on each side were then averaged over 60 crank cycles.

Based on the average crank power output measured for each limb, the Symmetry Index (SI) was calculated for each 360-degree crank cycle. The equation to compute symmetry index is based on previous research [13, 31] and it is as follows:

$$Symmetry\ Index\ (SI) = \left(\frac{Unaffected\ limb - Affected\ limb}{(Unaffected\ limb + Affected\ limb)/2}\right)$$

Values from this equation can be used to quantify the magnitude of contribution from each limb. A positive value indicates a greater contribution from the unaffected limb, while a negative value indicates a greater contribution from the affected limb [13]. This equation can be modified to evaluate the contribution of left versus right lower extremity contribution, or dominant versus non-dominant leg power. For the control group, leg dominance was determined by asking which leg they preferred to use to kick a ball [32-33].

$$Symmetry\ Index\ (SI) = \left(\frac{Dominant - Nondominant\ limb}{(Dominant\ limb + Nondominant\ limb)/2}\right)$$

Statistical analysis

For this case series a statistical analysis was not performed. Descriptive data associated with the experiment were presented.

Chapter III

Results

Due to difficulty in recruiting the PD patient population, only data for two individuals with PD and two age-and sex-matched controls were collected. For this small sample size, statistical analysis was not conducted. Descriptive statistics of the data collected are presented below.

Descriptive statistics for each pair of participants (i.e., Participant with PD and control) are presented below in **Table 1**.

Table 1. Participant demographic characteristics

Characteristics	PD Participant 1	Control Participant 1	PD Participant 2	Control Participant 2
Age (years)	67	67	70	70
Sex	female	female	female	female
Height (cm)	164	165	155	170
Mass (kg)	50.90	60.00	44.09	69.10
Average weekly cycling (min)	240	90	180	0
Other regular weekly physical activity (min)	665	200	240	240
State of PD (Hoehn & Yahr Scale)	2-3	NA	2-3	NA
Duration of disease (yrs)	6	NA	3	NA

NA = Not applicable.

Each participant's data relevant to their cycling performance and asymmetry is presented in the subsequent tables (Tables 2-5). Although the data presented are descriptive in nature, it shows that participants with PD demonstrated a greater degree of asymmetry in their pedaling performance. For example, the range of asymmetry index in participants with PD was 35-154% whereas for the control group, this range was 1-34%. In addition, the degree of asymmetry increased with pedaling cadence for three of the four participants. In only one healthy control, cadence did not systematically affect pedaling asymmetry.

Table 2. PD participant 1 cycling performance and asymmetry data

	Preferred PO			Fixed PO (60 W)		
	50 rpm	65 rpm	80 rpm	50 rpm	65 rpm	80 rpm
Cadence (rpm)	49.9	64.9	79.6	50.1	65.0	79.9
Total PO (W)	44.2	37.8	42.6	58.4	60.4	68.2
Absolute PO less affected limb (W)	34.4	32.5	37.4	43.3	46.1	50.4
Absolute PO more affected limb (W)	9.8	5.3	5.2	15.1	14.3	17.8
Relative PO less affected limb (%)	77.8	86.0	88.3	74.1	76.5	74.1
Relative PO more affected limb (%)	22.2	14.0	11.7	25.9	23.5	25.9
Asymmetry Index (%)	111.0	144.2	153.0	96.6	106.0	96.5

Note. PO = Power Output.

Table 3. Control participant 1 cycling performance and asymmetry data

	Preferred PO			Fixed PO (60 W)		
	50 rpm	65 rpm	80 rpm	50 rpm	65 rpm	80 rpm
Cadence (rpm)	50.5	65.7	80.6	50.7	65.2	80.0
Total PO (W)	74.3	79.4	67.6	58.0	59.3	63.1
Absolute PO dominant limb (W)	39.0	39.5	33.2	31.4	29.4	31.8
Absolute PO non-dominant limb (W)	35.4	39.9	34.4	26.7	29.9	31.3
Relative PO dominant limb (%)	52.4	49.7	48.9	54.0	49.4	50.3
Relative PO non-dominant limb (%)	47.6	50.3	51.1	46.0	50.6	49.7
Asymmetry Index (%)	9.4	-1.3	-4.4	16.0	-2.3	1.0

Note. PO = Power Output.

Table 4. PD participant 2 cycling performance and asymmetry data

	Preferred PO			Fixed PO (60 W)		
	50 rpm	65 rpm	80 rpm	50 rpm	65 rpm	80 rpm
Cadence (rpm)	50.2	64.9	77.5	49.1	64.1	78.6
Total PO (W)	32.6	30.3	35.9	64.1	68.2	71.3
Absolute PO less affected limb (W)	22.5	25.7	31.7	37.7	40.7	45.6
Absolute PO more affected limb (W)	10.1	4.6	4.2	26.5	27.5	25.7
Relative PO less affected limb (%)	69.0	85.2	88.5	58.7	59.7	64.0
Relative PO more affected limb (%)	31.0	14.8	11.5	41.3	40.3	36.0
Asymmetry Index (%)	76.0	140.8	153.9	34.9	38.8	56.1

Note. PO = Power Output.

Table 5. Control participant 2 cycling performance and asymmetry data

	Preferred PO			Fixed PO (60 W)		
	50 rpm	65 rpm	80 rpm	50 rpm	65 rpm	80 rpm
Cadence (rpm)	50.1	64.9	79.8	50.1	65.1	80.0
Total PO (W)	69.5	65.0	69.5	61.8	63.2	66.8
Absolute PO dominant limb (W)	33.2	31.3	28.9	29.3	29.2	28.2
Absolute PO non-dominant limb (W)	36.3	33.7	40.6	32.5	34.0	38.6
Relative PO dominant limb (%)	47.9	48.6	41.5	47.5	46.2	42.2
Relative PO non-dominant limb (%)	52.1	51.4	58.5	52.5	53.8	57.8
Asymmetry Index (%)	-8.5	-5.5	-34.0	-10.0	-15.0	-31.4

Note. PO = Power Output.

Chapter IV

Discussion

The purpose of this study was to examine the effects of pedaling cadence on interlimb asymmetry in crank power output in patients with PD compared to healthy controls. The limited data collected support the first hypothesis that interlimb asymmetry is greater in individuals with PD when compared to healthy age- and sex-matched controls. However, these data do not appear to support the second hypothesis that interlimb asymmetry in pedaling power decreases at faster pedaling cadences.

Data in the current study, although very small in sample size, support the hypothesis that individuals with PD exhibit a greater degree of asymmetry in pedaling power compared to healthy controls. In individuals with PD, clinical features such as resting tremors, bradykinesia, rigidity, and postural imbalance are commonly more distinct on one side of the body compared to the other [13]. Asymmetries in the manifestation of PD could lead to one side of the body contributing more force production than the other [12]. It is common for up to 80% of individuals affected by PD to experience one side of the body being more affected by the disease before the disease becomes bilateral [12]. This may be attributed to the reduction in movement sensation and awareness of joint position, or proprioception, from the depression of dopamine production [35-36].

In the current study, the range of asymmetry in pedaling power output was between 34.9-153.9% in individuals with PD compared to 1.0-34.0% in the healthy controls. These data are similar to results found by Penko et al. [13], who also investigated symmetry in pedaling mechanics for an incremental workload cycling test in individuals with PD. Penko et al. [13] reported symmetry indices for average power output ranging from roughly 0.2-1.2. Note that in the current study and that by Penko et al. [13], the index of symmetry was calculated identically except

the index was presented as percentage in the current study, whereas Penko et al. [13] presented their data as a ratio. So, dividing the index of symmetry values obtained in the current study by 100 will make the data be directly comparable to that reported by Penko and associates [13]. Although the degree of asymmetry in people with PD is similar in the current study compared to the study by Penko et al. [13]; in the current study, there was an experimental control of pedaling workload and cadence whereas Penko et al. [13] did not directly control these parameters.

Interlimb asymmetry in effort appears to be a common observation across different motor tasks for individuals with PD. These motor tasks include, but are not limited to, walking and standing balance. Boonstra and colleagues [12] examined the effect of static standing perturbations on postural stability and balance in individuals with PD and healthy individuals. They observed that individuals with PD showed a greater degree of asymmetry in weight-bearing proportion and balance-control contributions whereas the healthy controls distributed their weight more evenly and equal amounts of torque were exerted by both legs [12]. Yogev et al. [37] examined gait asymmetry patterns in individuals with PD, elderly individuals with a history of falling, and healthy controls. They observed a significantly higher degree of asymmetry in the individuals with PD, followed by the elderly "fallers" when compared to the healthy controls. In summary, interlimb asymmetry is a common manifestation of PD observed across different motor tasks such as walking [37], standing balance [12], and cycling [13].

With respect to the second hypothesis (i.e. pedaling asymmetry decreases at faster cadence), three of the four participants in the current study showed an opposite trend. For these three participants when cycling at faster cadence, asymmetry in pedaling power increased. One participant did not show a clear trend in pedaling power when cycling cadence systematically became faster. In research done on young healthy cyclists, it was found that when pedaling

faster, asymmetry became less pronounced [32, 38-39]. Interlimb asymmetry is commonly observed in healthy young recreational and competitive cyclists, and they exhibit a range from five to twenty percent during cycling [38], yet these values decreased as cadenced increased from 40-120 rpm [32, 38-39]. It is also prudent to note that a recent study reported that interlimb asymmetry is unaffected by cadence as well as external workload in older healthy individuals and those with knee osteoarthritis [34]. Data from the current study and the other studies mentioned thus far [32, 34, 38-39], show that young adults, older adults, and individuals with PD do not show consistent effect of pedaling cadence on asymmetry of pedaling effort. One factor contributing to this inconsistency in results, could be that participants in the current study and that by Buddhadev et al. [34] did not cycle at higher cadences (50-90 rpm) compared to the studies with healthy, young participants (40-110 rpm) [32, 38-39]. Future studies should reexamine the effects of cadence in individuals with PD using cadences higher than those used in the current study.

For individuals with PD, the investigation of the effect of pedaling cadence on cycling performance (i.e. symmetry of effort) was important because therapeutic benefits of cycling are only found at faster cadences. Ridgel et al. [9, 14] and Alberts and colleagues [20] observed that the individuals who pedaled at faster cadences (80-90 rpm) when compared to slower cadences (60-65 rpm) experienced an improvement in motor functions as well as an improvement in cortical and motor response. This data suggests that in order to elicit a beneficial change in individuals with PD, faster cadences are required.

One noteworthy strength of the current study was the use of both fixed workload (i.e. 60 W) and preferred, self-selected workload for assessment of interlimb asymmetry in pedaling power. The analysis of asymmetry at a fixed workload exhibits high internal validity, because Penko et al. [13] found that systematic increase in workload reduced asymmetry in pedaling power

in patients with PD. Experimentally controlling pedaling workload provides a more precise assessment of the effects of cadence on asymmetry because the confounding effects of pedaling workload are removed. Conversely, assessment of asymmetry in pedaling power at self-selected workload exhibits high external validity. Generally, when patients with PD pedal during their training or rehabilitation sessions, they self-select the pedaling workload (i.e. resistance).

Limitations

An important limitation of the current study was the small sample size. The data collection has not been completed for the study due to difficulty in recruiting individuals with PD, especially under the age of 70 years. There is a need to collect more data to obtain an adequate sample size, as estimated in the statistical power analysis. A descriptive analysis was presented for the data collected thus far. However, with an adequate sample size, statistical analysis can be performed to determine if data do or do not support the experimental hypotheses.

An important observation in the current study was that at higher pedaling power output asymmetry in pedaling mechanics were lower in individuals with PD. For participants with PD, the preferred pedaling power was lower (30.3-44.2 W) compared to the experimentally fixed power output (60W). For the two participants with PD, a consistent trend of having lesser asymmetry at higher power output was observed. At experimentally controlled power output (60 W), asymmetry ranged from 34.9-106.0 % whereas for the preferred power output condition, asymmetry ranged from 76.0-153.9 % for both participants. These data suggest that asymmetry decreases when the individual cycles at a power output greater than their self-selected resistances. Penko et al. [13] did examine the effect of workload on asymmetry in crank power in individuals with PD during an incremental test performed at self-selected cadence. They found that with systematic increase in workload interlimb asymmetry reduced [13]. However, prior

research shows that cadence affects symmetry of pedal power [32, 38-39] and thus, there is a need to examine the systematic effect of workload at fixed cadences on asymmetry in pedaling power.

Conclusion

Based on the limited data collected, participants with PD exhibit substantially greater degree of asymmetry than healthy controls, and a systematic increase in cadence did not have an effect on the degree of asymmetry in pedaling power output.

Chapter V

Review of Pertinent Literature

Cycling at faster pedaling rates leads to symptomatic improvement in patients with Parkinson's disease (PD). However, these patients show inter-limb asymmetry in pedaling power when cycling at their slower self-selected cadence. The effects of faster pedaling cadence on symmetry of effort between limbs is unknown. This chapter will introduce the reader to relevant information about PD, neurorehabilitation via cycling, assessment of symmetry in cycling, and cycling cadence (a mechanical variable that affects both symptoms and symmetry in cycling). This pertinent review of literature provides evidence to support the testing protocol and procedures used in the current study.

Overview of Parkinson's disease

Etiology

Parkinson's disease (PD) is the second most common, progressive neuromuscular condition, after Alzheimer's disease, affecting more than 10 million individuals worldwide [1-3, 40]. Both the prevalence and the incidence of the disease increases with age. For individuals age 60 years or higher, the incidence of PD is 1-2% [40-41]. Though the prevalence rates compared between sexes has shown to be insignificant, more males have been reported to have the disease [40], with incidence showing significance in the age range of 60-69 and 70-79 [42]. The exact cause for the disease is unknown, but studies have shown that both genetic and environmental factors play a role in the development of PD [40-41, 43-44].

Neurophysiology

Parkinson's disease is characterized by changes in the brain, more specifically the basal ganglia. The basal ganglia are a group of subcortical nuclei that are highly connected with many

areas of the brain including the cortex, thalamus, and brain stem. These nuclei are associated with many functions of life, including voluntary movement, cognition, and emotion. Synaptic pathways between the basal ganglia and the cortical systems are affected by dopaminergic status, and dysfunction in these connections may lead to Parkinson's disease symptomology [5, 44].

Within the basal ganglia is a structure known as the substantia nigra, which plays a role in movement and reward. Degeneration of the dopaminergic neurons within the substantia nigra pars compacta leads to as much as a 90% reduction in dopamine in the striatum, depriving the basal ganglia of the dopamine that it requires to initiate and facilitate movement and postural control required of daily living. This deprivation leads to many of the motor and non-motor signs and symptoms observed in PD [3, 6, 40, 43]. de Lau et al. [1] speculated that dysfunction at the muscular level, such as mitochondrial dysfunction, oxidative stress, and protein mishandlings, may play a role in the pathogenesis of PD.

Symptomology

PD is characterized by motor and non-motor symptoms. As the disease progresses, it becomes an increasing social and economic burden on those affected. Four cardinal motor symptoms associated with PD are resting tremors, bradykinesia or akinesia, rigidity, and postural imbalances. Resting tremors are an involuntary oscillatory movement produced when a limb is fully supported against gravity and the muscles involved are not active [7]. Bradykinesia or akinesia are defined as a slowness or absence in movement initiation and execution. There is also an observed reduction in the amplitude of movement up until complete cessation of the movement [8]. Diminished levels of dopamine and associated reduced motor control output in patients with PD, is suggested to influence bradykinetic movements and impaired sensory integration [9].

Rigidity refers to an increase in resistance when passively stretching a muscle [10]. As PD progresses, patients begin to exhibit abnormal body posture, including an increase in flexion of the head and cervical spine, an increase in thoracic kyphosis, and other postural imbalances that greatly affect daily life [1, 11]. Even though these symptoms are very common in patients with PD, some of these symptoms are not always observed. The current criteria for the diagnosis of PD includes the presence of at least two of these motor symptoms [1]. The non-motor symptoms include sensory deficits, insomnia, and emotional problems such as depression, lack of facial expression, a slowing of gastrointestinal function, and reduction in the sense of smelling [45-46].

Diagnosis and Classification

Unified Parkinson's Disease Rating Scale

Though there exists a paucity of reliable and valid tools for these assessments, the Unified Parkinson's Disease Rating Scale (UPDRS) has been widely used to assess many factors of PD including activities of daily living (ADLs), motor symptoms, mentation, and treatment complications in these patients [25-26]. Ramaker et al. [25] reports high internal consistency, inter-rater reliability, and a moderate construct validity for this assessment. The UPDRS has specific use in PD, covers many arrays of the widespread scope of PD in differing severities, as well as clinimetric properties, especially in ADLs, and motor examination. In 2009, the release of the Movement Disorder Society-UPDRS (MDS-UPDRS) improved on the older version of the test to cover multiple groups at differing levels of severity [47]. The MDS-UPDRS consists of four parts: I: non-motor experiences of daily living; II: Motor experiences of daily living; III: Motor examination; IV: Motor complications. Patient and caregiver or administrator complete questions in each section on a rating scale of zero to four, with zero being normal, one being slight, two being mild, three being moderate, and four being severe [48]. The MDS-UPDRS rates sixty-five

items, taking the patient and caregiver approximately thirty minutes to complete [48].

Hoehn and Yahr scale

The Hoehn and Yahr scale has been widely accepted and utilized in the research of PD [18, 49-50]. In a research setting, the Hoehn and Yahr scale is primarily used to define inclusion/exclusion criteria [49]. The scale consists of five stages, with each stage increasing in the severity of the disease.

The modified Hoehn and Yahr scale is as follows: [47]

Stage 0: No signs of disease

Stage 1.0: Symptoms are very mild; unilateral involvement only

Stage 1.5: Unilateral and axial involvement

Stage 2: Bilateral involvement without impairment of balance

Stage 2.5: Mild bilateral disease with recovery on pull test

Stage 3: Mild to moderate bilateral disease; some postural instability; physically independent

Stage 4: Severe disability; still able to walk or stand unassisted

Stage 5: Wheelchair bound or bedridden unless aided

Pharmacological management with Levodopa

Since PD remains a progressive, and thus far, a non-curable disease, rehabilitation has focused on decreasing the rate of progression as well as aiding in alleviating the side-effects that are common from the debilitating disease. For nearly the past half century, the use of the drug Levodopa (L-dopa) has been used to help alleviate the symptoms of PD [51]. Further research found that administration of L-dopa in lab animals led to an excretion of dopamine in the urine, suggesting that dopamine levels were elevated [9, 51-52]. Although, as the disease progresses, complications arise from Levodopa use, including either inadequate dopaminergic tone, where

the drug wears off or there are dose failures, or excessive dopaminergic tone that can cause levodopa-induced dyskinesia [52]. Though alternative medication can be used once L-dopa begins to have these side-effects, alternative medication is generally only used once a tolerance to L-dopa develops [52].

Neurorehabilitation for PD

PD is identified as a dysfunction in sensorimotor integration, leading to common symptoms such as bradykinesia and other atypical movement. Alternative rehabilitation methods have been researched regarding how they can positively elicit changes in the symptoms observed in PD [2-3, 8-9, 14]. Neurorehabilitation programs are an increasingly favored method for the rehabilitation of PD [53]. Huang et al. [53] also stated since the mechanism for the symptoms of PD, including weakness and fatigue, are unknown and often subjective, challenges arise when constructing neurorehabilitation programs. Though exercise has shown to combat other side-effects such as sleep deprivation and depression, finding a regimen that can improve kinesthetic deficits as well can be difficult [17]. Many studies have shown an increased attention to interventions that promote changes in neural drive [9, 13]. These studies have shown that an increase in not just motor output, but sensory input may play a role in these motor improvements, and since drugs like levodopa do not improve these kinesthetic deficits, neurorehabilitation interventions like these are greatly needed [14]. High intensity exercise has been highly suggested as a method to increase neural drive and promote neural plasticity as well as neuroprotection against dopaminergic cell loss [14]. Though the exact method is still undetermined, non-invasive trans-magnetic stimulation has been used to show a decrease in the dysfunction of corticomotor excitability in people with PD [54]. These changes in corticomotor excitability could be at the base of symptomatic improvements.

Neurorehabilitation through cycling

An increasing interest in cycling specifically has occurred in researchers studying the effects of neurorehabilitation interventions for PD [16]. Penko et al. [13] stated that pedaling is a bipedal motor task, similar to walking, that requires the same principles of lower extremity coordination, so quantifying pedaling kinetics can give a more precise measurement of lower extremity function. The exact protocol for cycling has been studied largely by researchers hoping to find a protocol that improves kinesthetic deficits the most [9, 13-14, 16]. Alberts et al. [16] stated that in order for the patients to gain a benefit from exercise, the rate of the exercise must be increased to trigger a release of neurotrophic factors and possibly dopamine.

Mode of cycling

A wide array of protocols have been examined regarding cycling, and can be classified into three distinct categories; Active, active-assisted, and passive. Active, also known as voluntary cycling, is performed by the patient alone, usually at a self-selected pace [55]. Granted, individuals do see some improvements in symptomology from an active protocol, the other modes of exercise have been shown to elicit greater improvements [9, 13-14, 16, 55]. Active-assisted cycling involves the individual biking with the assistance of an able-bodied individual on a tandem bicycle. The exact mechanism for a greater response to active-assisted cycling is unknown, however it is hypothesized that patients are cycling at a cadence faster than their preferred speed, promoting an increase in afferent input to the central nervous system [56]. The hypotheses further states that during active-assisted cycling, sensory feedback coming from the periphery along with subsequent activation of the basal ganglia circuits may be combatting the abnormal motor output that is observed in individuals with PD [14]. Ridgel et al. [14] found that patients in an active-assisted group showed a 13% greater increase in UPDRS scores than

compared to a voluntary group. In a practical sense, active-assisted cycling may not be the best mode in terms of resources as well as at-home protocols. Not every individual will be able to have an able-bodied assistant to help them during at-home sessions. Passive cycling, or forced exercise (FE), has been researched to work around these limitations. During FE, the individual is assisted through a motorized bike that is set at a specific cadence. Patients are told to cycle with the cadence of the motorized bike, so it is not passive in the sense that the patient is not cycling, but they do not need to exert the force required to increase the cadence past their comfortable range [14, 16]. It has been proposed that FE promotes angiogenesis and synaptogenesis, and for individuals with PD the formation of new blood vessels and synapses within the brain decreases. Acute aerobic exercise, in this case through a forced-cycling regimen, has been shown to release neurotrophins such as brain-derived neurotrophic fact (BDNF) and glial-derived neurotrophic factor (GDNF) as well as dopamine, which aids in supporting neuroplasticity as well as protect against cell loss in the basal ganglia. The key to this difference between FE and VE is the increase in intrinsic feedback, given by the faster pedaling rate [16].

Mechanical variables critical for cycling performance assessment

Cadence

The specific modality of the cycling training program has been extensively studied as to which modality is the most beneficial, and there has been an increasing interest in speed-based training. Uygur et al. [18] examined the effects of an acute cadence-derived protocol primarily on the symptoms of bradykinesia in Parkinson's disease patients. Three groups were included; no exercise, voluntary cycling, and high cadence-low resistance (HC:LR) cycling. For the HC:LR group, the cycled at a self-selected pace, similar to the voluntary group, but during the first 15-seconds of minutes 5-24, they pedaled at a self-selected fast cadence. They found that subjects in

the HC:LR group had significant improvement during a 4-square step test and 10-minute walk test, primarily in walking velocity. It is suggested that this exercise facilitates locomotor central pattern generators, which are generally impaired in the Parkinson's disease population.

Power output

Pedaling power output from each leg is representative of that lower extremity's effort and it can be quantified using force-sensing pedals and trigonometric equations [23]. In cycling pedaling power outputs are therefore, commonly used for assessment of asymmetry between limbs [13]. During cycling, power output is representative of the total contribution of the lower extremities, and a net power output can be maintained by reducing the output of one leg, and correspondingly increasing the output of the other leg [22]. Hunt and associates [23] examined interlimb asymmetry in individuals with and without an anterior cruciate ligament (ACL) injury while cycling and found that the individuals with ACL injuries demonstrated substantial interlimb asymmetry (~50%). These individuals contributed significantly less with their injured limb and compensated by increasing the power output of the ACL-intact limb. The authors suggested the interlimb asymmetry observed in these individuals may compromise the therapeutic benefits of cycling towards restoring strength in the limb post-injury.

Buddhadev et al. [34] also examined interlimb asymmetry in power output for individuals with knee osteoarthritis and healthy controls. Their data showed that individuals with knee OA demonstrated significant interlimb asymmetry (~10%) whereas healthy controls did not show asymmetry. The interesting finding was individuals with knee OA were asymmetrical with their more affected leg generating more power output than their less affected leg. This direction of asymmetry is opposite to that observed for people with ACL injuries [23] and those with PD [13].

Penko et al. [13] studied the effects that power output has on interlimb asymmetry in power output in subjects with PD during an incremental cycling task. They tested their subjects by having them cycle on a cycle ergometer beginning at 20W for three minutes at a self-selected cadence. They then increased the power by 20W every two minutes until the fourth stage (eighth minute), when 40W increases were made until exhaustion. A symmetry index was calculated to determine whether the affected limb was contributing more or less as power increased. They found that subjects with PD showed large interlimb asymmetry in power output. The more affected side produced less power and as a compensation the less affected side correspondingly increased its power output. They also reported a decrease in the symmetry index as workload increased, indicating that symmetry was increasing. The results of their study helped support a claim for a therapeutic intervention that provides higher quality and quantity afferent information through the use of augmented pedaling motion, as seen in forced exercise.

Measurement of cycling and its importance in rehabilitation

Asymmetry

As PD progresses, individuals experience a decrease in gait function, postural stability, and coordination of voluntary movements. Every human exhibits some degree of asymmetry that mostly goes unnoticed throughout the gait cycle [57], but individuals with PD exhibit a greater degree of asymmetry that affects their activities of daily living. With age, the increase in asymmetry may also lead to injury. Portegijs [58] examined elderly healthy women, and elderly women who sustained hip fractures. They introduced the women to an exercise protocol to strengthen the lower limbs and found that with this protocol, the healthy group had a difference in lower-limb power between limbs of an average of 15%. The injured group had significantly

weaker injured limbs, but after the exercise protocol, an improvement of power led to decreases in asymmetry and improvements in mobility.

During cycling, asymmetry can be directly quantified by measuring the crank power output of a modified cycle ergometer [13]. Identifying asymmetry in Parkinson's disease patients would therefore provide a baseline to be later used to measure the effectiveness of an intervention [13]. Also, identification of the limb that is contributing less to the overall power output can lead to training regimens focused on strengthening the said limb, or reducing the degree of asymmetry.[32] One of the primary goals of exercise regimens for individuals with PD should be reducing asymmetry, thus improving symmetry during normal daily activity. Most healthy individuals exhibit a degree of asymmetry between 5-20% [38], but as the degree of this asymmetry increases, detrimental outcomes such as risk of injury increases [31].

Asymmetry has been examined in individuals with other lower limb conditions such as anterior knee pain and knee osteoarthritis across different physical activities. Radin et al. [59] examined lower limb kinetics and kinematics in individuals with activity-related knee pain and asymptomatic subjects. They observed significant differences in heel strike and angular velocity in the individuals with knee pain. They suggested that these observations lead to future damage if not corrected. Buddhadev et al. [34] examined the effects of pedaling power and cadence on interlimb asymmetry in individuals with knee OA. They observed a significant difference in the contribution to total power from each limb. The more affected limb contributed a higher power output than the less affected limb, which according to these authors could limit the efficacy of a rehabilitative process.

Index of asymmetry

Researchers have used the Symmetry Index as a method of evaluating the degree of

interlimb asymmetry in different populations. For example, Penko et al. [13] calculated the symmetry index using the equation below:

$$\boldsymbol{Symmetry\ Index\ (SI)} = \frac{\text{Unaffected limb} - \text{Affected limb}}{(\text{Unaffected limb} + \text{affected limb})/2}$$

Using this equation, the researchers could evaluate the degree of contribution from each limb, with a positive value indicating a greater contribution by the unaffected limb, and a negative number indicating a greater contribution from the affected limb [13]. These variables could be modified to evaluate left versus right leg contribution.

Other methods have been used for analyzing interlimb asymmetry by researchers Buddhadev et al. [34] and Hunt et al. [23]. Buddhadev et al. [34] reported the two asymmetry indices for the individuals with knee osteoarthritis and healthy controls, respectively:

$$Asymmetry\ Index\ (\%) = \frac{Less\ affected\ leg\ power - More\ affected\ leg\ power}{\text{Less affected leg power}} \text{ x } 100$$

$$Asymmetry\ Index\ (\%) = \frac{\text{Dominant leg power} - \text{Nondominant leg power}}{\text{Dominant leg power}} \text{ x } 100$$

Similarly, Hunt et al. [23] calculated interlimb asymmetry as a ratio using the equation below:

$$Asymmetry\ Index\ = \frac{a}{\text{b}} - 1$$

Where *a* was the mean power output from either the right limb of the uninjured subject, or the ACL of the intact limb for the injured subject, and *b* was the mean power output of the left limb of the uninjured subject, or the ACL-deficient limb of the injured subjects.

Many different equations exist for the representation of asymmetry, however for the current study, the method utilized by Penko et al. [13] was used because the current study is examining the same population (i.e. individuals with PD) for the same mechanical task (i.e. stationary cycling) as these authors.

Summary

In this review of literature, important gaps in the research relevant to interlimb asymmetry in pedaling performance in patients with PD have been identified. In addition, this systematic review also explored the mechanisms underlying asymmetry in this population and methods used to evaluate interlimb asymmetry.

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Appendix A

Western Washington University
Health and Human Development Department

Consent to Take Part in a Research Study

Project: Does cycling speed affect leg asymmetry in pedaling power in individuals with Parkinson's disease?

You are invited to participate in a study investigating the effects of pedaling speed on how evenly you are pushing the pedal with each leg in individuals with or without Parkinson's disease (PD). Previous research has shown that cycling at faster cadences benefits individuals with PD. Despite these known benefits of cycling, little to no research has addressed the effect of cadence on interlimb asymmetry in individuals with PD.
If you agree to participate in this study, you will complete one testing session lasting 45 minutes to one hour. If you have PD, you will need to visit a local neurologist for diagnostic purposes when you are off your PD medication for 12 hours. After this visit, you will complete the single testing session. You are asked not to perform any exhausting lower body exercises within 48 hours prior to the testing session.
I UNDERSTAND THAT:

1. The testing session at Western Washington University will begin with completing the informed consent document. I will also complete a health history and physical health questionnaire to help researchers confirm that I qualify for their project.
2. My height and weight will be measured using a stadiometer and balance beam scale, respectively.
3. I will wear cycling shoes provided by the investigators. These shoes allow the researchers to clip them into the pedals.
4. Next the seat height, seat front-back adjustment, and handle position on the stationary bicycle ergometer will be adjusted following standard bike fitting guidelines.
5. I will then perform a 5-minute warm-up at a low workload and comfortable pedaling rate.
6. Next, I will complete six workload-cadence combinations that form the six test conditions for the experiment: (This is the equivalence of approximately 9 mph)
    a. Self-selected pedaling resistance at 50 rpm
    b. Self-selected pedaling resistance at 65 rpm
    c. Self-selected pedaling resistance at 80 rpm
    d. 60 Watts resistance at 50 rpm
    e. 60 Watts resistance at 65 rpm
    f. 60 Watts resistance at 80 rpm.
7. I will pedal for 3 minutes under each condition. I will be given a rest of 3-5 minutes between trials, but if needed, I can rest longer than 5 minutes between trials.
8. As I pedal under these experimental conditions, the researchers will collect data from the force pedals which will later be entered into I-Crankset software to examine my pedaling mechanics.
9. I will then perform a 5-minute cool down at a low workload and comfortable pedaling rate.

10. If I have PD, I will visit a local neurologist (Dr. Bruce Mackay) to assess the stage of the disease within 4-weeks after the testing sessions at Western. This will be a free session. I will be off PD medication for 12 hours prior to this free session. Being off medication for this time may cause the effects of the medication to wear off some and thus, make the symptoms of PD more apparent. Hence, I may experience some mild aggravation of my PD symptoms. I understand that exercise can lead to fatigue and muscular and/or joint discomfort or pain. Rest intervals that follow each cycling trials should reduce fatigue. I understand that if at any point exercise testing becomes uncomfortable, I can stop at any time. If I feel like I cannot or should not perform any of these tasks, I could opt out from the participation in this study.
11. I understand that there may be a risk of falling and if I have any undiagnosed cardiac conditions, this may trigger cardiovascular events. I understand that the researchers will be standing by near the bicycle at all times and observing me as I exercise.
12. In the event of an injury, I understand the study will be stopped immediately and appropriate first aid will be given by the researcher.
13. By participating in this research study, I could gain knowledge about my pedaling asymmetry. In addition, the results of this study may aid in future research.
14. All information collected will be kept in a locked cabinet separate from the data collection forms for the project data. My name will not be associated with any of my data collected throughout the study. These data will be labeled with an ID number and separate list connects the ID number and my identifiers. The data with the ID numbers and separate lists will be stored in different secure locked cabinets in the Applied Neuromechanics research laboratory in the Carver Academic Facility.
15. I may choose not to participate in this study. I am free to withdraw at any time, without penalty. If I withdraw from the study, the researchers will retain the data collected up until that point. I may submit a request to the researchers to withdraw my data up until the study ends. After the study ends, the researchers will not be able to link me with my data.
16. I must be 18 years or older to participate
17. I understand that the link between my name and my study ID will be removed when the researchers have completed analyzing the data.
18. My signature on this form does not waive my legal rights of protection.
19. Any questions you I have regarding the study procedures will be answered by the primary researchers (Gary Wiley, Harsh Buddhadev) who can be contacted at wileyg@wwu.edu (360-441-4248) or Harsh.Buddhadev.wwu.edu (360-650-4115). Any questions about my rights as a research subject should be directed to the WWU Office of Research and Sponsored Programs (RSP) at compliance@wwu.edu or (360) 650-2146. . If any injury or adverse effect of this research is experienced I should contact Gary Wiley, Harsh Buddhadev, or the RSP.

♦♦♦

I have read the above descriptions and agree to participate in this study.

____________________________________ ____________________

Participant's Signature Date

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Participant's PRINTED NAME

Appendix B

Western Washington University
Health and Human Development Department

Consent to Take Part in a Research Study

Project: Does cycling speed affect asymmetry in pedaling effort between legs in people with Parkinson's disease?

You are invited to participate in a study examining the effects of pedaling speed on how evenly you are pushing the pedal with each leg in individuals with or without Parkinson's disease (PD). Previous research has shown that cycling at faster speeds benefits people with PD. Despite these known benefits of cycling, little to no research has addressed the effect of cycling speed on unevenness in pedaling effort between legs in individuals with PD.
If you agree to participate in this study, you will complete one testing session lasting 60 to 90 minutes. You are asked not to perform any tiring lower body exercises within 48 hours before the testing session.
I UNDERSTAND THAT:

1. The testing session at Western Washington University will begin with completing the informed consent document. I will also complete a health history and physical health questionnaire to help researchers confirm that I qualify for their project.
2. My height and weight will be measured.
3. I will wear cycling shoes provided by the researchers. These shoes allow the researchers to clip them into the pedals.
4. Next the stationary cycle will be adjusted according to my body size.
5. I will then perform a 5-minute warm-up at a low resistance and comfortable speed.
6. Next, I will complete six speed-resistance combinations that form the six test conditions for the study:
    a. Self-selected pedaling resistance at 50 rpm
    b. Self-selected pedaling resistance at 65 rpm
    c. Self-selected pedaling resistance at 80 rpm
    d. 60 Watts resistance at 50 rpm
    e. 60 Watts resistance at 65 rpm
    f. 60 Watts resistance at 80 rpm.

    (60 W is the equivalence of approximately 9 mph)

7. I will pedal for 3 minutes under each condition. I will be given a rest of 3-5 minutes between trials, but if needed, I can rest longer than 5 minutes between trials.
8. As I pedal under these conditions, the researchers will collect data from the force pedals which will measure the unevenness in pedaling effort between legs.
9. I will then perform a 5-minute cool down at a low resistance and comfortable speed.
10. I understand that there may be a risk of falling and if I have any undiagnosed cardiac conditions, this may trigger heart conditions. I understand that the researchers will be standing by near the stationary cycle at all times and observing me as I exercise.
11. In the event of an injury, I understand the study will be stopped immediately and appropriate first aid will be given by the researcher.

12. By participating in this research study, I could gain knowledge about my pedaling unevenness. In addition, the results of this study may help in future research.
13. All information collected will be kept in a locked cabinet separate from the data collection forms for the project data. My name will not be associated with any of my data collected throughout the study. These data will be labeled with an ID number and separate list connects the ID number and my identifiers. The data with the ID numbers and separate lists will be stored in different secure locked cabinets in the research laboratory in the Carver Building.
14. I may choose not to participate in this study. I am free to withdraw at any time, without penalty. If I withdraw from the study, the researchers will retain the data collected up until that point. I may submit a request to the researchers to withdraw my data up until the study ends. After the study ends, the researchers will not be able to link me with my data. I understand that the link between my name and my study ID will be removed by August 2019.
15. I must be 18 years or older to participate
16. My signature on this form does not waive my legal rights of protection.
17. Any questions you I have regarding the study procedures will be answered by the primary researchers (Gary Wiley, Harsh Buddhadev) who can be contacted at wileyg@wwu.edu (360-441-4248) or Harsh.Buddhadev.wwu.edu (360-650-4115). Any questions about my rights as a research subject should be directed to the WWU Office of Research and Sponsored Programs (RSP) at compliance@wwu.edu or (360) 650-2146. If any injury or adverse effect of this research is experienced I should contact Gary Wiley, Harsh Buddhadev, or the RSP.

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I have read the above descriptions and agree to participate in this study.

___________________________________ ____________________

Participant’s Signature Date

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Participant’s PRINTED NAME