MUSCLE RELAXATION IN PARKINSON'S DISEASE: IMPLICATIONS FOR FUNCTION

by

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ABSTRACT

Older adults (OA) experience a decline in mobility due to reduced power and physical slowing. The symptom of bradykinesia in Parkinson's disease (PD) further slows reaction time and movement with additional consequences in mobility. Mechanical power predicts function more than muscular strength. This highlights the importance of movement speed because power is the product of force and velocity. Logically, much research has focused on the rate at which the nervous system can activate muscles to develop muscular force. However, less is known about the ability to relax or 'turn off' muscles in OA and people with PD. Appropriately-timed muscle relaxation is likely important for direction changes, fall prevention, and rapid cyclical movements. This thesis included two projects related to the relaxation of muscle force and mobility. The **first project** used an isometric handgrip model to accomplish three research aims. **Aim 1** was to compare peak rates of isometric muscle force development and relaxation between young adults (YA), older adults and people with PD. **Aim 2** was to examine the associations between segmented motor output and force development, force relaxation and mobility in people with PD. **Aim 3** was to compare mobility tests between the three groups and to relate measures of force development and force relaxation to mobility in OA and people with PD. The **second project** extended the scientific inquiry from isometric to dynamic conditions.

Participants pedaled a stationary recumbent bicycle against low resistance in cadence conditions from 40 to 120 revolutions per minute (rpm). Surface electromyograms were obtained in six lower extremity muscles. **Aim 4** was to compare muscle activity patterns during recumbent cycling between YA, OA, and people with PD at increasing pedaling cadences. **Aim 5** was to examine associations between muscle activation patterns during bicycling and performance of timed tests of mobility in people with PD. The results of each project are reported in two separate chapters. The first project provided evidence that the rate of muscle force relaxation is slowed with aging and further impaired by force segmentation in PD. While correlations between muscle force relaxation and mobility were generally stronger than those involving force development, they were not particularly strong in PD. The second project revealed a prolonged duration of knee extensor muscle activity in PD at higher pedaling cadences. The duration of this EMG activity was positively and strongly correlated with timed tests of mobility, indicating that a prolonged duration of EMG bursts during cycling predicts poor performance in timed mobility tests.

Chapter 1

BACKGROUND AND SIGNIFICANCE

Aging

The ability to continue performing activities of daily living independently is important for quality of life as adults age. However, this can become increasingly difficult as many factors contribute to the loss of mobility in older adults. The aging process involves a progressive loss of skeletal muscle mass and associated function, or sarcopenia, as well as increases in intermuscular adipose tissue which decreases muscle quality. This leads to losses in strength, power, and physical performance (36). Muscle power is a better predictor of one's ability to perform activities of daily living than strength or aerobic capacity in older adults (32). Unfortunately, power declines with age earlier than muscle strength (29) due to many reasons including decreases in muscle cross-sectional area, strength, neuromuscular function, and muscle quality (31). However, muscle power can be improved with high-speed training interventions (31, 32), and lead to improvements in tests of mobility (5, 29).

Parkinson's Disease

Parkinson's disease (PD) is the second most common neurodegenerative disorder and is estimated to affect 128-187 per 100,000 people (9). The disease causes progressive neurological degeneration that results in motor symptoms including bradykinesia, tremor, rigidity, dyskinesia and postural instability. Bradykinesia involves a slowing of information processing and movement initiation with reductions

in the velocity or amplitude of the subsequent movement. These symptoms have a progressively negative effect on mobility which leads to poor performance in activities of daily living (18).

PD pathology originates in the basal ganglia, which is a set of nuclei that contribute to the initiation and control of movement, as well as learning and cognition. Within the basal ganglia, PD results from the loss of brain cells in the substantia nigra that produce dopamine. The resulting dopamine deficiency and intracellular accumulation of α-synuclein are characteristics of the disease. Neural activity within the basal ganglia filters through two pathways: the excitatory direct pathway, and the inhibitory indirect pathway. In the direct pathway, the substantia nigra disinhibits the globus pallidus interna (GPi) in order to project information to the thalamus to promote movement. Dopamine deficiency makes the substantia nigra unable to disinhibit the GPi which inhibits the motor systems. In the indirect pathway, the substantia nigra disinhibits the globus pallidus externa (GPe), which allows the GPi to inhibit the thalamus and thus the motor systems. Over-activity of the indirect pathway results in a lack of movement in PD (6, 14, 25, 27).

There is no known cure for PD, but several treatment options exist to manage motor symptoms of PD. Levodopa (a dopamine precursor) is considered the most effective pharmacological treatment of PD. Although it can dramatically improve function in PD, several symptoms are resistant to the drug including postural abnormalities, freezing episodes, speech impairment, autonomic dysfunction, mood and cognitive impairment. Additionally, prolonged use of the drug can cause disabling side effects that are difficult to treat such as dyskinesia (35) .

Exercise has been proposed as an alternative treatment option to address motor symptoms that cannot be treated with medication or surgery. Research indicates that exercise can improve brain function in PD by slowing neural degeneration. Aerobic exercise has been shown to improve gait, quality of life and the effectiveness of levodopa therapy (18). Similar to studies with healthy older adults, research indicates power training interventions are successful at improving mobility in PD. Meng et al found that a 12 week high-speed resistance training improved clinical measures of bradykinesia, peak power, and perceptions of performance in mobility and activities of daily living (21). Additionally, Uygur et al found that PD improved in functional measures of the four square step test and the 10 m walk test after a single 30 minute session of high-speed cycling intervals (37).

Isometric Force Pulse Characteristics

The performance of brief rapid isometric contractions is a research model with a long history of scientific inquiry into questions of control, optimal performance, aging and pathology. Healthy adults exhibit a "speed control" strategy in which they scale the speed of contraction to the target amplitude to achieve a constant time to peak force during rapid isometric contractions to different amplitudes. In other words, the larger the amplitude of an isometric force pulse, the faster the rate of contraction. The neural control of this rate is evident in the electromyogram (EMG) of the agonist muscle. The magnitude of the agonist burst is scaled with the amplitude of the intended contraction while duration of the burst remains constant to control the time to reach the target (11, 12). Bellumori et al quantified this speed control strategy in rapid isometric force pulses as rate of force development scaling factor (RFD-SF), which is the slope of the relationship between rate of force development (RFD) and peak force

(PF) in pulses of different amplitudes (4). Although healthy older adults do still exhibit this control strategy, there is a decline in the RFD-SF, which Bellumori et al reported to be 28-33% less than young adults in isometric elbow extension and index finger abduction (3). Klass et al similarly found that older adults had a 26% longer average time to peak torque during rapid contractions than young adults and a 48% decrease in maximum rate of force development (19).

Adults with PD, regardless of medication, show impairments in this control mechanism. Irregularities in motor performance are seen as greater variability in force rise time and peak force in pulses of different target amplitudes. In PD, time to reach peak force increases as force amplitude increases and higher peak forces are often achieved through abnormally segmented EMG bursts and/or a wider overall burst width (39). Additionally, EMG is often not scaled well for changes contraction speed or amplitude (18). This decrease in speed of RFD in PD is well studied (28, 34, 39). However, less information is available about force relaxation and its associated EMG activity. Corcos et al found that the time to relax muscular force in isometric elbow flexion and extension pulses was actually more impaired than RFD and was significantly correlated with the Unified Parkinson's Disease Rating Scale score (8). This suggests that relaxation time and related measures may be important indications of clinical status in PD patients. Other researchers similarly found that the rate of force relaxation is more impaired than RFD in Parkinson's patients, regardless of medication (17, 23, 34). Additionally, Wierzbicka et al reported a disjointed or segmented appearance of the force-time curve, which they credited to abnormal single motor unit firing behavior. They also observed irregularities in the relaxation phase of the force pulses that were quantified as the number of zero crossings of the derivative

of the force-time curve (39). Pilot isometric force pulse data from our laboratory also demonstrate that some, but not all, people with PD have segmented force pulses that include multiple changes in direction of dF/dt while the participant attempts to rapidly achieve maximum force and return to rest. This irregular segmentation of force production and relaxation in PD has only once been quantified in the literature (33) but would likely be a better indicator of PD pathology than some other force measures being used currently (39). Indeed, while slowed rates of force development or force relaxation might be partly indicative of aging or low fitness, force segmentation is a clear sign of pathology.

Grip

Various grip models have been used to study isometric force control in PD (17, 28, 40). They are of interest due to their functional relevance. Isometric handgrip strength and rate of force development are somewhat related to performance in timed tests of mobility such as the timed up and go, as well as lower body strength-to-weight ratio in older adults (1, 7), which may make it an indicator of overall strength capacity in aging populations. Additionally, handgrip strength is a reliable test in people with PD (38).

Muscle Relaxation

At the cellular level, skeletal muscle relaxation involves decreasing the sarcoplasmic Ca^{2+} concentration following contraction. This occurs by dissociating Ca^{2+} from troponin, moving Ca^{2+} near the entrance of the sarcoplasmic reticulum, the reuptake of Ca^{2+} into the sarcoplasmic reticulum (SR) by the Ca^{2+} pump, and the detachment of cross-bridges. Aging causes a slowing in involuntary muscle relaxation

rate and time due to factors such as atrophy of type II muscle fibers, a reduction in calcium uptake by the SR, decreased Ca^{2+}-ATPase activity, and changes to the dissociation of the actin-myosin crossbridge (15, 22).

Slowing of muscle relaxation decreases muscle power output and its inefficiency limits performance during dynamic exercise with rapidly alternating movements or task switching. Improving skeletal muscle relaxation has been suggested to improve the efficiency of joint movements by reducing co-contraction of antagonist muscle pairs (16, 24). Therefore, the impairment of relaxation seen in isometric contractions in PD likely increases the difficulty, energy cost of such contractions, and joint stiffness. It is unknown whether these impairments in isometric force relaxation transfer to dynamic movements, and if so, how that may potentially challenge continuous movement during activities of daily living.

Bicycling

Bicycling is a bipedal motor task that requires lower extremity coordination and repetitive motion generation, similar to walking (26). In young, healthy adults, the specific patterns in EMG activity during cycling are well studied, and include specific timing of muscle activation amongst antagonist pairs at each joint, that alter with increased speeds or load. Figure 1 represents typical EMG activity of the muscles involved in cycling in a full pedal revolution in different cadence and load conditions (2).

As pedaling cadence increases, EMG activity occurs earlier in the crank cycle which results in peak force occurring at the same position in the crank cycle. Coordination during cycling in healthy adults results from the net moments of the agonist-antagonist pairs at each active joint including the dorsiflexors and

plantarflexors at the ankle, the extensors and flexors at the knee, and the extensors and flexors of the hip (20). As cadence changes, coordination is altered between the knee and ankle antagonist muscle pairs (2).

Duffy et al found that older women had 43% lower peak power and significantly lower root mean square EMG than younger women, suggesting a decrease in the number of active motor units or discharge rate (10). Additionally, Sacchetti et al found that older competitive cyclists were less mechanically efficient at higher cadences than younger cyclists (30).

Despite the fact that bicycling is a commonly prescribed training modality, it is not well studied in PD and research is limited to coordination asymmetries between sides (26), and biceps femoris and tibialis anterior EMG at different pedal angles (13), when a more representative picture of cycling may be given with EMG recordings of additional muscles to assess coordination between antagonist pairs.

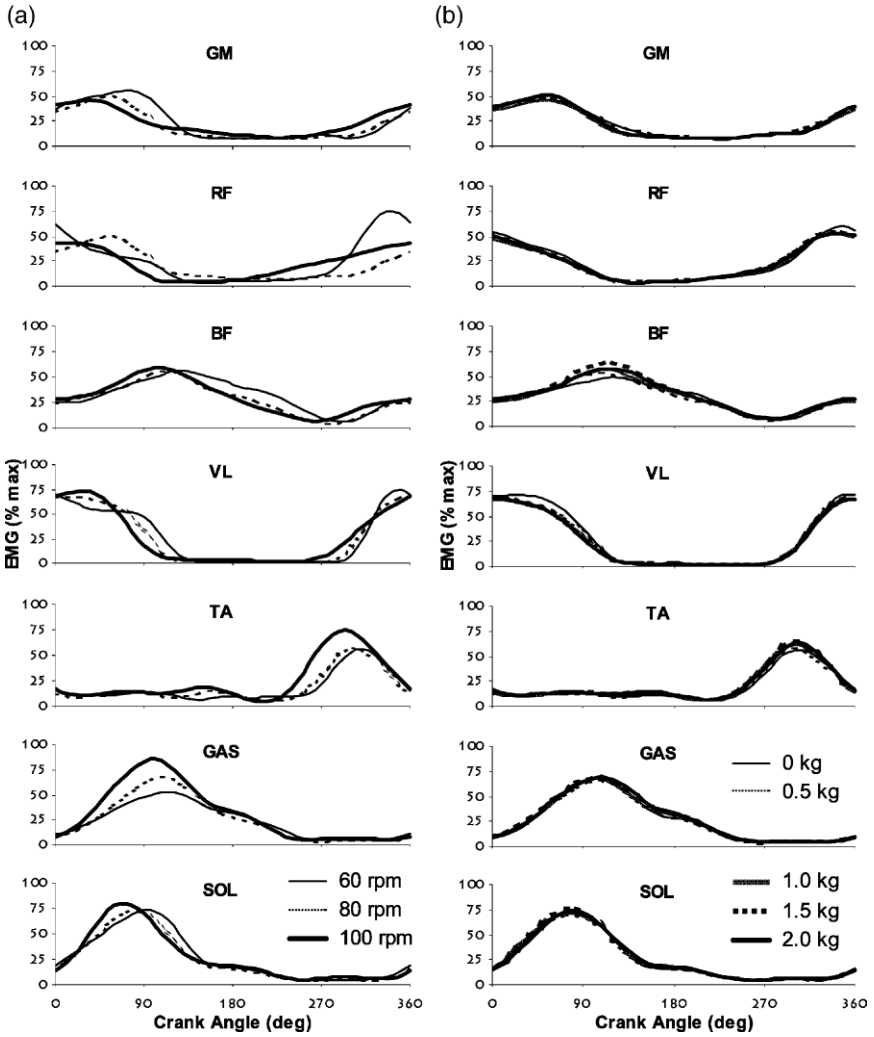

Figure 1 Mean ensemble curves of EMG activity for each muscle across (a) cadence and (b) load conditions. The crank angle range represents TDC to next TDC, 0–360°. EMG curves for each participant were scaled to the maximum value observed across all 15 conditions. The mean curves here were calculated from the scaled individual curves of gluteus maximus (GM), rectus femoris (RF), biceps femoris (BF), vastus lateralis (VL), tibialis anterior (TA), gastrocnemeus (GAS) and soleus (SOL) (2).

Innovation

This study will help fill the substantial gap in the literature regarding the relaxation phase of muscle activity in isometric force production and during dynamic cycling, and how relaxation may be related to successful performance in activities of daily living. Additionally, this study will be the first to systematically quantify the irregularity in isometric force pulses in PD using a new variable called segments. Providing information regarding this topic may help to better inform practitioners about how the symptom of bradykinesia affects both the speed of muscle relaxation and the quality of movement.

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Chapter 2

ISOMETRIC RELAXATION PERFORMANCE IS IMPAIRED IN PARKINSON'S DISEASE WITH INCREASED SEGMENTATION

Abstract

In people with healthy neuromotor control, rapid isometric contractions are produced with a linear relationship between rate of force development (RFD) and peak force that results in relative invariance in time to peak force (TPF). Bradykinesia is a symptom of Parkinson's disease (PD) that often results in prolonged force development and relaxation. In many cases, this slowing is accompanied by disruptions in motor output that cause discontinuity in the rate of change in force and a segmented appearance in force-time curves. Aim 1 was to compare rates of muscle force development and relaxation, as well as segmentation between young adults (YA), older adults (OA), and people with PD in rapid isometric contractions. Aim 2 was to determine the effects of segmentation on force development and relaxation and on mobility in people with PD. Aim 3 was to determine whether measures of force relaxation are related to performance on timed tests of mobility in OA and PD. Participants performed rapid isometric grip force pulses to 30-50% of their maximal voluntary contraction (MVC) force. Dependent variables related to force development were TPF, peak RFD, average RFD, and the number of force segments from rest to peak force. Dependent variables related to force relaxation were half relaxation time

(HRT), full relaxation time (FRT), peak rate of force relaxation (RFR), average RFR, and the number of force segments from peak force to full relaxation. Mobility tests were the 3 meter timed up and go (TUG) and the four square step test (FSST). People with PD had significantly poorer performance in all measures compared to healthy OA and YA. Compared to YA, OA had lower RFR and longer HRT and FRT, but were not different in force development measures. Additionally, a subset of 8 people with PD was identified to have abnormal segmentation, and showed significant impairments compared to the remaining 6 non-segment dominant participants. The non-segment dominant PD participants were not different from OA in all dependent variables. Relaxation measures were strongly correlated with TUG and FSST in OA but not in PD. Thus, segmentation of motor output alters the isometric force profile in some PD and represents more severe impairment in isometric force development and relaxation in this population.

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder that affects 2-3% of adults aged 65 years and older. Characterized by neuronal loss in the substantia nigra, it leads to a dopamine deficiency and development of motor symptoms such as tremors, bradykinesia, rigidity, and postural instability (7, 22). In rehabilitation research on PD, impaired control of rapid isometric contractions has been observed (21, 27, 28, 32). Whereas healthy populations utilize a precise scaling of rate of force development (RFD) with isometric force pulse amplitude to maintain a constant time to peak force (8, 9), people with PD often display a prolonged and more variable time to peak force as peak force amplitude increases (32). Additionally, during rapid muscular contractions, some people with PD have disruptions in their neural output that result in interrupted force production, and a stepwise appearance in their progression to peak force (27, 32). In this chapter we refer to this abnormal force control as segmentation.

Some slowing in rates of force development and output are natural outcomes of aging and/or inactivity, due to a decreased motor unit discharge frequency (16) as well as a slowing of muscle contractile properties (26). However, many people with PD display additional impairments in their rapid isometric force performance. Since people with mild to moderate PD have normal isometric rates of force development when muscle is electrically stimulated, declines in their volitional RFD represent central rather than peripheral dysfunction (11). Studying this central dysfunction is of

interest since a decreased ability to produce force rapidly is related to a higher incidence of falls (3).

In PD, there is also an impairment in isometric force relaxation (15, 20), and some literature suggests that force relaxation is actually more affected by the disease than force development (6, 15, 17, 25). However, this impaired relaxation has received comparatively little attention, and many questions remain unanswered. For example, how do force development and relaxation rates relate to whole body mobility? The ability to produce force quickly is more related to mobility in healthy aging than strength (1). Although force development and relaxation measures in PD are related to scores on the Unified Parkinson's Disease Rating Scale (UPDRS) and Kings College Rating Scale (KCRS) (6, 15, 25), their relationship to timed tests of mobility have not been clearly established. It is thus of interest to determine how these impairments may contribute to a person's ability to perform activities of daily living, and whether force relaxation has a stronger relationship with mobility than force development.

The **first aim** of this study was to compare rates of muscle force development and relaxation between young adults (YA), older adults (OA) and people with PD in rapid isometric contractions. It was hypothesized that people with PD would exhibit poorer force development and relaxation performance than YA and OA as evidenced by slower rates of force development and relaxation, and longer durations of force development and relaxation phases. The **second aim** was to determine the effects of segmentation on force development and relaxation and on mobility in people with PD. It was hypothesized that participants with more segmentation would have greater

impairments in all force pulse variables and poorer performance on timed tests of mobility. The **third aim** of this study was to compare performance during mobility tests between the three groups, and to relate measures of force development and relaxation to mobility in OA and people with PD. It was hypothesized that YA and OA would have better performance in timed tests of mobility than people with PD, and that measures of relaxation would have relatively greater correlations with mobility than measures of force development in both OA and PD.

Methods

Participants

This study included 14 young adults (aged 23.1 ± 3.1 years, 1.74 ± 0.06 m tall, 71.9 ± 9.2 kg, BMI = 23.7 ± 2.7 kg•m^{-2}, 5 females), 14 older adults (aged 67.9 ± 6.2 years, 1.71 ± 0.11 m tall, 82.5 ± 18.7 kg, BMI = 27.8 ± 5.2 kg•m^{-2}, 7 females), and 14 people with PD (aged 68.6 ± 4.4 years, 1.74 ± 0.11 m tall, 92.1 ± 20.1 kg, BMI = 30.1 ± 4.8 kg•m^{-2}, 5 females, 6.4 ± 5.4 years since diagnosis, Hoehn and Yahr stage 1-3). Prior to testing, all participants read and signed institutionally-approved informed consent documents. All participants were able to walk without assistance and were capable of following instructions. Participants with PD were instructed to take their usual medications prior to testing. Healthy young and older adults were free of any neurological disease.

Functional Tests

Participants performed the four square step test (FSST) and the three meter timed up and go (TUG) as done by Uygur et al (31). After a practice trial, participants performed two trials of each test "as quickly and safely as possible". The fastest time was used for analysis.

Rapid Isometric Contractions

The participants' dominant or more affected side for PD was tested. The participants were seated with their elbow supported by an armrest, and held a custom force sensor with the thumb and fingers wrapped firmly around the middle of the device. The device was 5 cm wide by 11 cm tall by 2 cm thick and contained a strain gauge force transducer (SM-50, Interface Inc., Scottsdale, AZ, USA). The force signal was amplified within a 5V range using a strain gauge transducer amplifier (Model SGA, Interface Inc.).

Participants performed three 3-second maximal isometric handgrip contractions (MVC) with one minute of rest in between trials. The greatest peak force was used to convert force data to a relative percentage of MVC. Next, participants were instructed to perform rapid isometric handgrip force pulses to 30, 40, and 50% of MVC with real-time visual feedback of their force production on a bar graph. Participants were instructed to perform rapid force pulses to 30, 40 and 50% MVC and received verbal "go" cues for each pulse approximately every two seconds. Participants were told to prioritize initiating the force quickly and relaxing instantly once the peak height was achieved rather than reaching the exact peak force, since

instructions for accuracy are known to decrease the speed of force production (9). Three to four 60 second trials were completed to collect approximately 50 to 75 pulses within the desired force range. Participants performed a final MVC after all handgrip trials to ensure that they did not experience fatigue from the protocol. Pre and post MVCs were confirmed to not be different with two one-sided tests of equivalence with an upper and lower bound of 5% ($t=1.155$, $p=0.872$).

Signals from the force transducer were amplified and filtered with a second order low pass filter (-12 db/oct) with a cutoff frequency of 50 Hz (Model SGA, Interface, Inc.). Force was digitized at 2000 Hz (NI cDAQ-9178, Module 9329, National Instruments, Austin, TX, USA) and DASYlab software (Measurement Computing Corporation, Norton, MA, USA) was used to control the digitization and provide real-time visual feedback of force.

Data Processing

LabVIEW software (National Instruments) was used to analyze the force data. Force was low pass filtered with a 4rth order zero lag Butterworth filter with a cutoff of 20 Hz. A conservative force threshold was set at 5% of the MVC force as done by Wierzbicka et al (32). Pulse duration was defined as the time between on and off thresholds. Time to peak force (TPF) was calculated from force threshold to the maximum force within each pulse. Full relaxation time (FRT) was calculated from peak force back down to threshold. To examine a measure that was less sensitive to variability in full relaxation time, half relaxation time (HRT) was computed from peak force to 50% of peak force. First and second derivatives of force (dF/dt and d^2F/dt^2,

respectively) were calculated using a moving slope across a 100 ms window. Peak rates of force development (RFD_{pk}) and force relaxation (RFR_{pk}) were calculated as the maximum and minimum values of dF/dt from force initiation to peak force and from peak force to full relaxation, respectively. Additionally, average rate of force development (RFD_{avg}), and average rate of force relaxation (RFR_{avg}) were calculated for the same periods of time. Segmentation is a variable used to quantify the disruption of motor output during rapid force pulses in people with PD. Stelmach et al counted zero crossings in the second derivative quantify the disjointedness of force production in people with PD (27). In the present paper, the number of interruptions in the force-time curve was called segments, and was similarly quantified using the second derivative from force threshold to peak force (seg_{up}) and peak force to full relaxation (seg_{down}) as follows:

$$\frac{\#\ zero\ crossings\ in \frac{d^2F}{dt^2} + 1}{2}$$

Additionally, force impulse was calculated for the total pulse duration (J_{tot}), from force threshold to peak force (J_{up}) and from peak force to full relaxation (J_{rel}).

After variables were calculated for all pulses, a subset of pulses between 35-45% MVC was selected for analysis. A wider subset was chosen, rather than the three specific force levels sampled, in order to have an adequate sample size of pulses for each subject while still controlling for peak amplitude. Measures within this range were averaged within each participant. This method was chosen to reduce the variance

due to varied amplitudes of the contractions since rate of force development will scale with peak force (4, 8) and timing measures are more variable with changes in peak force in people with PD (21, 27), While time to peak force can be prolonged in handgrip pulses with amplitudes greater than 50% in healthy adults (29), we are primarily interested in rapid contractions to force levels that are more common in activities of daily living.

Statistical Analysis

IBM SPSS software version 24.0 was used to perform all statistical analyses. A one-way analysis of variance was used to confirm that pulse amplitudes did not differ across groups. Independent t-tests were also used to compare participant characteristics. Due to violated assumptions of normality and homogeneity of variance in some dependent variables, non-parametric statistics were used to test differences between groups. The nonparametric Kruskal-Wallis test was used to test group effects for all dependent variables. Wilcoxon rank-sum tests with p-values adjusted for rank ties were used for post-hoc pairwise comparisons. Additionally, within the PD group, participants were classified as being "segment dominant" if greater than 10% of pulses had more than one segment. This criteria was determined based on a visual inspection of frequency distributions of segmentation within the PD group, and the finding that young and older adults groups had ≤ 3% of pulses having greater than one segment. Wilcoxon rank-sum tests were also used to assess differences between segment-based PD subgroups. Wilcoxon results are reported as Z-scores to facilitate the discussion of effect sizes. With the sample size of each group being equal (n=14), Z-scores provide

a surrogate for the effect size r, which is equal to Z divided by the square root of n (Field, 2005). Spearman's correlations were used to assess relationships between TUG and FSST performance and force pulse measures in OA and people with PD. All statistical tests were evaluated at an alpha level ≤ 0.05.

Results

Figure 2 contains representative force pulses from each group. While force pulses from YA, OA and the non-segmented PD subgroup (Figure 2, A-C) are qualitatively similar, the pulse representing the segmented PD subgroup (Figure 2, D) is markedly abnormal. Comparison of rate-related measures across groups is facilitated by the finding that average pulse amplitude was not significantly different ($F=2.22$, $p=0.12$). People with PD and OA also had no differences in age, height, weight or BMI ($p \geq 0.30$), but YA had lower age, weight, and BMI ($p<0.05$) than people with PD and OA.

It was expected *a priori* that there would be high correlations among dependent measures that quantify aspects of force development or force. High correlations were observed between corresponding measures that quantify duration, average rate, and impulse ($\rho \geq 0.976$, $p<0.001$). Therefore, for efficiency and to reduce experiment-wise error rates, HRT, average rate and impulse variables are not reported.

Group differences

All group effects were significant (Table 1), with the lowest χ^2=7.61. Greater χ^2 statistics and mean differences indicated that group effects were consistently larger for measures of force relaxation than measures of force development. Pairwise comparisons (Wilcoxon rank-sum test, Table 2) indicated that people with PD had significantly less grip strength, slower force pulse performance, and more segmentation compared to young adults (all $|Z|\geq 2.25$, all $p\leq 0.024$). Compared to older adults, people with PD were not significantly different in grip strength (Z=-0.138, p=.890) but had slower force pulse performance and more segmentation (all $|Z|\geq 2.39$, all $p\leq .017$). Compared to YA, OA had less grip strength (Z=-2.53, p=0.012), prolonged total pulse duration (Z=-2.44, p=0.015), relaxation time (Z=-2.85, p=0.004) and lower RFR_{pk} (Z=-1.00, p=0.010) but were not significantly different in any force development measures. In Table 2, there is a trend in which the Z-scores for force relaxation measures are greater than those for the corresponding force development measure in either comparisons of OA or PD to YA. Z-scores for force development and relaxation measures are more similar in the comparisons between OA and PD.

Force segmentation in PD

Based on ≥15% of pulses containing more than one segment, eight participants with PD were categorized as segment dominant. Some segmentation existed in young and older adults, but young adults subjects had ≤ 1.3% pulses with more than one segment, and older adults had ≤ 3.0% of pulses with more than one segment. These

participants had significantly poorer performance during the rapid isometric force pulses compared to the six non-segment dominant participants (all $|Z| \geq 2.34$, all $p \leq 0.013$, Table 3), although they did not have differences in RFR_{pk}, MVC strength, or mobility test performance (all $|Z| \leq 1.94$, all $p \geq 0.059$). Non-segment dominant participants had no differences from OA in any force pulse or mobility measure (all $p \geq 0.4$).

Correlations between force pulse measures and mobility

One subject with PD was unable to complete the FSST. People with PD had poorer performance in FSST and TUG than OA and YA. OA had poorer FSST than YA but TUG was not different between OA and YA (Figure 3). Based on data from all groups combined (n=42, Table 4), correlations between performance on the FSST and all isometric handgrip measures were significant ($0.43 \leq |\rho| \leq 0.74$, all $p \leq 0.005$). Similarly, correlations between TUG and all isometric handgrip measures were significant ($|\rho| \geq 0.38$, $p \leq 0.02$), except for the correlation involving MVC force ($\rho = -0.30$, $p = 0.06$). A paired t-test of Fisher transformed correlation coefficients $p < .001$ indicated that the correlations between force relaxation measures and mobility tests were stronger than those involving force development measures.

Within the PD group, however, performance on timed tests of mobility were not related to force pulse measures, and in YA, the only significant relationship found was between TPF and FSST (Table 5). In OA, there were stronger relationships

between FSST and total pulse duration (ρ=0.791, p=0.001), FRT (ρ=0.747, p=0.003) and RFR_{pk} (ρ=0.626, p=0.022). Also in OA, stronger relationships were observed for TUG performance and pulse duration (ρ=0.593, p=0.033), FRT (ρ=0.714, p=0.006), and RFR_{pk} (ρ=0.626, p=0.022).

Discussion

The first aim of this study was to compare the rates of force development and relaxation among young adults, older adults and people with Parkinson's disease. In the present conditions with a target force pulse amplitude of approximately 40% MVC, total pulse duration quantifies the entire task performance. Under the instructions to reach the target force and then relax as quickly as possible, superior performance would be marked by force pulses that are more succinct. It was not surprising that OA and PD groups had significantly greater pulse durations than YA and that PD had a greater pulse duration than OA. While this finding was expected, our main interest within Aim 1 was to learn whether the differences associated with aging and PD are greater during force development or force relaxation.

Recognizing that mechanical power is a good predictor of function and performance in sport, older adults and special populations (2, 18, 24), it is natural to focus on power, rates of force development and neural activation in rehabilitation research. Indeed, previous literature has found an age-related decrease in the ability to produce force quickly (3, 16, 30). However, the ability to relax a muscle during discrete or cyclical movements and during direction changes might also have

significant impact on activities of daily living. There were significant group differences for all measures of force development and relaxation. The corresponding χ^2 statistics indicated that the magnitude of the group effect was consistently greater for force relaxation measures than for force development measures. For example, χ^2 values were 12.89 and 21.22 for TPF and FRT, respectively, and a greater magnitude of effect was observed for relaxation-related measures in all variable pairs at the group level (Table 1) and in post-hoc comparisons to YA (Table 2).

It was hypothesized that older adults would have a greater time to peak force than young adults (3, 15, 16). Although OA did have a slower time to peak force, the difference was not significant ($p=0.17$). We propose two possible explanations. In order to approximately match the ages among older adults and people with PD, the mean age of the older adult sample (67.9 years) was lower than in other studies on aging. Second, 10 of the 14 OA participants self-reported that they regularly participated in exercise, which may preserve their RFD capacity compared to inactive OA (1). Evidence of favorable fitness of the OA sample is visible in their TUG performance, which was not different from that of YA (Figure 3). OA did, however, have poorer relaxation performance than YA, as indicated by a longer time to reach full force relaxation and a slower peak rate of force relaxation. Others have found a decline in peak relaxation rate and longer HRT during electrically-induced contractions in OA compared to YA, which may be due to atrophy of type II muscle fibers, a reduction in calcium re-uptake by the sarcoplasmic reticulum, and changes to the dissociation of the actin-myosin crossbridge (14, 19).

While there were significant differences between old and young adults in some measures, all measures were significantly different between young adults and the PD group, with consistently greater effect sizes for relaxation-related measures indicated by the greater Z scores. Furthermore, all measures were significantly worse in PD than in OA. Thus, as one would expect, PD affects force development and force relaxation more than age alone.

It was hypothesized that in people with PD, force relaxation would be more impaired than force development compared to OA. This was not the case. While all measures were significantly worse in PD than in OA, the Z values were similar for force development and force relaxation measures (Table 2). Previous studies have found that during rapid isometric force pulses, relaxation measures improve to a greater extent with medication than excitation measures in people with PD, suggesting that muscle relaxation is more impaired by the disease (6, 15, 25). However, it appears that while participants were medicated, both force production and relaxation may be impaired to a similar extent as healthy aging. Likewise, Jordan et al found that although rates of force production and relaxation were impaired in un-medicated newly diagnosed people with PD as well as in medicated people with PD compared to healthy controls, Z scores from these group comparisons were similar for force production and force relaxation (15). This disagrees with Kunesch et al, who found medicated people with PD to have greater FRT but a similar TPF compared to healthy controls (17). Although force relaxation impairments were similar to force development impairments in people with PD in the present study, the overall

prolonged force development and relaxation times, and total pulse duration compared to healthy participants were consistent with other literature (15, 20, 28).

Force Segmentation

Aim 2 was to better understand the role of segmented motor output, as observed by others during rapid isometric contractions, on rates of change in force and mobility. It was hypothesized that greater segmentation would be accompanied by poorer performance in isometric contractions and mobility tests. Interestingly, the participants in the non-segment group were not different from healthy OA in isometric force performance. This is similar to the finding of Wierzbicka et al, where participants with fewer interruptions in the force-time curve had greater maximal strength, and their TPF was not different from healthy controls. Wierzbicka et al also found that the rate of force production up to the peak of the first segment was not impaired compared to healthy controls, but the first bout of motor output was not sufficient to reach the intended peak force. For individuals with force segmentation, the inability to quickly achieve peak force in PD results from an interrupted neural drive to the muscle, evidenced by silent periods in the agonist surface electromyogram before the end of each force segment (32). This phenomenon may be similar to abnormalities documented by Hallett & Khoshbin in the triphasic burst pattern in rapid dynamic movement (10). In healthy adults, rapid elbow flexion results from an agonist burst alternating with an antagonist burst, and another agonist burst in the surface electromyogram (EMG), with increases in burst amplitude as the duration of the movement increases. In most of the people with PD, however, the first triphasic burst

cycle often was not adequate to complete the movement. As the movement duration increased, additional triphasic burst cycles were required to reach the same end position that healthy participants were able to complete from a single triphasic burst cycle (10). This mirrors differences in the EMG during rapid isometric force production, in which people with PD that required multiple agonist bursts to reach a target force had inadequate amplitude of the first burst to reach peak force, and that the discrepancy in required and actual burst magnitude gets larger with increasing target peak force (32). Wierzbicka et al found that the individual segments were produced relatively quickly and although the relationship between the RFD_{pk} and amplitude of each individual segment was similar to that between RFD_{pk} and peak force in healthy control, the RFD_{pk} for the first segment was not adequate to reach the total peak. Considering that pulses with multiple segments have spurts of normal behavior but an overall impairment, it is not surprising that segment-dominant PD was accompanied by greater differences in RFD_{avg} than RFD_{pk} compared to non-segmented PD (Table 3). The overall impairment caused is great, as Stelmach et al reported that increased zero crossings in $d2F/dt^2$ were accompanied by nearly doubled TPF and lower RFD_{avg} in PD patients compared to healthy OA and YA (27).

In the present sample, it seems that segmented motor output and not a general slowing drove the differences between OA and PD in isometric force production. Due to the impact segmentation has on isometric force performance, future studies should separate those who exhibit multiple segments into a subgroup for analysis. These variations in central control within the PD population warrant further study in the

understanding of muscle relaxation, how force segmentation contributes to these impairments, and why it occurs. It is possible that segmentation is related to tremor, although that hypothesis was not tested in this study. The average frequency of seg_{up} was 7.5±2.3 Hz, and seg_{down} was 7.1±1.3 Hz. These are both within the range of action tremor (23), though more investigation is needed to determine if segmentation is related to this symptom.

The third aim of this study was to compare performance in timed tests of mobility between the three groups, and to determine whether isometric force performance measures are related to mobility test performance in OA and PD. As expected, YA and OA performed better than PD in the mobility tests, as indicated by lower times for the FSST and TUG. Interestingly, the FSST was more sensitive to age-group differences than the TUG. People with PD who had the longest FSST times seemed most challenged by backwards steps and lifting the feet high enough to step over the thin (1 cm) strips of wood that separated quadrants.

While there were moderate correlations between force pulse measures and FSST performance for all groups combined, the relationships within the PD group were quite low. Although it was hypothesized that relaxation measures would be correlated with FSST and TUG times in OA and PD, a significant correlation was only found in OA. Interestingly, pulse duration had the greatest correlation with FSST, followed by FRT. Thus, older adults with better mobility also produce more succinct force pulses in the upper extremity. While not significant, the correlations with FSST in PD were greater for force relaxation than force development measures and the

reverse was the case in young adults, in whom the pulses were most symmetrical and succinct.

Previous work has found that handgrip RFD_{avg} was related to TUG performance in OA (5), and the present study provides evidence that rate of force relaxation is also related to function in OA. Since performance in the mobility and isometric force tests was less variable in YA (see standard deviations in Table 1), there may not have been enough of a range between participants to observe relationships in this group. The lack of clear relationship between force pulse performance and function in PD was also unexpected. Others have found that scores on the UPDRS and KCRS were related to isometric force production and relaxation measures (6, 25), including a rapid isometric grip task (15). These rating scales, however, assess full body function and a wide range of PD symptoms, whereas the present grip based measures are based in the upper extremity. Even in the comparison between subgroups of people with PD with or without segmentation, mobility tests were not significantly different (Table 3). This suggests that the degree of handgrip impairment is not related to lower body function in this sample, that was medicated at the time of testing and relatively high function. Furthermore, when one uses correlation to explain the variance in Y with variance in X, there should be careful consideration of all possible sources of variance, which might be greater in number for the FSST in PD compared to OA and YA. Force pulse measures represent performance after a contraction or movement has been initiated. During the FSST, PD likely brings the additional sources of variance such as lower confidence, apprehension and impaired initiation,

especially with the backward steps where the line separating the quadrants is outside of the focal visual field. Thus, the force-pulse measures reported here are blind to delays that occur prior to movement initiation.

Regional differences may occur in some people with Parkinson's disease that affect the upper and lower extremity function differently. For example, tremor is caused by central not peripheral pathology (13), but it commonly occurs unilaterally in the upper extremity while it rarely occurs in the legs (12). This study tested the dominant or more affected hand of each participant with PD, which may not have been representative of full body function. Several participants had noticeable tremor that was restricted to the one side, and some mentioned that they use the more affected hand less since developing the tremor. Testing the more symptomatic side therefore may not have been the best indicator of lower body function. It is possible that a different model such as knee extension or elbow extension may be more helpful in understanding relationships between neuromuscular function and mobility. Testing the affected side, however, did allow us to document impairments due to the disease which were important to this line of investigation.

This study provided a comprehensive examination of force relaxation and segmentation in people with PD, and supports the use of a grip model to study force control in this population. Future research should evaluate the presence of tremor in participants with segmentation to determine its relationship, and assess the neural contributions to this impairment.

Conclusion

During rapid isometric force pulses, many people with PD exhibit prolonged force rise and relaxation times compared to healthy young and older adults. In this study, differences due to age and PD were greater for force relaxation measures than force development measures. In PD, these decrements in performance were related to an abnormal number of segments within the force pulses. Segmentation appears to be an important contributor to rate dependent function in PD, due to disruptions in neural drive to muscle. Further study should explore how it contributes to isometric and dynamic force control, as well as its prevalence in people with PD. Additionally, relaxation measures in rapid handgrip contractions were related to timed tests of function in OA, but not people with PD. This may indicate that relaxation impairments may be region-specific, and grip may not be a good method to assess lower body functional abilities.

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Table 1: Mean (standard deviation) maximal voluntary contraction (MVC) force and rapid force pulse measures in each group of 14 participants. The Kruskal-Wallace χ^2 statistic indicates significant ($p<.05$) group effects for all measures. See methods for variable names. Bold text identifies significance at the $p<.05$ level.

	Young Adults	**Older Adults**	**People with PD**	χ^2	**p**
MVC (N)	403.8 (100.4)	289.5 (138.9)	298.1 (123.8)	7.61	**0.022**
Pulse Duration (ms)	207.0 (23.6)	247.3 (45.3)	361.8 (119.6)	18.29	**<0.001**
TPF (ms)	96.3 (12.8)	107.5 (20.6)	158.2 (58.9)	12.89	**0.002**
FRT (ms)	110.7 (13.7)	139.8 (28.7)	203.6 (63.6)	21.22	**<0.001**
RFD_{pk} (%MVC•s^{-1})	434.4 (39.8)	420.4 (50.9)	354.4 (83.3)	11.29	**0.004**
RFR_{pk} (%MVC•s^{-1})	-395.4 (41.4)	-345.3 (51.4)	-297.1 (48.0)	19.42	**<0.001**
Seg_{up}	1.00 (0.00)	1.00 (0.01)	1.11 (0.15)	13.69	**0.001**
Seg_{down}	1.00 (0.00)	1.01 (0.02)	1.24 (0.28)	18.89	**<0.001**

Table 2: Post-hoc pairwise comparisons (Wilcoxon rank-sum test) between groups for maximal voluntary contraction (MVC) force and rapid force pulse measures. See methods for variable names. Bold text identifies significance at the p<.05 level.

	Young Adults vs. Older Adults		**Young Adults vs. People with PD**		**Older Adults vs. People with PD**	
	Z	**p**	**Z**	**p**	**Z**	**p**
MVC (N)	-2.53	**0.012**	-2.25	**0.024**	-0.138	0.890
Pulse Duration (ms)	-2.44	**0.015**	-3.68	**<0.001**	-2.94	**0.003**
TPF (ms)	-1.38	0.168	-3.22	**0.001**	-2.67	**0.008**
FRT (ms)	-2.85	**0.004**	-4.09	**<0.001**	-2.71	**0.007**
RFD_{pk} (%MVC•s^{-1})	-0.597	0.550	-3.12	**0.002**	-2.57	**0.010**
RFR_{pk} (%MVC•s^{-1})	-2.57	**0.010**	-4.09	**<0.001**	-2.39	**0.017**
Seg_{up}	-1.00	0.317	-2.96	**0.003**	-2.62	**0.009**
Seg_{down}	-1.80	0.072	-3.75	**<0.001**	-3.00	**0.003**

Table 3: Differences (Wilcoxon rank sum test) between segment-dominant and non-segment dominant people with PD in maximal voluntary contraction (MVC) force, mobility tests and rapid isometric force pulse measures. See methods for variable names. Bold text identifies significance at the p<.05 level.

	Segment Dominant PD	**Non-Segment Dominant PD**	**Z-Score**	**p (Adjusted for ties)**
N	8	6	--	--
% Pulses with >1 segment	36.8 (21.5)	2.0 (3.1)	-3.165	**0.002**
MVC (N)	275.2 (123.8)	328.5 (91.2)	-1.033	0.302
FSST (s)	8.49 (1.55)	8.04 (0.75)	-0.571	0.568
TUG (s)	7.78 (1.77)	7.68 (0.76)	-0.072	0.943
Pulse Duration (ms)	439.1 (93.3)	258.7 (52.1)	-2.97	**0.001**
TPF (ms)	194.5 (49.3)	109.7 (25.9)	-3.10	**0.001**
FRT (ms)	244.5 (46.7)	149.0 (34.7)	-2.84	**0.003**
RFD_{pk} (%MVC•s^{-1})	310.6 (43.2)	412.8 (91.0)	-2.45	**0.013**
RFR_{pk} (%MVC•s^{-1})	-271.1 (36.8)	-331.6 (45.3)	-1.94	0.059
Seg_{up}	1.19 (0.16)	1.01 (0.02)	-2.34	**0.029**
Seg_{down}	1.42 (0.24)	1.01 (0.02)	-3.13	**0.001**

Table 4: Spearman correlation coefficients (ρ) between timed tests of mobility and rapid force pulse measures across all groups (n=42). Correlations were generally greater in magnitude for force relaxation measures compared to force development measures. In the bottom six rows, thick borders indicate force development/relaxation variable pairs. See methods for variable names. Bold text identifies significance at the $p<.05$ level.

	FSST		**TUG**	
	ρ	**p**	**ρ**	**p**
MVC	-0.437	**0.005**	-0.304	0.06
Pulse duration	0.700	**<0.001**	0.571	**<0.001**
TPF	0.584	**<0.001**	0.454	**0.004**
FRT	0.743	**<0.001**	0.608	**<0.001**
RFD_{pk}	-0.500	**0.001**	-0.381	**0.017**
RFR_{pk}	0.718	**<0.001**	0.624	**<0.001**
Seg_{up}	0.478	**0.002**	0.484	**0.002**
Seg_{down}	0.593	**<0.001**	0.608	**<0.001**

Table 5: Spearman correlation coefficients (ρ) between timed tests of mobility and rapid force pulse measures in each group. Force segmentation was observed only in people with PD. See methods for variable names. Bold text identifies significance at the p<.05 level.

	Young Adults				**Older Adults**				**People with PD**			
	FSST		**TUG**		**FSST**		**TUG**		**FSST**		**TUG**	
	ρ	**p**	**ρ**	**p**	**ρ**	**p**	**ρ**	**p**	**ρ**	**p**	**ρ**	**p**
Pulse Duration	0.440	0.648	-0.140	0.648	0.791	**0.001**	0.593	**0.033**	0.126	0.681	0.014	0.964
TPF	0.610	**0.027**	-0.220	0.470	0.549	0.052	0.451	0.122	0.093	0.762	-0.047	0.879
FRT	0.401	0.174	-0.201	0.511	0.747	**0.003**	0.714	**0.006**	0.170	0.578	0.072	0.816
RFD_{pk}	-0.467	0.108	0.154	0.615	-0.489	0.090	-0.352	0.239	0.110	0.721	0.281	0.353
RFR_{pk}	0.181	0.553	-0.105	0.734	0.626	**0.022**	0. 626	**0.022**	0.297	0.325	0.228	0.453
Seg_{up}	--	--	--	--	--	--	--	--	0.197	0.519	0.266	0.379
Seg_{down}	--	--	--	--	--	--	--	--	0.301	0.318	0.181	0.553

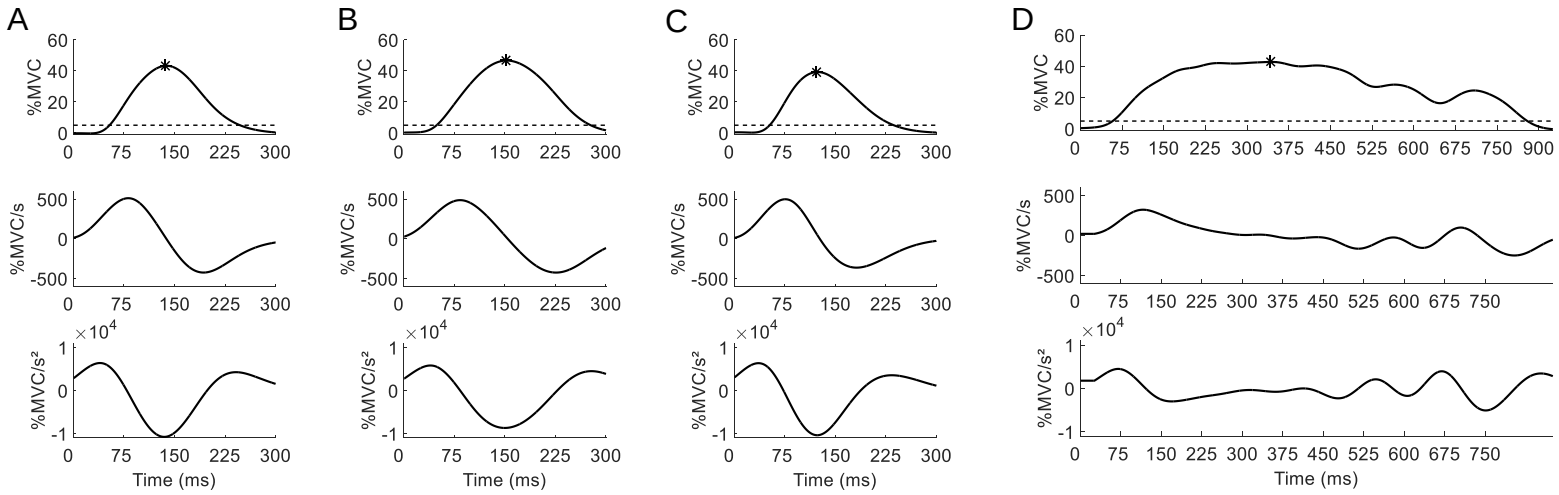

Figure 2 Example force pulses from A) one young adult B) one older adult C) a non-segment dominant person with PD and D) a segment-dominant person with PD. The top panel shows the force-time curve. The middle panel shows the first derivative of force curve. The bottom panel shows the second derivative of force curve. Force threshold is shown by the horizontal dashed line and peak force is indicated by a * in the top panel.

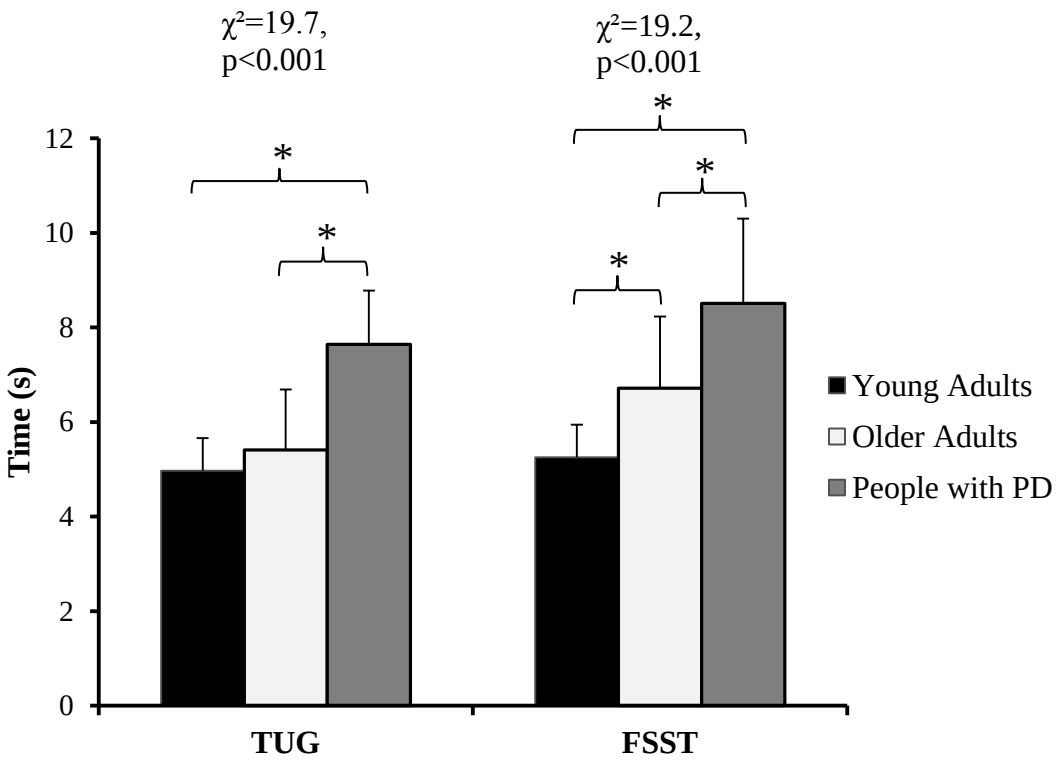

Figure 3 Timed up and go (TUG) and four square step test (FSST) performance in YA, OA, and PD. χ^2 values are from the Kruskal-Wallis test. * indicates a significant difference between groups at $p<0.05$. In each group, n=14, except for the FSST, in which only 13 people with PD performed the test.

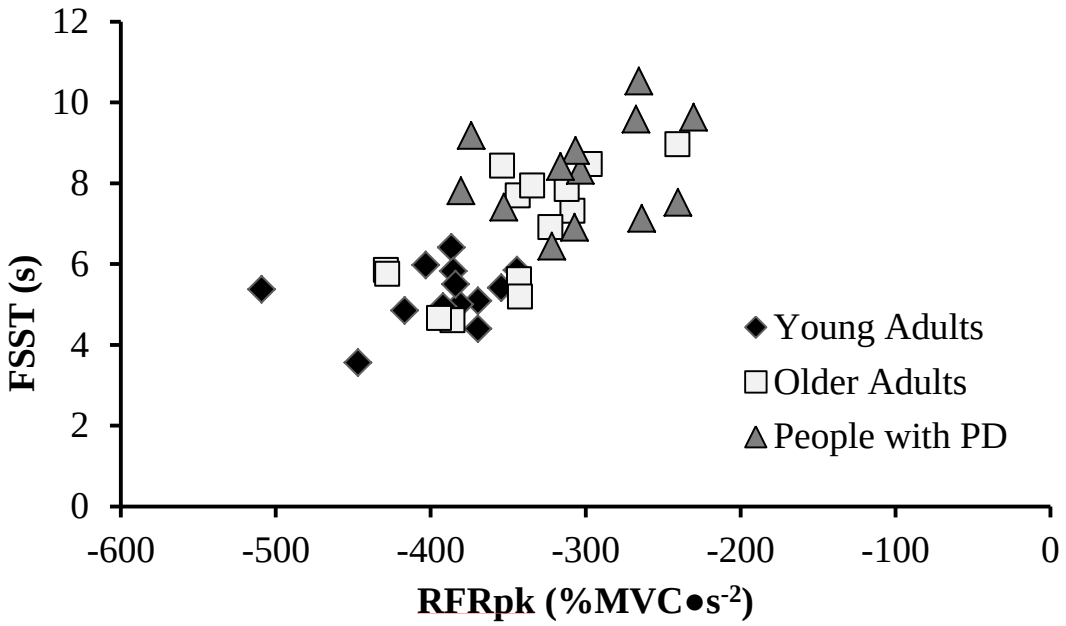

Figure 4 Relationship between average rate of force relaxation (RFR_{pk}) and four square step test (FSST) in YA (group 1), OA (group 2) and people with PD (group 3). The overall Spearman correlation was $\rho=0.714$, $p<0.001$. Within-group correlations were not significant for YA ($\rho=0.302$, $p=0.316$) or PD ($\rho=0.093$, $p=0.762$), but were significant for OA ($\rho=0.731$, $p=0.005$).

Chapter 3

DIFFERENCES IN MUSCLE ACTIVITY DURING CYCLING IN HEALTHY AGING AND PARKINSON'S DISEASE

Abstract

Muscle activity patterns in cycling are well studied in healthy young adults (YA) and trained cyclists. Stationary cycling provides a safe means to study coordination in older adults (OA) and people with Parkinson's disease (PD), yet little is known about the timing of muscle activity in these groups. Stationary cycling is also a commonly prescribed exercise modality in these populations. Aim 1 was to compare patterns of muscle activity among young adults (YA), OA and people with PD at increasing cadences. It was hypothesized that people with PD would exhibit less discrete bursts, evidenced by prolonged burst duration, compared to OA and YA, as well as greater EMG amplitudes. Aim 2 was to compare muscle activity measures during cycling to performance on mobility tests in people with PD. It was hypothesized that greater muscle duration and amplitude of muscle activity during cycling would be related to poorer mobility. Surface electromyograms (EMG) were recorded from the vastus lateralis (VL), medial gastrocnemius (MG), biceps femoris (BF), soleus (SO), tibialis anterior (TA), and rectus femoris (RF) of the dominant leg during recumbent bicycling in 40, 60, 80, 100 and 120 revolutions per minute (rpm) conditions at the lowest resistance setting. EMG was normalized to the peak EMG during the 60 rpm

condition in each muscle and a 4rth order low pass Butterworth filter with a cutoff of 7 Hz was used to create linear envelopes. From the ensemble of five revolutions, the timing of EMG burst onset and offset and burst duration were calculated in relation to top dead center in each speed condition. People with PD performed the three meter timed up and go (TUG) and four square step test (FSST). Cadence effects were observed in burst duration of all muscles ($p<0.001$), and activation increased with increasing speed due to increased amplitude and duration. People with PD had greater activation in VL and RF compared to YA and OA. YA had greater BF and TA activation than OA and PD. Additionally, duration and amplitude of muscle activity in VL were positively correlated to times on the TUG and FSST in people with PD. These results suggest that increased activation in the knee extensors during cycling alter muscle activity patterns in people with PD, and negatively affect mobility.

Introduction

Recumbent bicycling is a commonly prescribed exercise modality for both healthy adults and populations that have poor postural control or balance such as some older adults (2) (OA) and people with Parkinson's disease (PD) (6, 20). In healthy young adults, the cycling motion is achieved by discrete bursts of muscle activity during specific times in the pedaling cycle. In healthy aging, a decrease in lower peak power has been observed (16). These decreases in peak power are related to lower muscle activation during cycling in OA, likely due to a decrease in the number of active motor units or discharge rate (9). Although not many differences have been

found in the average amplitude of EMG bursts between healthy OA and YA during cycling, OA may have greater alterations in EMG amplitude with increasing cadence than YA (4). It is still unknown whether healthy aging also contributes to differences in onset and offset timing of muscle activity bursts.

PD may add additional challenges beyond aging to the pedaling motion. During cycling-based exercise interventions conducted in our lab, several participants with PD had greater difficulty keeping their feet on the pedals, even with the use of foot straps, and particularly at faster cadences. These observations led us to consider whether inappropriate timing of muscle activity produces resultant force vectors at the pedal that are incompatible with the cycling motion. Despite these perceived difficulties while performing the movement and the frequent use of this modality during exercise interventions, very little research has investigated the muscle activity patterns during cycling in PD. However, investigations of walking gait, a similar rhythmic bipedal motor task, have revealed that people with PD have altered muscle activation patterns compared to healthy older adults (OA). These differences include altered magnitude, durations, onset and offset timing of bursts, as well as increased co-activation (5, 7, 8, 15), which contribute to difficulties in gait in this population. The stationary bicycling modality may provide a means to examine the altered muscle activation patterns in people with PD with specific advantages over gait studies because faster movements can be achieved, the confounding influence of balance is minimized and bodyweight loading is minimal.

Therefore, the first aim of this study was to determine differences in muscle activity patterns during recumbent cycling between young adults, older adults, and people with PD at increasing pedaling cadences against low resistance. It was hypothesized that people with PD would have greater EMG burst durations and peak amplitudes as well as different timing characteristics than both old and young adults, and these group differences would become more exaggerated with increasing cadences. The second aim was to determine whether the measures of muscle activation during bicycling in people with PD are correlated with performance on timed tests of mobility. It was hypothesized that greater burst durations and overall muscle activity would be related to poorer performance on mobility tests.

Methods

Participants

Fifteen young adults (23.3 ± 3.1 years old, 1.75 ± 0.06 m tall, 73.4 ± 8.9 kg, 24.0 ± 2.7 $kg \bullet m^{-2}$, 4 females), 15 healthy older adults (69.0 ± 7.8 years old, 1.73 ± 0.10 m tall, 80.8 ± 17.5 kg, 26.9 ± 4.1 $kg \bullet m^{-2}$, 6 females) and 15 people with PD (70.7 ± 7.1 years old, 1.75 ± 0.09 m tall, 86.9 ± 15.6 kg, 28.4 ± 4.8 $kg \bullet m^{-2}$, 4 females, Hoehn-Yahr stage 1-3, disease duration 7.3 ± 5.7 years) were recruited into this study. None of the participants had participated in speed-based cycling exercise for at least three months prior to testing, but 13 of the people with PD were involved in some form of exercise program, as well as 10 of the OA and 12 of the YA. Participants

signed an informed consent document that was approved by the Institutional Review Board.

Data Collection

Cycling

Surface electromyograms were recorded from the rectus femoris (RF), vastus lateralis (VL), biceps femoris (BF), tibialis anterior (TA), soleus (SO), and medial gastrocnemius (MG) muscles of the dominant leg. A common reference electrode was placed on the bony site at the distal end of the ulna on the same side of the body. Electrode placement was located according to SENIAM guidelines and prepared by shaving, abrading and cleaning the skin (10). MA-411 EMG double differential preamplifier electrodes (Motion Lab Systems, Baton Rouge, LA, USA) were affixed to each site parallel to the reported orientation of muscle fibers (10). Recordings were digitized at 2000 Hz (cDAQ-9178, module NI-9239, National Instruments, Austin, TX, USA) and bandpass filtered between 30 Hz and 3 kHz with amplification adjusted to optimize the resolution of the signal within a 10 V range (MA-300 EMG system, Motion Lab Systems). DASYlab software (Measurement Computing Corporation, Norton, MA, USA) was used to control the digitization of the signal.

Participants pedaled on a stationary recumbent bicycle (RT2 G3, Monark, Sweden, EU). The recumbent model was chosen for safety concerns with adults with PD, who may have difficulties mounting the ergometer and maintaining an upright posture during testing. The ergometer was set at the lowest resistance setting, and seat location was adjusted so that the subject's knee was positioned at approximately five

degrees of flexion when the pedal was at the greatest distance from the body. A magnet-activated switch on the right side of the pedal crank was used to provide an event marker at top-dead-center (TDC) that was synchronized with the EMG recordings and also used to provide feedback of cadence in revolutions per minute (rpm). One complete cycle was bounded by consecutive event markers identifying TDC and cadence was calculated as the number of cycles per unit time. Cadence conditions of 40, 60, 80, 100, and 120 rpms were used to represent a range of slow to fast cadences. The cycle ergometer reported that cadence conditions corresponded to 41.9 W, 64.9 W, 87.8 W, 110.8 W, and 133.7 W of power, respectively.

Subjects were given visual feedback of their pedaling speed on the bike monitor, and were asked to maintain a given cadence for approximately 10 seconds so that 5 revolutions could be collected for analysis. The participants were given as much rest as they required in between each trial to minimize fatigue. After the trials, participants were asked to pedal as quickly as they could to determine their maximum pedaling cadence (RPM_{max}).

Functional tests

Participants performed the four square step test (FSST) and the three meter timed up and go (TUG) as done by Uygur et al (21). After a practice trial, participants performed two trials of each test "as quickly and safely as possible". The fastest time was used for analysis.

Data Processing

LabVIEW software (National Instruments) was used to analyze the EMG records. EMG was demeaned, rectified, and filtered with a 4th order zero-lag Butterworth filter with a cut-off frequency of 7 Hz (1). Average curves were created from five consecutive cycles that were within 3 rpm of the desired speed condition. EMG amplitude was then normalized to the peak EMG amplitude from the 60 rpm condition. Dependent measures were calculated from the average curves for each participant, muscle and speed combination.

The total integral was calculated over the 360 degree cycle (Figure 10), and normalized to the peak EMG during the 60 rpm condition. The percentage of degrees in the cycle that was greater than 50% of peak EMG during the 60 rpm condition was also calculated (Figure 11). To study timing characteristics within each muscle, burst onset and offset times were determined based on a threshold set at 35% of the peak EMG amplitude recorded during the 60 rpm condition. The 60 rpm condition was chosen because it could be performed by all individuals. Burst duration was the difference between onset and offset values. Consistent with the literature, burst onset (ON), offset (OFF) and duration are reported in degrees relative to top dead center (Figure 12). Accordingly, a burst with a greater duration (angular excursion) may actually have a shorter duration in units of time, at the greater cadences. Normalized peak EMG amplitude is also reported as %EMG60. When multiple bursts occurred in close proximity within a single revolution, OFF was specified as end of the last burst similar to Sarre et al (18).

Statistical Analysis

SPSS 24.0 was used to perform statistical tests. A one-way analysis of variance was used to test for differences in maximum pedaling speed between the groups. A three (group) by five (cadence) ANOVA with repeated measures on cadence was used to test for differences between groups and cadence conditions. In the presence of a significant interaction, tests of simple main effects were performed and post hoc (pairwise) comparisons were made with a Bonferroni correction to account for experimentwise error rates. Pearson correlations were used to quantify relationships between cycling measures and performance on mobility tests. An alpha level of 0.05 was the threshold for significance for all statistical tests.

Results

Due to technical difficulties with EMG electrodes, BF was not collected from one participant with PD. Five participants in the OA group were unable to reach the 120 rpm speed condition. Additionally, ten in the PD group were unable to perform the 120 rpm speed condition. One participant with PD was unable to complete any condition above 60 rpm. For one representative subject in each group, linear envelopes for VL at the different cadences can be seen in Figure 6.

Maximum Pedaling Speed

Older adults ($p<0.001$) and people with PD ($p<0.001$) had slower maximum pedaling cadence than YA. People with PD had slower maximal pedaling cadence than older adults ($p<0.001$) as seen in Figure 5.

Total Activation

A significant group by cadence interaction was found in VL integral ($F=4.75$, $p<0.001$), in which people with PD had greater increases VL integral in the 120 rpm condition compared to the people in the YA or OA groups. Integrals increased as cadence increased in VL ($F=136.97$, $p<0.001$), BF ($F=45.48$, $p<0.001$), SO ($F=43.83$, $p<0.001$), TA ($F=21.42$, $p<0.001$), MG ($F=67.28$, $p<0.001$), and RF ($F=29.48$, $p<0.001$). People with PD had greater integrals than OA and YA in VL ($F=17.01$, $p<0.001$) and greater integrals in RF compared to OA ($F=3.15$, $p=0.045$). YA had greater integrals in BF ($F=4.74$, $p=0.01$) and TA ($F=3.06$, $p=0.049$) compared to PD.

There were no significant interactions between group and cadence for the percent of the cycling revolution that EMG was above 50% of EMG_{60} (%act, all $F<1.0$, $p>0.70$). Increasing cadence increased %act in VL ($F=159.53$, $p<0.001$), BF (72.40, $p<0.001$), SO ($F=38.43$, $p<0.001$), TA ($F=43.15$, $p<0.001$), MG ($F=65.38$, $p<0.001$), and RF ($F=34.12$, $p<0.001$). OA and people with PD had higher %act in VL ($F=7.645$, $p=0.001$) than YA, and PD had higher %act in SO than YA ($F=4.01$, $p=0.019$). People with PD had lower %act in BF than YA ($F=4.49$, $p=0.012$).

Burst Duration, Onset and Offset Timing

A significant group by cadence interaction was found for VL burst durations ($F=2.11$, $p=0.037$), in which PD had longer burst durations than YA in the 120 rpm condition. Cadence effects were significant for burst durations in VL ($F=79.01$, $p<0.001$), SO ($F=21.32$, $p<0.001$), BF ($F=18.50$, $p<0.001$), TA ($F=51.38$, $p<0.001$),

MG ($F=30.45$, $p<0.001$), and RF ($F=35.61$, $p<0.001$), where burst durations increased as speed increased for all muscles. Burst durations were longer in people with PD than YA in VL ($F=16.13$, $P<0.001$), and RF ($F=4.27$, $p=0.015$). YA had longer burst duration in BF than OA and PD ($F=4.57$, $p=0.011$).

There were no significant interactions between group and cadence for the timing of EMG ON (%act, all $F<1.40$, $p>0.20$). ON timing occurred earlier with increasing speeds in VL ($F=24.48$, $p<0.001$), BF ($F=6.40$, $p<0.001$), SOL ($F=3.37$, $p=0.011$), TA ($F=13.08$, $p<0.001$), MG ($F=7.23$, $p<0.001$), and RF ($F=27.66$, $p<0.001$). ON timing occurred earlier in SO in PD and OA compared to YA ($F=4.83$, $p=0.009$).

A significant group by cadence interaction was found for RF OFF timing ($F=2.04$, $p=0.044$), in which PD had later OFF times than YA or OA at 100 and 120 rpm conditions. Cadence effects were seen in OFF timing for VL ($F=6.40$, $p<0.001$), MG ($F=2.44$, $p=0.048$), RF ($F=3.10$, $p=0.017$), and SO ($F=5.66$, $p<0.001$), with OFF times occurring later with increasing speeds. OFF timing occurred earlier in OA for BF compared to YA ($F=6.68$, $p=0.002$) and later in PD in RF ($F=6.53$, $p=0.002$) compared to OA and YA. OA had earlier off times in TA ($F=4.29$, $p=0.015$) and MG ($F=6.35$, $p=0.002$) than YA.

Peak EMG Amplitude

A significant group by cadence interaction was found for peak EMG amplitude in VL ($F=5.69$, $p<0.001$), in which PD had a greater increase in peak EMG at 120 rpm

than YA or OA. Peak EMG amplitude increased with increasing speed in VL ($F=110.66$, $p<0.001$), RF ($F=15.58$, $p<0.001$), MG ($F=87.89$, $p<0.001$), TA ($F=21.09$, $p<0.001$), SO ($F=40.71$, $p<0.001$), and BF (40.42, $p<0.001$). People with PD had greater peak EMG in VL ($F=8.35$ $P<0.001$) and RF ($F=5.32$, $p=0.006$) than OA and YA.

Correlations with Mobility Tests

One subject with PD was excluded from correlations due to additional orthopedic limitations that impaired their ability to perform the test. Measures from the VL during the 60 rpm condition were chosen for the analysis of correlations with mobility tests since it showed the greatest differences between OA and YA, had generally larger effect sizes (based on F-values) compared to other muscles, and included complete data in all PD participants. FSST performance was highly correlated to VL burst duration ($r=0.874$, $p<0.001$) (Figure 9), and VL integral ($\rho=0.881$, $p<0.001$). TUG performance also had strong relationships with VL burst duration ($r=0.783$, $p<0.001$) (Figure 9) and VL integral ($r=0.757$, $p<0.001$).

Discussion

The primary aim of this study was to compare muscle activity patterns between YA, OA and people with PD across increasing pedaling cadences. Based on observed difficulties with the direction of force application on the pedal in PD we hypothesized that people with PD would have greater burst durations and peak amplitudes as well as

different timing characteristics than both old and young adults, and these differences would become more exaggerated with increasing speeds.

In terms of absolute performance, YA had greater maximal pedaling cadence than OA and PD, and people with PD had a slower maximum cadence than OA. This was not surprising since YA are known to produce greater maximal power output than OA (16). Significant group by cadence interaction effects were found in the burst duration, peak EMG and total integral of the VL muscle, as well as OFF timing in the RF muscle, with greater separation of the PD group at 120 rpm. Additionally, that 10 of 15 people with PD were not able to complete the 120 rpm condition is indirect evidence of a group by cadence interaction in their performance. It is possible that these individuals with PD were unable to reach the fastest cadence condition because burst durations in VL became too long. Inappropriate durations of muscle activation could increase co-activation with antagonist muscles, as well as causing an incorrect direction of force application to stay in line with the path of the pedals. Prolonged knee extensor activation could prevent the knee from flexing quickly enough in the cycle to reach the fastest pedaling speed. It is possible that burst duration has an upper limit that limits the maximum pedaling speed. Since people with PD had longer burst durations in the knee extensors than OA or YA, they may have reached their maximum capacity at a lower speed than the other groups. The large increase in peak VL amplitude was likely due to the fact that the 120 rpm condition was a much higher percentage of maximum effort for the people with PD than YA or OA.

Overall, muscles turned on earlier in the cycle as cadence increased, resulting in longer burst durations and greater measures of total activation in all groups. These increases in burst duration and earlier onset timing are consistent with the existing literature in healthy adults, although they occurred in more muscles in the current study than previous investigations (1, 3, 12, 17), and some discrepancies have been observed likely due to methodological differences (13). The present methods may have been more sensitive to changes with increasing cadence because EMGs were normalized to a condition (60rpm, 65 W) that would likely require a lower level of activation than previous in studies.

Others have hypothesized that EMG onset occurs earlier with increasing speeds in order to contribute to peak net force at the same position in the crank cycle (11, 12, 14). Assuming a constant electromechanical delay, the onset of muscle activity would have to occur at an earlier angle to trigger the same motor response, as the time of a single revolution decreases as speed increases (11). Our results in duration and ON/OFF timing, however, are not the same as absolute time. For example, an 80 degree burst at 40 rpm would last a third of a second, whereas the same 80 degree burst at 120 rpm would last only a ninth of a second. A measure of excursion was used to quantify duration instead of time to better compare the muscle's behavior over one revolution across speeds. Even though duration in degrees increased with increasing cadence, the time for each burst to occur decreased.

OA generally did not exhibit the hypothesized differences from YA in this study aside from a greater total activation (%act) in VL. OA had a lower %act and

duration of BF activity in OA compared to YA, as well as some differences in ON and OFF timing in the BF, TA, SO, and MG. In a previous study by Buddhadev & Martin, the only difference due to age in average EMG activity was increased activity in the MG (4). Furthermore, in their study , average VL and BF activation were not different in YA versus OA, but age by cadence interaction effects were present in VL and BF. Average BF activity decreased with increasing cadence in YA, while it increased in OA. Additionally, TA had no differences in average activity due to age (4). Although the previous study found differences in an EMG amplitude measure, results in the current study only support age-related differences in timing duration variables. The discrepancies in findings could be due to methodological differences, including differences in measures reported, a constant and higher power used in the previous study, and normalization from a lower power condition in the current study (65 W at 60 rpm) versus the previous study (125 W at 90 rpm). In the BF specifically, normalization difficulties occurred in YA, since many YA did not have discernable bursts in the BF until higher pedaling cadences, likely due to the low resistance. Thus, using the 60 rpm condition for normalization caused activation at higher speeds to appear uncharacteristically longer in duration. Although normalizing to a higher rpm condition would have been preferred, the 60 rpm condition was chosen since it was the highest speed condition all subjects were able to successfully achieve. Overall, however, in both the previous and current studies, few differences existed in cycling muscle activity due to age.

People with PD had more differences in muscle activity than were found due to aging alone. These included longer durations and greater total integrals in the VL, and RF compared to YA, as well as increased %act in VL and SO, and increased peak EMG in VL and RF. Despite this, there were very few differences in timing variables. Similarly, gait studies have shown that people with PD have increased amplitude and prolonged activation of the proximal leg muscles during walking (8, 15). In gait literature, distal leg muscles have similar timing of activation but a lower amplitude in people with PD as compared to age-matched controls (8, 15). Although there were some differences in timing of the SO, amplitudes were not different in people with PD. TA had lower total integral in people with PD than YA. Gait studies have also found that the TA has lower amplitudes of muscle activity in people with PD compared to healthy adults (5, 7, 8). Despite these similarities, the current investigation still found fewer differences in people with PD compared to healthy participants than seen in previous gait studies. Gait and bicycling are both tasks that require performance of rhythmic alternating leg movements. However, cycling is a more constrained movement that requires considerably less weight bearing and is easier to maintain balance compared to gait (4). Even in healthy adults, differences in muscle activity exist between cycling and walking (19). Often people with PD who have severe impairments in gait are still able to bicycle, which could be due to differences in the required amount of sensory-spatial and motor planning as well as muscular demands (19). Thus, it is not surprising that fewer differences between PD and OA were found in the current cycling study than previous investigations using

gait. The participants with PD in this study were also a highly active sample, which could contribute to fewer differences seen from OA.

The second aim of the present study was to determine the relationships between measures of activation in the VL in people with PD to performance on the FSST and TUG. It was hypothesized that increased burst duration and overall activation would be related to poorer performance on mobility tests. The relationships found were very strong (Figure 9). In YA and OA, VL activity was not related to mobility performance ($\rho<0.51$, $p>0.05$). This may indicate that patterns in knee extensor activation are more indicative of impairment during activities of daily living for people with PD than OA or YA. Interestingly, the movement speed at 60 rpm may be comparable to stride rate for people with PD compared to OA or YA. It further supports that the findings found in cycling were similar to those found in gait.

The novelty of the present study is that it provides a comprehensive description of muscle activity patters during stationary cycling in YA, OA, and people with PD. The inclusion of the three groups provides the opportunity to consider the effects of aging and disease separately and the results address a significant gap in the literature. This study found that people with PD have prolonged knee extensor activity, lower maximum pedaling speeds and strong relationships between knee extensor activation measures and mobility. These findings suggest that inappropriately prolonged knee extensor activation during cycling may impair function in this population. Future research should investigate whether this difference still exists when comparing muscle

activity during maximal pedaling cadences between healthy adults and people with PD.

Conclusion

People with PD had poorer absolute performance and greater duration and amplitude of muscle activation during each cycling revolution than YA and OA in the knee extensors. Inappropriate durations of muscle activity in people with PD may adversely affect the direction of force application during the cycle, making pedaling at high speeds more difficult in this population. Additionally, increases in knee extensor activation in people with PD were similar to those seen in other gait studies, and strong relationships between knee extensor activation measures in cycling and mobility test performance indicate that impairments seen in cycling may be related to the ability to perform activities of daily living in people with PD.

Acknowledgments

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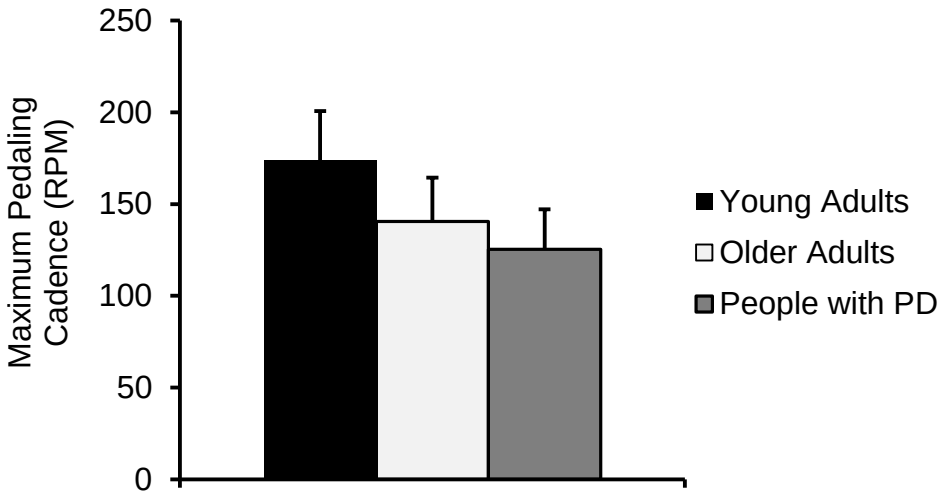

Figure 5 Young adults had a higher maximum pedaling cadence than older adults and people with PD. People with PD had a slower maximum pedaling cadence than OA. Group differences were significant at $p<.05$.

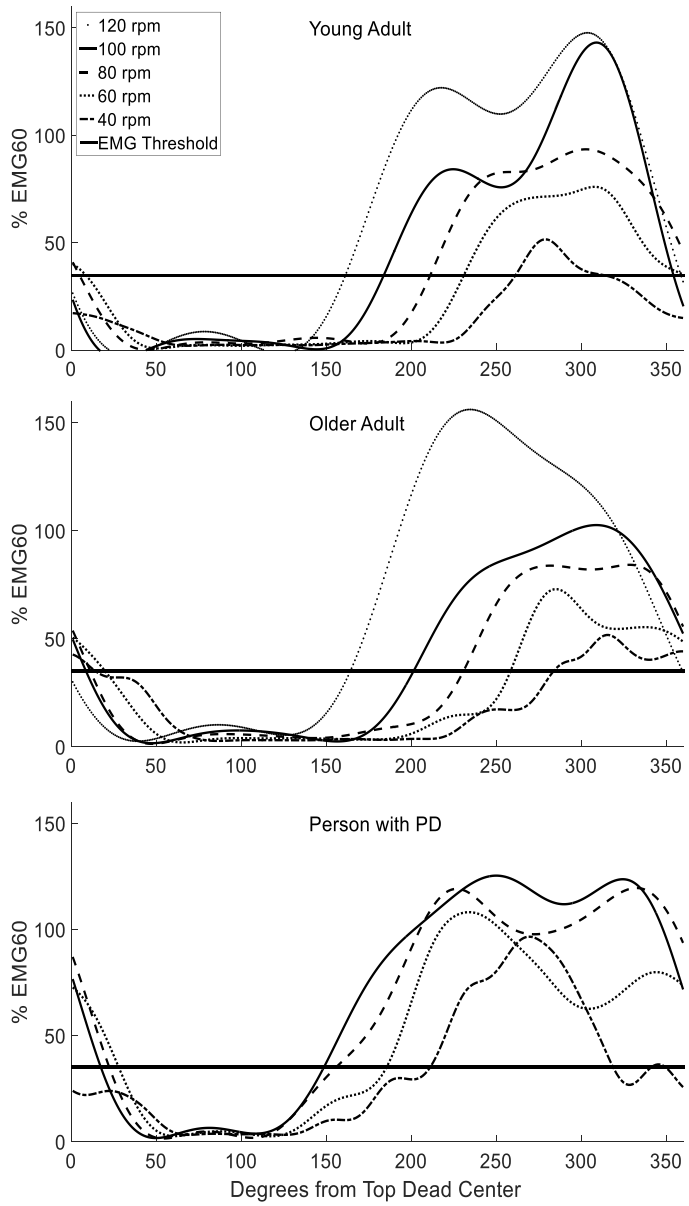

Figure 6 Representative averages of smoothed EMG records calculated for five cycles in each cadence condition for the vastus lateralis muscle in a young adult, an older adult and a person with PD. Zero degrees indicates top dead center. The 120 rpm condition is not shown for the PD group because 10 of the 15 participants in this group could not achieve this cadence.

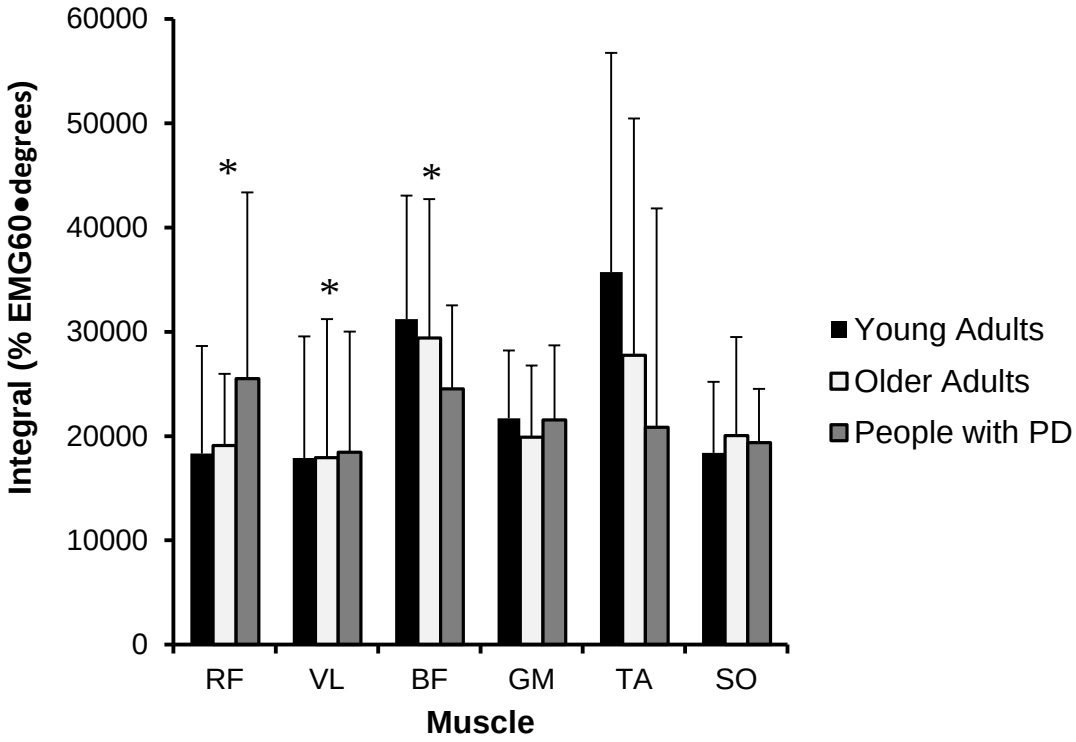

Figure 7 EMG integral calculated over complete revolutions during the 100 rpm condition. Significant overall group effects are noted by * at $p<0.05$.

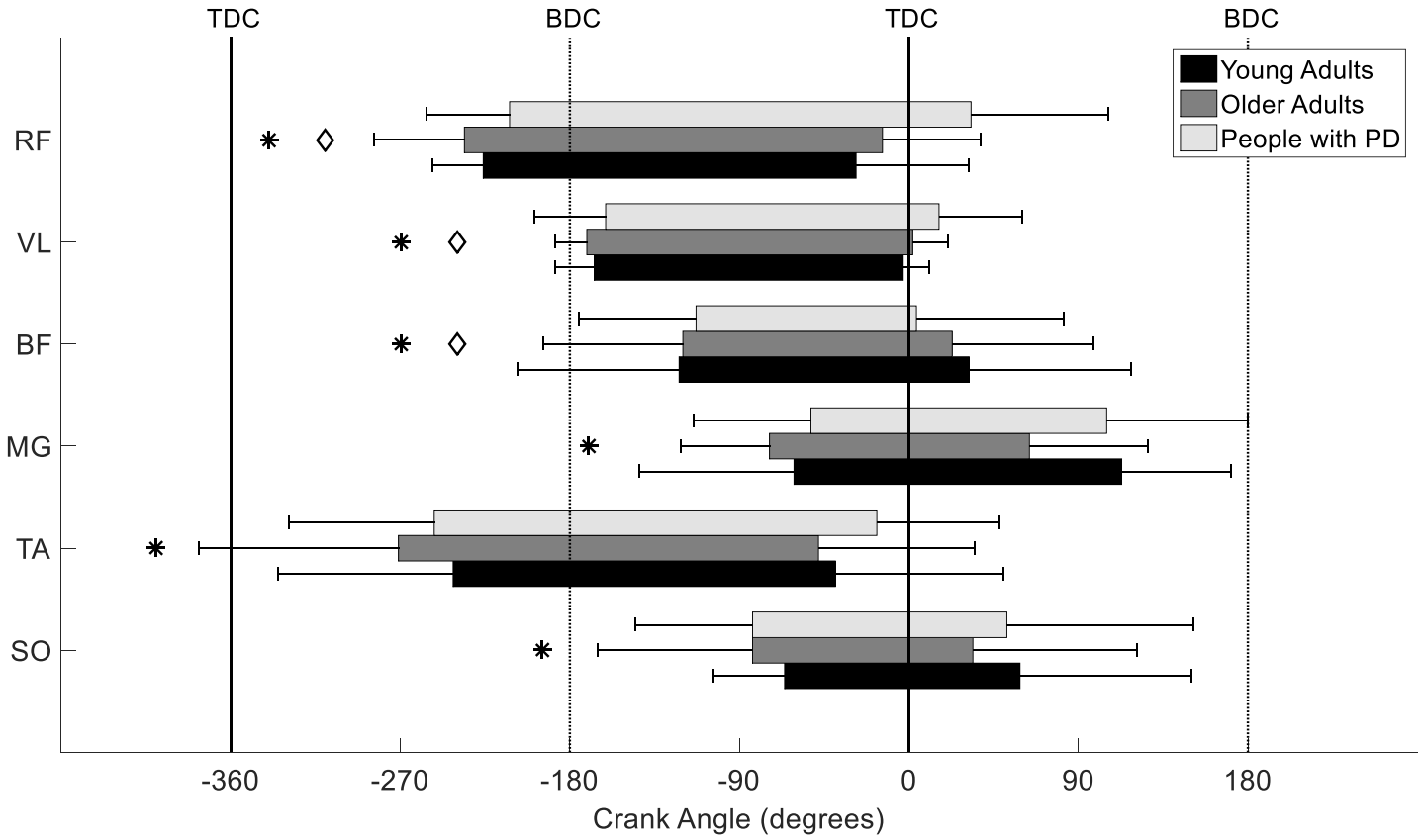

Figure 8 Average onset, offset and duration of EMG bursts from linear envelopes across groups during the 100 rpm cadence condition. * represents a significant cadence effect and ◊ represents a significant group effect for burst durations at $p<0.05$. BDC indicates the location of bottom dead center, and TDC indicates top dead center within the cycle.

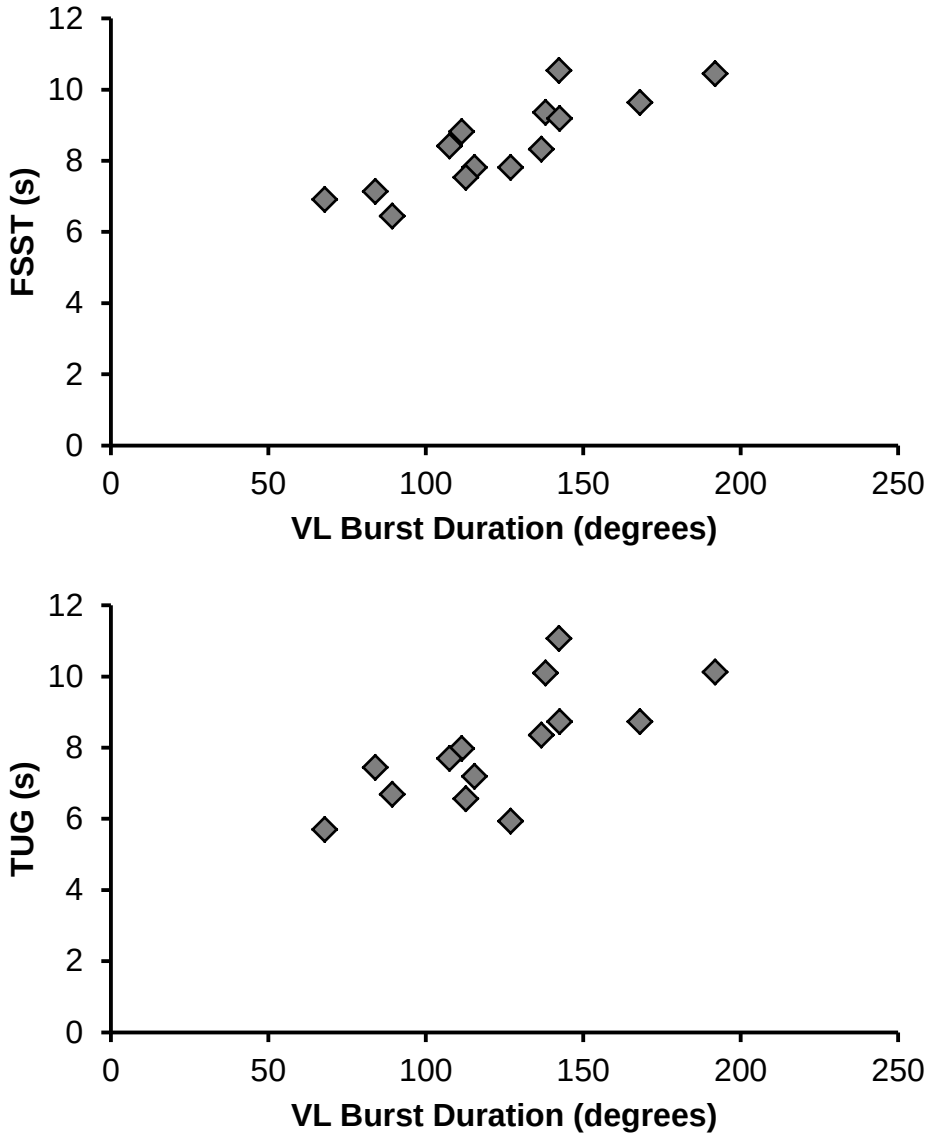

Figure 9 A) Burst duration in the vastus lateralis was correlated to performance on the four square step test (FSST) in people with PD (n=14). Pearson's correlation coefficients were strong. B) Burst duration in VL was correlated to timed up and go (TUG) performance in people with PD (n=14).

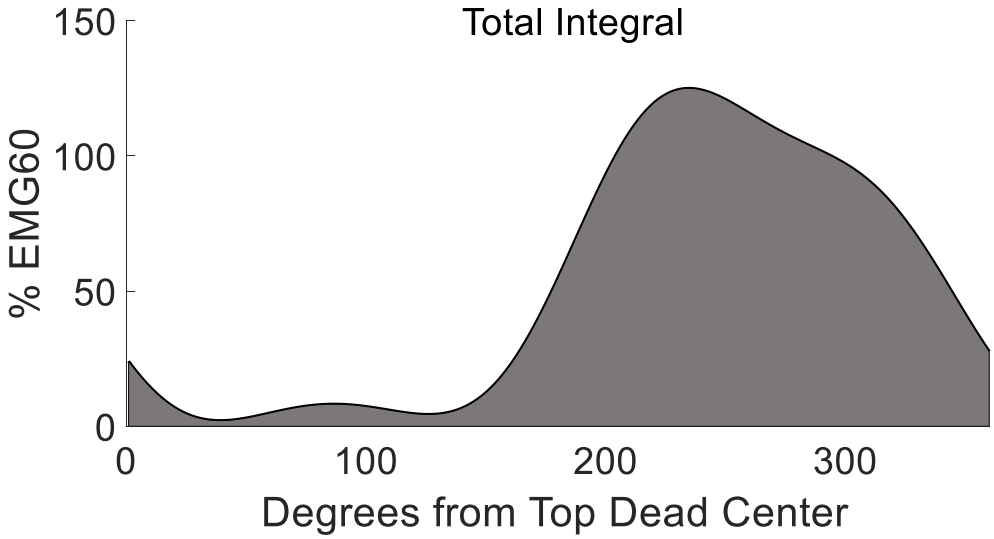

Figure 10 Total integral was calculated over the 360 degree cycle, indicated by the shaded gray area.

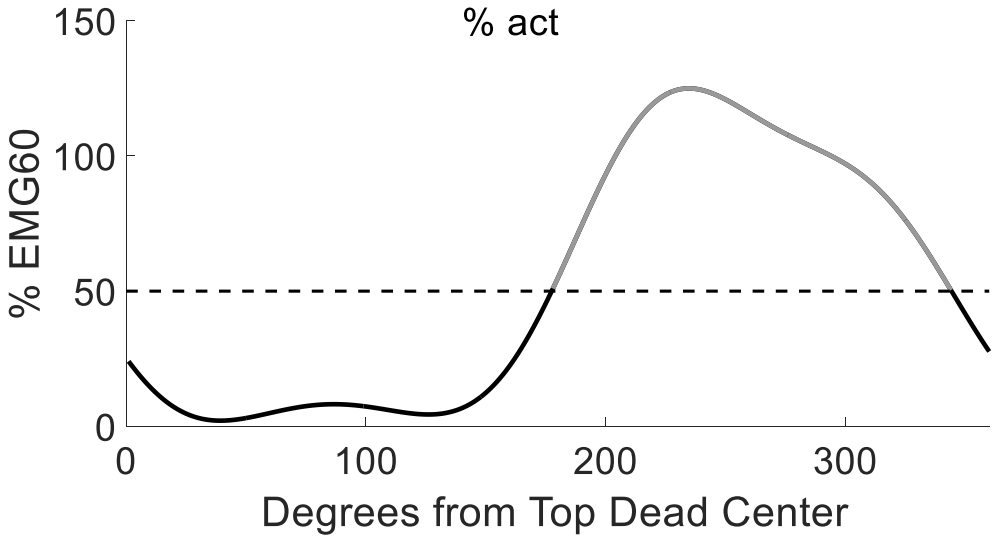

Figure 11 The percentage of points over 50% of peak EMG during the 60 rpm condition was calculated, indicated by the gray curve over the dotted line in this figure.

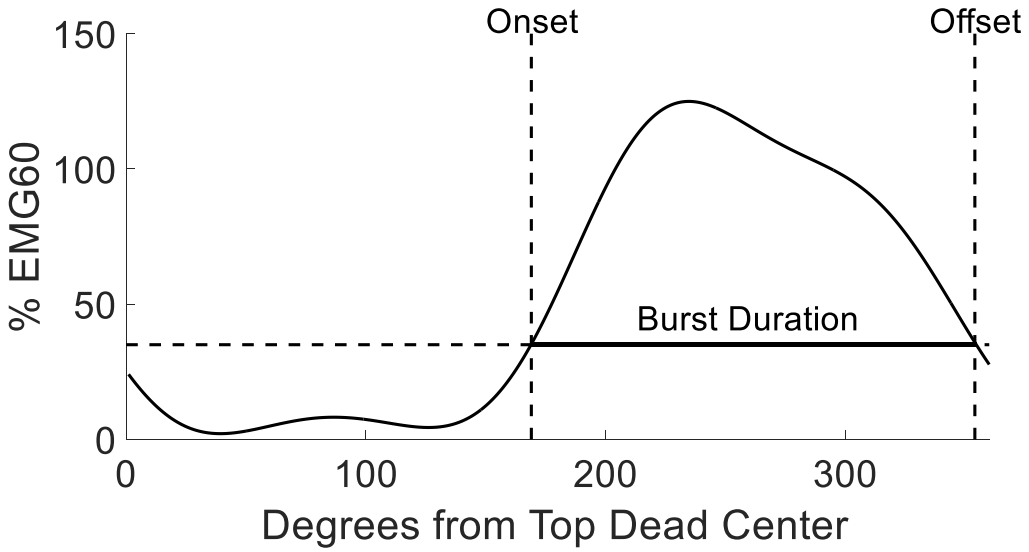

Figure 12 Burst duration, onset, and offset variables. The horizontal line indicates the threshold set at 35% of the peak EMG during the 60 rpm condition. Vertical dotted lines indicate onset and offset times, where the EMG curve crosses the threshold. Burst duration is indicated by the solid black line between onset and offset.

Appendix A

INSTITUTIONAL REVIEW BOARD APPROVAL LETTER

UNIVERSITY OF DELAWARE
RESEARCH OFFICE

210 Hullihen Hall
University of Delaware
Newark, Delaware 19716-1551
Ph: 302/831-2136
Fax: 302/831-2828

DATE:	January 23, 2018
TO:	Christopher Knight, PhD
FROM:	University of Delaware IRB
STUDY TITLE:	[681895-5] Neural determinants of quickness: aging, Parkinson's disease and exercise.
SUBMISSION TYPE:	Amendment/Modification
ACTION:	APPROVED
APPROVAL DATE:	January 23, 2018
EXPIRATION DATE:	November 18, 2018
REVIEW TYPE:	Expedited Review
REVIEW CATEGORY:	Expedited review per 45 CFR 46.110(b) (2)

Thank you for your submission of Amendment/Modification 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 Expedited 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 all 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.