PILOT STUDY ON THE INTERACTION BETWEEN EXERCISE AND MEDICATION IN THE MANAGEMENT OF PARKINSON’S DISEASE SYMPTOMS

by

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# TABLE OF CONTENTS

LIST OF TABLES .......................................................... vi
LIST OF FIGURES ............................................................. vii
ABSTRACT ........................................................................ viii

Chapter

1 INTRODUCTION ..................................................................... 1

1.1 Significance ........................................................................ 1
1.2 Symptoms .......................................................................... 1
1.3 Dopamine Replacement Therapy ........................................... 3
1.4 Exercise ............................................................................ 4
1.5 Specific AIMS ....................................................................... 6

2 METHODS .............................................................................. 8

2.1 Participants .......................................................................... 8
2.2 Testing Schedule ................................................................. 8
2.3 Exercise Protocol ................................................................. 9
2.4 Functional Tests ................................................................. 9
2.5 Isometric Muscle Contractions ............................................. 10
2.6 Statistical Analysis ............................................................. 12

3 RESULTS ............................................................................. 13

3.1 Overall Assessment ............................................................. 13
3.2 ICC Reliability ................................................................. 14

4 DISCUSSION ....................................................................... 26

4.1 Overview ........................................................................... 26
4.2 Segmentation Reliability ..................................................... 27
4.3 Limitations of Thesis ........................................................... 29
5 CONCLUSIONS .................................................................................................................. 30
REFERENCES ..................................................................................................................... 31
Appendix
A IRB APPROVAL LETTER ................................................................................................. 37
LIST OF TABLES

Table 1 Characteristics of Subjects................................................................. 15
Table 2 Effects of Treatment on tests .................................................................. 16
Table 3 ICC Reliability.......................................................................................... 17
LIST OF FIGURES

Figure 1  Force Steadiness .................................................................................. 18
Figure 2  Segmentation ....................................................................................... 19
Figure 3  Grip Strength ....................................................................................... 20
Figure 4  Timed up and Go ................................................................................. 21
Figure 5  Functional Reach .................................................................................. 22
Figure 6  SD of Force .......................................................................................... 23
Figure 7  Segments .............................................................................................. 24
Figure 8  Time to Peak Force .............................................................................. 25
ABBREVIATIONS

ABSTRACT

Motor symptoms of Parkinson’s disease (PD) include tremor, bradykinesia (slow movement), rigidity and impaired postural control. Symptoms are treated with dopamine replacement therapies (DRT) and it has been shown that exercise helps slow disease progression and improve mobility. In studies involving rapid isometric contractions, some have reported abnormally segmented force production that could impair multiple aspects of mobility. There has been little development of segmentation measures. Aim 1 was to determine if one bout of speed-based exercise can reduce symptoms and improve mobility at a time when the efficacy of a DRT dose is beginning to diminish. Grip strength, timed up and go (TUG), static balance, force steadiness (tremor) and isometric force pulses were measured before and after three treatment conditions in ten subjects with PD (Hoehn-Yahr ≤ 3.0): 1) no exercise, DRT only; 2) no DRT and a 30-minute high-speed low resistance (HS-LR) bicycling session; and 3) DRT plus HS-LR bicycling session. It was hypothesized that the medication plus exercise condition would result in the greatest acute improvement in function. Aim 2 was to evaluate test-retest reliability of force segmentation and time to peak force (TpF) measures. Results: Paired t-tests did not support any treatment effects (all p>.055). Delaying an afternoon dose of medication was more challenging for some subjects than others and individual exercise responses varied considerably. Segmented force pulses were observed in most subjects and the mean segmentation was strongly correlated with TpF on all three visits (r=.806-.960) suggesting that slowing in force production is related to disrupted rather than reduced neural drive.
ICCs supported favorable test-re-test reliability of mean segments ($r=.88$) and TpF ($r=.86$) relative to ICCs of $r=.97$ and $r=.82$ for grip strength and TUG, respectively. The methodological approach to Aim 1 would likely require a larger sample size and individuals with a greater duration of DRT use or a more pronounced “wearing off” effect to determine whether afternoon exercise can boost function alone or with medication. Aim 2 results are promising in that mean segmentation has similar reliability to TUG, which is already accepted in rehabilitation research. Furthermore, strong correlations between segmentation and TpF support further inquiry into the role of disrupted neural drive in bradykinesia or PD subtyping.
Chapter 1

INTRODUCTION

1.1 Significance

Parkinson’s disease (PD) is characterized by the death of dopamine neurons in the substantia nigra and a reduced ability to produce adequate dopamine. The degenerative changes include neuronal deterioration and depigmentation in the substantia nigra (Nestler et al, 2015). There are numerous pharmacological treatments, but PD still leads to diminished quality of life (Frazzitta et al, 2015).

1.2 Symptoms

The main symptoms of PD are bradykinesia, rigidity, poor balance, and resting tremor. In addition to the effects of the disease, physical deconditioning in people with PD further contributes to altered gait, poor balance, and postural instability (Folland et al, 2011). As the disease progresses, patients may experience cognitive issues, such as, poor memory and slowness in motor tasks due to non-motor reasons (Peto et al, 1995). Dopamine replacement therapies (DRT) primarily affect three of the motor symptoms: bradykinesia, tremor and rigidity.

Bradykinesia or slowing of movement is a cardinal symptom. It has been hypothesized that bradykinesia results from insufficient or disordered neuromuscular excitation. Accordingly, the amplitude and/or rate of neuromuscular excitation, measured in electromyographic bursts, are insufficient and additional bursts are needed to complete a movement (Wierzbicka et al, 1991). Berardelli et al (2001)
suggest that bradykinesia results from a failure of the basal ganglia output to reinforce the mechanism that prepares and executes a movement.

Seventy-five percent of people with PD have resting tremor (Zach et al, 2015). Jankovic et al (1999) describes tremor as an involuntary motion that continues while the limb is at rest but can be diminished when the limb is in motion. Tremor usually involves the distal limbs and at rest occurs at a frequency of 4 to 6 Hz (Zach et al, 2015). Resting tremor does not always disappear when the limb is in motion but the amplitude may be reduced (Zach et al, 2015). The severity of tremor does not correlate with the severity of bradykinesia or rigidity. Tremor is an early sign of PD but can disappear as the disease progresses. Tremor does not respond to DRT in the same manner as bradykinesia and rigidity (Helmich, 2017).

Rigidity is one of the principal symptoms of PD (Zetterberg et al, 2015) and can be defined as an increased resistance when stretching a muscle passively or a feeling of stiffness (Berardelli et al, 1983). The origin of rigidity is in the central neuronal pathway, but recent work suggests that nonneuronal alterations in the biomechanical properties of the stretched tissues may contribute to rigidity. The possible mechanisms of rigidity are exaggeration of the monosynaptic stretch reflex, exaggeration of the long-latency stretch reflexes, the development of a tonic stretch reflex and the development of shortening reaction (Xia et al, 2011). The long-latency stretch reflex is the more commonly studied reflex in Parkinson’s disease according to Berardelli et al (1983). Rigidity can fluctuate and with the right treatment doses it can be reduced (Zetterberg et al, 2015).
1.3 Dopamine Replacement Therapy

There are two main dopamine pathways. The first is the nigrostriatal pathway, which is responsible for voluntary movements, and the second is the mesocorticolimbic pathway, which is responsible for reward and motivation-related processes. While the former pathway is targeted by DRT (pharmacological levodopa) to address tremor, rigidity and bradykinesia, the effects of DRT on the latter pathway has negative implications for any rehabilitation that is based on the [re-]learning of a movement. In Parkinson’s disease, the objective of DRT is to target the first pathway, but there is an “overflow” effect after progressive use of DRT and that sometimes leads to maladaptive decision-making and compulsive behavior (Ferrazzoli et al, 2016).

Long-term DRT leads to declining responsiveness and fluctuations in effectiveness. This decline causes the person to experience dyskinesia as the concentration of levodopa peaks after a dose. There is a rapid reversion to severe Parkinsonism towards the end of a dose (Nestler et al, 2015). The long-term use of DRT allows for restoration in the physiological synaptic plasticity in the dopamine-denervated striatum. This can also cause further functional short and long term alterations of neural transmission (Ferrazzoli et al, 2016).

Three common side effects of DRT include dyskinesia, motor fluctuations, and dopamine dysregulation syndrome (DDS). Dyskinesia can be defined as involuntary muscle movements. Half of the PD population experiences dyskinesia after 5-10 years of DRT (Ferrazzoli et al, 2016). Motor fluctuations include the “wearing off” and “on-off” phenomena. “Wearing off” is when PD patients experience a worsening of symptoms at the end of a dose. This is due to the short duration of the benefits of a
levodopa dose. “On-off” is a sudden unpredictable shift from “on” states to “off”. DDS occurs in 3-4% of people with PD. It is a pattern of addictive drug use in which people with PD begin to compulsively seek their DRT and the “on” effect. They become agitated in the “off” stage resembling withdrawal (Ferrazzoli et al., 2016). Together, these side effects are reasons why a person would be interested in modifying DRT with exercise.

Levodopa therapy is effective in the treatment of PD but the later development of motor complications is a source of disability. This problem affects 75-80% of people with PD who take levodopa for more than 5-10 years (Bhidayasiri et al, 2008). Motor complications occur in 3% of people within one year of treatment, 41% after six years, and 70% after more than nine years. The “wearing-off” is noted by the re-emergence of Parkinsonian symptoms within four hours or less after a single dose. There are a variety of strategies proposed to help with this issue, such as delaying/limiting levodopa or early administration of a dopamine receptor agonist (Bhidayasiri et al, 2008).

1.4 Exercise

It has been shown that exercise is an effective and complementary treatment for the management of PD. Exercise improves various aspects of motor performance and it may have a neuroplastic action that slows disease progression (Frazzitta et al, 2015). Physical rehabilitation is helpful in treating balance dysfunction, postural instability, and freezing of gait. The reason that these symptoms are not responsive to DRT is believed to be that they result from a different system outside of the dopaminergic structure. Exercise is thought to benefit the central nervous system by diminishing hyper excitability in the basal ganglia cortical circuits and inducing
compensatory changes in the dopamine handling and neurotransmission (Ferrazzoli et al., 2016).

Like drug therapies, exercise can be “prescribed” with varied combinations of frequency, intensity, times (duration) and types (modes). High-velocity power training and high intensity interval training have increasing support as a means to improve mobility in older adults (Sayers et al, 2016) and people with PD (Kelly et al, 2014). Bellumori et al (2017) developed a speed-based exercise program for older adults that is suitable for people with PD at a Hoehn-Yahr stage of three or less. The exercise consists of a five minute warm up and five minute cool down at a self-selected bicycling cadence. During the middle 20 minutes of the 30 minute session, participants pedal at a fast cadence for the first fifteen seconds of each minute (intervals). Applying this protocol to people with PD, Uygur et al (2015) showed acute improvements in two tests of whole body mobility after one exercise session. Participants adhered to their normal medication schedule in this study, so it was unclear if improvements were due to exercise or the effects of exercise on the medication, perhaps through increased metabolism of the drug or increased brain blood flow. In older adults, the six-week exercise session improved the production of rapid isometric force pulses and mobility tests (Bellumori et al, 2017). In people with PD, the same six-week exercise protocol improved several tests of mobility and scores in the motor section of the Unified Parkinson’s Disease Rating Scale (UPDRS-III; Uygur et al, 2017). In another study with a similar focus on speed of movement in their exercise strategies, power training and speed yoga both improved UPDRS and balance measurements more than a control condition that involved stretching. There
was no significant difference between yoga and power-training groups (Ni et al, 2016).

It was also shown that intensive goal-based rehabilitation treatment allows for reduced dyskinesias (Frazzita et al, 2012a, b). Goal-based rehabilitation consisted of responding to auditory and visual cues on a treadmill. Repetitious rehabilitation has demonstrated the reacquisition of lost autonomic movements and the ability to initiate habits using goal-directed triggers. Ferrazzoli et al (2016) believe DRT stimulates the dopamine-denervated striatum and rehabilitation promotes activity-dependent neuroplasticity and together they synergistically exploit the physiological mechanism of cortico-striatal plasticity in PD. While the proposed study was focused on the acute effects of exercise on the primary symptoms of PD during the “wearing-off” period, it is important to recognize evidence that exercise also has the potential to treat the secondary symptoms of long term DRT.

1.5 Specific Aims

The first aim was to determine if one bout of speed-based exercise can reduce symptoms and improve mobility at a time when the efficacy of a DRT dose is beginning to diminish. On three different days, symptoms and mobility were measured during the wearing off phase before and after three conditions: drug alone, exercise alone, and drug plus exercise. It was hypothesized that one bout of speed-based exercise can reduce symptoms and boost mobility at a time when the efficacy of a DRT dose is beginning to diminish. It was also hypothesized that the combination of exercise and DRT will be superior to both DRT and exercise alone.
The second aim was to evaluate test-retest reliability of an emerging measure of force segmentation and time to peak force (TpF) during rapid isometric finger abduction contractions. The pre-condition tests were used to compute intraclass correlation coefficients for the two measures from rapid contractions and for standard tests of function for which reliability is already accepted (Grip strength: Villafañe et al, 2016, Timed Up and Go: Morris et al, 2001, and functional reach: Giorgetti et al, 1998).
Chapter 2
METHODS

2.1 Participants
Ten people diagnosed with Parkinson’s disease (8 male and 2 female; mean (SD) age: 70.1 (7.6) years; body mass: 92.3 (18.6) kg; height: 1.8 (0.1) m; BMI: 92.3 (18.6) kg/m²; and time since diagnosis: 5.9 (4.4) years) were recruited from the local community. All participants read and signed an institutionally approved informed consent document. The inclusion criteria were: a) at least 4 weeks of participation in the high speed bicycling exercise program b) the stable use of dopamine replacement therapy to manage symptoms and c) willingness to modify the timing of their medication. The exclusion criteria included a known Hoehn-Yahr stage above three (self-reported), an inability to stand and walk to the laboratory without the assistance of another person, and/or orthopedic limitations that prevented them from participating in the exercise or performing the functional tests.

2.2 Testing Schedule
This study involved three visits to the exercise intervention laboratory that were separated by two days and completed within one week. Each visit was scheduled at the same time of day to reduce variability in symptoms (Bonuccelli et al, 2000, Uygur et al, 2015). The three conditions were presented in a counterbalanced order to prevent an order effect. The drug alone condition was intended to reveal changes in symptoms and function due to the next dose of a drug taken during the wearing-off
phase. After the pre-test, the participant ingested their DRT, performed a standardized set of light daily activity (e.g. walking the hallway) for 35 minutes and was then post-tested. In the exercise condition, the participant performed the pre-test and, instead of taking their next dose, participated in a 30-minute session of high speed low-resistance (HS-LR) bicycling interval exercise. They rested for five minutes and were then post-tested. In the drug plus exercise condition, the participant was pre-tested, took their DRT, and performed the 30-minute session of HS-LR bicycling interval exercise, rested for five minutes and was then post-tested.

2.3 Exercise Protocol

In the two conditions involving exercise, subjects participated in a 30-minute HS-LR bicycling exercise session. The session consisted of a five-minute warm-up and cool-down at a preferred cadence. During the middle 20 minutes of the session, participants pedaled at a self-selected fast pedaling cadence between 120-140 RPM for 15 seconds of every minute for 20 minutes (20 high speed intervals). Pedaling resistance was the same during both conditions involving exercise. Depending on the effects of wearing-off and the treatment condition (exercise or exercise plus med.), there was some within-subject variance in the ability to pedal fast. Heart rate and blood pressure were monitored throughout the exercise session for safety (Uygur et al, 2015).

2.4 Functional Tests

Each functional test was performed three times before and after each condition. There were at least 15- 30 seconds of rest between trials. The best score was used in
further analysis. Timed up-and-go (TUG) is an assessment of whole body mobility. The participant is instructed to rise from a chair, walk as quickly and as safely as possible three meters, turn around, walk back, and sit back down (Ellis et al, 2011; Lam et al 2010). The participant was instructed to perform the TUG “as quickly and as safely as possible”.

Isometric grip strength was used since it is simple, takes little time, and has good test-retest reliability (Bohannon et al, 2005). Grip strength also has good predictive validity with lower values predicting falls and disability (Bohannon et al, 2005; Roberts et al, 2011). Grip strength was recorded using a dynamometer (Jamar Plus, Patterson Medical). The seated participant was asked to hold the device with a 90 degree elbow angle in their dominant hand and squeeze as hard as they could for 3 seconds.

Functional reach was used as a test of static balance. The participant was asked to stand upright with their arms extended in the anterior direction at shoulder height. The location of the metacarpophalangeal (MCP) joint in the anterior-posterior direction was marked prior to reaching. The participant was asked to reach as far as they could while maintaining standing posture. The final MCP joint position was measured and the displacement from the initial position was reported in centimeters (Jenkins et al, 2010).

2.5 Isometric Muscle Contractions

Isometric force tremor (or force steadiness in the absence of periodic tremor, Figure 1) was measured in an index finger abduction task. To stabilize the hand, participants grasped a wooden support with their first (thumb), third, fourth and fifth
digits. The extended index finger affixed to a force transducer (MB-25, Interface Inc., Scottsdale, AZ, USA) using an elastic strap similar to the methods of Bellumori et al. (2011). Data were amplified, low-pass filtered (30Hz, Grass LP122, Astro-Med, Inc.) and sampled at 200 Hz (NI-9239, National Instruments, Austin, TX, USA). After measuring maximal voluntary contraction (MVC) force for scaling, participants performed two trials in which they produced 10% of their MVC for 90 seconds as steadily as possible. Force steadiness is reported as the standard deviation (SD) of the stable region of force recording after removal of the best-fitting linear trend. The average of the SD measures from two trials was calculated for each subject. Tremor was quantified from the detrended segment as the mean spectral power within bands from 4-8 Hz and 8-12 Hz (Vaillancourt et al, 2001).

Most-rapid isometric force pulses were used to evaluate neuromuscular contributions to bradykinesia (Figure 2). Force pulses were recorded using the same index finger abduction apparatus described above. Participants were asked to perform four sets of fifteen pulses in the range from 20 to 60 %MVC. Time to peak force was computed as the time from force initiation (3% MVC) to peak force. Force segmentation refers to the disruptions in the typically smooth rise in force from rest to peak force. Some people with PD exhibit minor changes in the slope of force during the rising phase of the pulse (inflections) or complete reversals in the direction of force development followed by a return to a positive slope. Both types of segmentation can be detected by examining the second derivative of force. Using the formula below the number of segments is computed based on the total number of zero-crossings in both the positive and negative direction. In a smooth, unimodal force pulse that is characteristic of healthy neuromuscular control, the result of ‘1’
indicates that there was a single uninterrupted segment of motor output from baseline to peak force.

\[
Number \ of \ Segments = \frac{\text{(# of zero crossings in } F''(t)) + 1}{2}
\]

2.6 Statistical Analysis

All statistical tests were performed in SPSS (version 24, IBM SPSS Statistics, Armonk, NY). Within each individual, the analyzed dependent measures were the best scores for grip strength, TUG, and functional reach, the mean number of segments from all 60 force pulses, the mean time to peak force from all 60 force pulses, and the mean standard deviation of force from the two 10% MVC trials. One-tailed significance tests were used due to the directional hypothesis of improved function in Aim 1.

For Aim 2, the pre-treatment measures from each lab visit were used for the analysis of test-retest reliability. Intraclass correlation coefficients (ICC) were computed using a two-way mixed effect model with specifications for single measurement and absolute agreement (Koo and Li, 2016). Pearson’s correlation coefficient was used to quantify the association between the number of segments and time to peak force.
Chapter 3

RESULTS

3.1 Overall Assessment

All participants completed testing without any adverse events. Only one participant used Rasagiline instead of Carbidopa/Levodopa. Rasagiline is a Monoamine Oxidase Inhibitor and it helps to increase natural dopamine. The remaining nine participants used dopamine replacement therapies. The investigators were familiar with the participants due to their prior participation in the exercise program and could observe that some were more affected than others during the wearing-off phase. Two participants used both deep brain stimulation and DRT. The average HS-LR cadence during the high speed bicycling intervals was 131 revolutions per minute (RPM). Only two participants exhibited pronounced spectral peaks in the frequency range of tremor. Therefore, in the absence of tremor among the majority of subjects, spectral measures are not compared in Aim 1 and reliability of spectral measures is not evaluated in Aim 2.

Table 2 presents the results for all measures in each of the three conditions. None of the changes reached the 95% confidence level for one-tailed tests of statistical significance and there were no clear patterns in what might be considered trends towards significance. Top panels in figures three through eight show measures for each individual and the bottom panels show individual change scores from pre- to post-treatment.
3.2 ICC Reliability

Table 3 shows the reliability (ICC) results for segments and time to peak force with selected functional measures that are accepted as reliable in clinical research and force steadiness. While grip strength exhibited superior test-retest reliability than both measures from isometric force pulses, number of force segments and time to peak force, both had comparable or superior reliability compared to the timed up and go and functional reach tests. The standard deviation of force had the lowest test-retest reliability of the measures observed. The top panels of figures three through eight show results for each subject in each condition for visual assessment of within vs. between subject variance. Correlations between the number of segments and time to peak force on each of the three test days ranged from \( r=.806 \) to \( r=.960 \).
Table 1: Characteristics of subjects.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age (years)</th>
<th>Time since diagnosis (years)</th>
<th>Affected Side</th>
<th>Drug</th>
<th>Doses per Day (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>64</td>
<td>14</td>
<td>L</td>
<td>carbidopa/levodopa</td>
<td>4x 50/200</td>
</tr>
<tr>
<td>M</td>
<td>62</td>
<td>11</td>
<td>L</td>
<td>carbidopa/levodopa</td>
<td>5x 20/100</td>
</tr>
<tr>
<td>F</td>
<td>69</td>
<td>2</td>
<td>L</td>
<td>carbidopa/levodopa</td>
<td>3x 25/100</td>
</tr>
<tr>
<td>M</td>
<td>74</td>
<td>11</td>
<td>L</td>
<td>carbidopa/levodopa</td>
<td>7x 50/200</td>
</tr>
<tr>
<td>M</td>
<td>69</td>
<td>1.5</td>
<td>L</td>
<td>rasagiline</td>
<td>1x 1</td>
</tr>
<tr>
<td>M</td>
<td>77</td>
<td>5</td>
<td>R</td>
<td>carbidopa/levodopa</td>
<td>3x 50/100</td>
</tr>
<tr>
<td>M</td>
<td>57</td>
<td>4</td>
<td>L</td>
<td>carbidopa/levodopa</td>
<td>4x 25/100</td>
</tr>
<tr>
<td>M</td>
<td>82</td>
<td>3</td>
<td>L</td>
<td>carbidopa/levodopa</td>
<td>3x 25/100</td>
</tr>
<tr>
<td>M</td>
<td>79</td>
<td>1.17</td>
<td>R</td>
<td>carbidopa/levodopa</td>
<td>3x 25/100</td>
</tr>
<tr>
<td>F</td>
<td>68</td>
<td>6</td>
<td>L</td>
<td>carbidopa/levodopa</td>
<td>4x 25/100</td>
</tr>
</tbody>
</table>
Table 2: Pairwise comparisons of treatment effects for each measure. Positive t statistics indicate differences in the hypothesized direction of improvement. P-values are for one-tailed t-tests.

<table>
<thead>
<tr>
<th>Test</th>
<th>Mean (SD) Pre</th>
<th>Mean (SD) Post</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exercise</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grip Strength (kg)</td>
<td>40.09 (12.84)</td>
<td>40.33 (13.10)</td>
<td>0.270</td>
<td>0.397</td>
</tr>
<tr>
<td>TUG (s)</td>
<td>9.07 (1.70)</td>
<td>9.38 (2.21)</td>
<td>-0.986</td>
<td>0.175</td>
</tr>
<tr>
<td>Functional Reach (cm)</td>
<td>27.50 (10.12)</td>
<td>24.60 (7.68)</td>
<td>-1.773</td>
<td>0.055</td>
</tr>
<tr>
<td>Time to Peak Force (s)</td>
<td>0.610 (0.32)</td>
<td>0.599 (0.32)</td>
<td>1.208</td>
<td>0.129</td>
</tr>
<tr>
<td>Segments (No.)</td>
<td>3.72 (2.04)</td>
<td>3.45 (2.13)</td>
<td>0.784</td>
<td>0.227</td>
</tr>
<tr>
<td>SD Force (%MVC)</td>
<td>1.00 (0.63)</td>
<td>0.98 (0.86)</td>
<td>0.111</td>
<td>0.457</td>
</tr>
<tr>
<td><strong>Medicine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grip Strength (kg)</td>
<td>41.30 (12.45)</td>
<td>40.13 (12.29)</td>
<td>-1.494</td>
<td>0.085</td>
</tr>
<tr>
<td>TUG (s)</td>
<td>9.54 (2.12)</td>
<td>9.34 (1.54)</td>
<td>0.498</td>
<td>0.315</td>
</tr>
<tr>
<td>Functional Reach (cm)</td>
<td>25.15 (7.94)</td>
<td>25.10 (7.30)</td>
<td>-0.031</td>
<td>0.488</td>
</tr>
<tr>
<td>Time to Peak Force (s)</td>
<td>0.658 (0.36)</td>
<td>0.365 (0.30)</td>
<td>0.688</td>
<td>0.255</td>
</tr>
<tr>
<td>Segments (No.)</td>
<td>3.69 (2.16)</td>
<td>3.32 (1.86)</td>
<td>1.219</td>
<td>0.127</td>
</tr>
<tr>
<td>SD Force (%MVC)</td>
<td>0.94 (0.65)</td>
<td>0.88 (0.51)</td>
<td>0.895</td>
<td>0.197</td>
</tr>
<tr>
<td><strong>Medicine and Exercise</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grip Strength (kg)</td>
<td>40.80 (13.24)</td>
<td>40.83 (13.29)</td>
<td>0.027</td>
<td>0.490</td>
</tr>
<tr>
<td>TUG (s)</td>
<td>8.78 (1.15)</td>
<td>8.60 (1.29)</td>
<td>0.584</td>
<td>0.287</td>
</tr>
<tr>
<td>Functional Reach (cm)</td>
<td>26.15 (9.87)</td>
<td>29.60 (7.99)</td>
<td>1.508</td>
<td>0.083</td>
</tr>
<tr>
<td>Time to Peak Force (s)</td>
<td>0.608 (0.31)</td>
<td>0.598 (0.42)</td>
<td>0.166</td>
<td>0.436</td>
</tr>
<tr>
<td>Segments (No.)</td>
<td>3.33 (1.98)</td>
<td>3.49 (2.84)</td>
<td>-0.453</td>
<td>0.331</td>
</tr>
<tr>
<td>SD Force (%MVC)</td>
<td>1.25 (1.27)</td>
<td>1.10 (0.95)</td>
<td>1.300</td>
<td>0.113</td>
</tr>
</tbody>
</table>
Table 3: Intraclass correlation coefficients and 95% Confidence Intervals for the experimental measure of force segmentation (Aim 2, bold), clinically accepted measures of function and force variance. Reliability results for spectral measures are not reported because tremor was observed in only two subjects who exhibited spectral peaks in the 4-8 Hz bin.

<table>
<thead>
<tr>
<th>Measure</th>
<th>ICC</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lower Bound</td>
</tr>
<tr>
<td>Grip Strength</td>
<td>0.972</td>
<td>0.924</td>
</tr>
<tr>
<td>Timed up and go</td>
<td>0.794</td>
<td>0.526</td>
</tr>
<tr>
<td>Functional reach</td>
<td>0.804</td>
<td>0.550</td>
</tr>
<tr>
<td><strong>No. Segments</strong></td>
<td><strong>0.880</strong></td>
<td><strong>0.702</strong></td>
</tr>
<tr>
<td>Time to Peak Force</td>
<td>0.862</td>
<td>0.661</td>
</tr>
<tr>
<td>SD force</td>
<td>0.670</td>
<td>0.334</td>
</tr>
</tbody>
</table>
Figure 1: Top: A recording from the index finger abduction task of producing steady force at 10% MVC. Beneath the recording is the extracted and detrended segment for analysis in both the time (standard deviation) and frequency domains. Bottom: Frequency spectrum from a recording in one of the two subjects who exhibited periodic tremor during the 90-s 10% MVC isometric contractions. Tremor was quantified as the area under the spectrum in ranges from 4-8 Hz and 8-12 Hz. No spectral peaks were observed in the 8-12 Hz range in the present study.
Figure 2: Top: This panel shows a typical force pulse in which there is only one segment of force production from rest to peak force. The middle row shows the first derivative of force and the bottom row shows the second derivative of force. Bottom: This shows a person with PD and highly segmented force pulses. In the bottom row, there are eleven zero crossings between threshold and peak force which indicate six force segments.
Figure 3: Top: Best grip strength score for each participant prior to each treatment. Bottom: Individual changes in best grip strength scores from pre to post treatment.
Figure 4: Top: Best timed up and go score for each participant prior to each treatment. Bottom: Individual changes in best timed up and go scores from pre to post treatment.
Figure 5: Top: Best functional reach scores for each participant prior to each treatment. Bottom: Individual changes in best functional reach scores from pre to post treatment.
Figure 6: Top: Average SD of force from two 90 s 10% MVC steadiness trials for each participant prior to each treatment. Bottom: Individual changes in the average SD of force from pre to post treatment.
**Figure 7:** Top: Mean number of segments across 60 force pulses for each participant prior to each treatment. Bottom: Individual changes in the mean number of segments from pre to post for each participant.
Figure 8: Top: Mean time to peak force across 60 force pulses for each participant prior to each treatment. Bottom: Individual changes in mean time to peak force from pre to post treatment.
Chapter 4

DISCUSSION

4.1 Overview

Participants tolerated testing well. One advantage in the present study is that test anxiety was likely reduced due to the participants’ familiarity with the testing personnel, exercise protocol, and environment. Due to prior experience with other studies, each participant was familiar with the exercise protocol and the tests being performed. They were able to complete each test efficiently which allowed for short pre/post testing sessions.

Each participant reported how they felt on a scale of 1-10 at the beginning of testing pre and post treatment. Each participant varied, but no one reported less than five on the scale at arrival. Although numerous participants reported feeling and/or functioning better after a bout of exercise, there were no significant changes in any of the functional measures at the 95% level of confidence. This could be for three reasons. First, it is possible that the null hypothesis was true, and exercise was not a potent remedy for afternoon “wearing-off”. Second is that the present study design did not quantify the magnitude of the “wearing-off” effect, thus limiting our ability to confirm its presence and test its potential reversal. Note that in Table 1, six of the participants were diagnosed within five years which, according to Bhidayasiri (2008), might not be the duration in which consequences of long term DRT begin to appear. The third possibility is the lack of statistical power. There were no significant effects of any of the treatments; therefore, we were unable to compare the efficacy of the
tested conditions. The variability of participants played a key role in the ability to truly measure “wearing-off” (Figures 3-8). According to Jordan et al. disease chronicity alters the pattern of motor deficits and the duration and stage of disease have variable influences on motor control as well. It is also believed that cognitive deficits and depression can alter participant performance (Jordan et al, 1992). Each of these factors may explain some of the variability between participants. That the majority of participants reported feeling and or functioning better after exercise might be related to the phenomenon known as the runner’s high (Raichlen, 2012) and/or the possible effects of the placebo effect on dopamine in people with PD (de la Fuente-Fernandez & Stoessi, 2002).

4.2 Segmentation Reliability

The observed reliability of the number of segments measure and time to peak force was consistent with or slightly better than other measures that are accepted as reliable in clinical assessment (Grip strength: Villafañe et al., 2016, Timed Up and Go: Morris et al., 2001; Functional reach: Giorgetti et al., 1998). Atkinson and Nevill (1998) state that like Pearson’s r an ICC close to one is excellent, the range from 0.7-0.8 is ‘questionable’ and coefficients above 0.9 indicate ‘high’ reliability. Within this framework, Number of Segments and Time to Peak Force had greater than what is ‘questionable’ reliability. For segments and time to peak force, Figures 7 and 8 show the corresponding high ratio of between- to within-subjects variability which resulted in favorable intra-class correlation coefficients. Between-subject variability can be attributed to PD subtype and the general heterogeneity of this population (Jankovic et al., 1990, Simuni et. al, 2016; Eisinger et al., 2017). Whereas measures of tremor and
force segmentation specifically quantify aspects of the disease, tests such as the timed up and go and the functional reach are more likely to express the disease within the significant amount of variance related to age and fitness.

The implications of the present results on the segments measure are interesting to consider. To our knowledge, this is the first study to report the day-to-day reliability of disordered motor output that has been described as an important topic for continued inquiry by others (Wierzbicka, 1991). Also recall that isometric force tremor was only observed in two participants, whereas, segmentation was observed in six. One might wonder whether tremor and segmentation are expressions of one common aspect of PD or if they have neurologically distinct origins. Jankovic (1990) states that early onset PD progresses slower than late onset PD. Knowing that if a subject has tremor they are likely to progress slower than those without tremor (Konno et al., 2018), the segments measure might provide similar information about the progression of the disease. A mean segmentation value can be obtained from a relatively simple, brief, portable and noninvasive protocol. Accordingly, if segmentation and tremor do not co-exist in most patients, then segmentation might provide a useful measure for PD-subtyping and disease management. It is also becoming clear that segmentation during attempts at rapid movements is a substantial contributor to bradykinesia. While bradykinesia is quite generally defined as slow small movements, correlations make it clear that if someone exhibits greater segmentation then their TpF will be prolonged.
4.3 Limitations of Thesis

There are a few important limitations to consider: (1) the sample size was not large enough; therefore, there wasn’t a high enough power to determine conclusive results. (2) The sample of participants was well-functioning during testing; therefore, there were not large enough changes between pre and post. (3) The time since the last dose may have been too short to observe a significant “wearing-off” effect. Waiting 6 to 12 hours after last dose to perform testing is preferred over waiting 4 hours in a future study (Simuni et al., 2016).
Chapter 5

CONCLUSION

In Aim 1, a single 30-minute session of high-speed interval exercise did not elicit an acute functional improvement in participants who delayed a dose of dopamine replacement therapy. In Aim 2, the reliability of an experimental measure of force segmentation during rapid isometric contractions was supported. Further studies should control for clinical factors, such as, age at disease onset, duration of the disease, and nature of treatment (Jordan et al, 1992). A greater sample size and a greater time since the previous DRT dose is recommended to produce more definitive results about the potential of exercise to reverse the wearing-off effect.
REFERENCES


Bellumori, Maria, Mehmet Uygur, and Christopher A. Knight. "High-Speed Cycling Intervention Improves Rate-Dependent Mobility in Older Adults." Medicine and science in sports and exercise 49.1 (2017): 106-114.


Nutt, John G. "Motor fluctuations and dyskinesia in Parkinson's disease."
Peto, V., et al. "The development and validation of a short measure of functioning and
well-being for individuals with Parkinson's disease." Quality of life research
applications to practice.
Wired to run: exercise-induced endocannabinoid signaling in humans and
cursorial mammals with implications for the ‘runner’s high’. Journal of
Experimental Biology, 215(8), 1331-1336.
Roberts, Helen C., et al. "A review of the measurement of grip strength in clinical and
epidemiological studies: towards a standardised approach." Age and ageing
Rovini, Erika, Carlo Maremmani, and Filippo Cavallo. "How Wearable Sensors Can
Support Parkinson's Disease Diagnosis and Treatment: A Systematic Review."
performance with high-speed power training in older adults is optimized in
those with the highest training velocity. European journal of applied
physiology, 116(11-12), 2327-2336.
How stable are Parkinson's disease subtypes in de novo patients: Analysis of
the PPMI cohort?. Parkinsonism & related disorders, 28, 62-67.


Appendix

IRB APPROVAL LETTER

DATE: February 1, 2018

TO: Christopher Knight, PhD
FROM: University of Delaware IRB

STUDY TITLE: [1179082-1] Interaction between Exercise and Medication in the Management of Parkinson’s Disease Symptoms

SUBMISSION TYPE: New Project

ACTION: APPROVED
APPROVAL DATE: January 31, 2018
EXPIRATION DATE: January 16, 2019
REVIEW TYPE: Full Committee Review

Thank you for your submission of New Project materials for this research study. The University of Delaware IRB has APPROVED your submission. This approval is based on an appropriate risk/benefit ratio and a study design wherein the risks have been minimized. All research must be conducted in accordance with this approved submission.

This submission has received Full Committee Review based on the applicable federal regulation.

Please remember that informed consent is a process beginning with a description of the study and insurance of participant understanding followed by a signed consent form. Informed consent must continue throughout the study via a dialogue between the researcher and research participant. Federal regulations require each participant receive a copy of the signed consent document.

Please note that any revision to previously approved materials must be approved by this office prior to initiation. Please use the appropriate revision forms for this procedure.

All SERIOUS and UNEXPECTED adverse events must be reported to this office. Please use the appropriate adverse event forms for this procedure. All sponsor reporting requirements should also be followed.

Please report at NON-COMPLIANCE issues or COMPLAINTS regarding this study to this office.

Please note that all research records must be retained for a minimum of three years.

Based on the risks, this project requires Continuing Review by this office on an annual basis. Please use the appropriate renewal forms for this procedure.