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Can a Power Training Program Reduce Fall Risk Factors in Parkinson's Disease?

Brittany Intzandt
Concordia University, Montreal, Quebec, Canada, bnintzandt@gmail.com

CAN A POWER TRAINING PROGRAM REDUCE FALL RISK FACTORS IN PARKINSON'S DISEASE?

Brittany N. Intzandt

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Abstract

Introduction: Frequent falls in Parkinson's disease (PD) are likely partially due to impaired muscle function in PD (i.e. greater coactivation and decreased magnitude of activation in agonists) compared to older adults without PD. Reduced muscle strength and power (ability to generate force rapidly) are also risk factors and are likely occurring due to deficits in muscle parameters. Muscle parameters include: i) the amount of coactivation of antagonist muscles; ii) latency to onset of activation in agonist and antagonist muscles and; iii) the magnitude of activation of agonist and antagonist muscles. Rehabilitation should aim to improve impaired muscle parameters to reduce fall risk in PD. Therefore, two experiments were designed to address this gap in PD literature. Experiment one aimed to identify specific muscle parameters distinguishing fall status in PD, thus providing parameters that can be used to identify if a rehabilitation will be effective in reducing fall risk. Experiment two investigated whether power training (PWR) was more effective than strength training (ST) or a non-exercise control group (CTRL) at improving muscle parameters distinguishing fallers in experiment one. **Methods:** ***Experiment one*** - Forty-six individuals with PD were categorized based on fall status. A fall-like situation (lean and release) was used and electromyography (EMG) data was collected from muscles in both legs (stepping and stance leg): tibialis anterior (TA), lateral gastrocnemius (LG), biceps (BF) and rectus femoris (RF). **Results:** A Receiver Operating Characteristic (ROC) curve identified fallers vs. non-fallers by EMG measures in the stepping leg; an increased onset latency of LG and a greater TA activation. As well, in the stance limb, an increased coactivation of TA and a larger TA activation identified fallers. ***Experiment two***- Forty-four individuals with PD were randomized to PWR or ST groups, and seventeen individuals with PD volunteered for the CTRL group. Training occurred twice weekly for 12-weeks, where PWR completed the

concentric part of the movements rapidly. All groups completed the fall situation (at baseline, one to two weeks prior to the intervention, and one to two weeks after the intervention was complete) while muscle parameters were measured along with muscle strength and muscle power, disease severity and a weekly falls diaries. **Results:** No differences in muscle parameters were present at post-testing between groups. However, PWR and ST significantly improved muscle strength, and components of muscle power compared to CTRL. Disease severity was improved in PWR at post-testing. **Conclusion:** Muscle parameters distinguishing PD fallers were identified. As well, PWR and ST improved aspects of risk factors for falls similarly, providing two feasible rehabilitation strategies for PD.

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Chapter 1: Literature Review

Overview of Parkinson's disease

Parkinson's disease (PD) is a chronic neurodegenerative disease caused by a loss of dopaminergic neurons within the substantia nigra pars compacta of the basal ganglia (*Figure 1*). A reduction in dopaminergic neurons in PD causes underactivity of the direct pathway and over activation of the indirect pathway, resulting in a large inhibitory signal from the output nuclei of the basal ganglia. This creates tonic inhibition of the thalamus and ultimately a reduction in the amount of excitation from the motor cortex [1] (*figure 1*). Tonic inhibition of these cortical and subcortical areas results in the cardinal symptoms of PD: resting tremor, rigidity, akinesia and/or bradykinesia, as well as postural instability. Impairments in balance and muscular strength [2] are also experienced. The current standard treatment to address symptoms is dopaminergic therapy [3], unfortunately it does not address all of the symptoms.

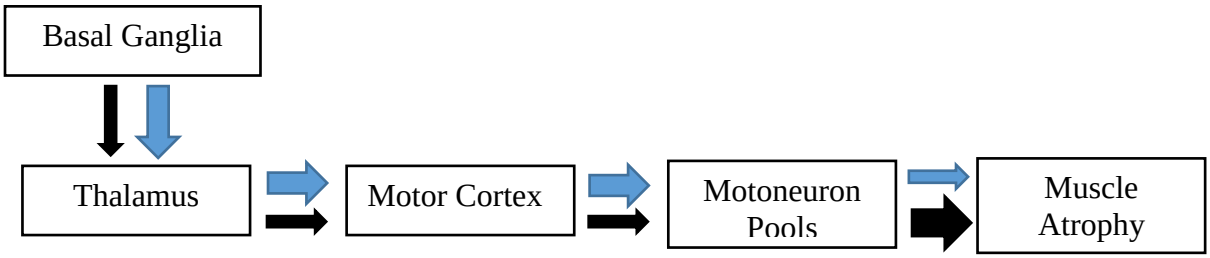

Figure 1: The blue arrows represent non-PD activity, whereas the black arrow represents the decreased amount of excitation that an individual with PD would demonstrate throughout this pathway, ultimately resulting in a greater amount of muscle atrophy

Balance impairments in PD are one of the symptoms that are not effectively improved through dopaminergic medication [4–6]. This is problematic, given that balance difficulties have severe consequences, such as falls. In fact, balance difficulties and falls have been rated as the number one research priority by individuals with PD and their caregivers [7]. Compared to that of healthy age matched older adults (individuals without PD, referred to as non-PD for the remainder of the thesis), the rate of falls is doubled in PD [8], with at least two thirds of falls occurring while individuals report being on medication (at the peak of dopaminergic medication

intake) [9]. It has been suggested that falls occur while on medication, as mobility and gait speed are improved, but balance is not. Thus, even though they are able to move more and faster on medication [9], their postural responses remain compromised, thereby increasing the risk of falls. The number of individuals with PD who report at least one fall in a year is 68% [10] and those reporting weekly falls is 13% [6], with such falls leading to injuries, some as serious as fractures, which occur in 20% of all falls in PD [11]. Moreover, falls are the primary reason for hospitalization in PD, with 13% of hospitalizations related to falls [12]. For these reasons, falls cause a reduction in the quality of life of those in PD due to injuries sustained and fear of future falls [13]. As the incidence of PD is expected to rise to almost 150,000 in Canada by 2031 [14], the burden on the health care system will intensify as well, with direct costs projected to more than double from the current per annum amount of $120,358,000 in the next fifteen years [14]. Thus, the treatment of balance impairments and preventing falls is a critical issue in PD. A better understanding of the specific contributors to poor balance in PD is necessary in order to design a rehabilitation strategy to reduce falls.

Balance Dysfunction in PD

Individuals with PD experience balance impairments that affect both static and dynamic balance. The deficits observed during dynamic balance in PD, particularly in the presence of external perturbations (inducing fall-like situations), can give insight into underlying issues leading to falls, and is therefore the concentration of this thesis. External perturbations cause an individual's balance to be challenged as the centre of mass (COM) is forced close to or outside of the base of support, such as during a trip, a slip or if a collision occurs with another individual or object. Compensatory balance responses are the modifications the central nervous system generates in response to a perturbation. These responses include the ankle strategy, the hip

strategy and/or a stepping strategy (*see figure 1*). The ankle and hip strategy are considered to be "fixed-support" responses as the base of support does not change [15], the COM is slowed by generating rapid muscle torque primarily in the ankles and hips [16]. The stepping strategy is a "change-in-support" strategy, where the perturbation was large enough to cause an individual to be close to a fall, requiring a change in the base of support, achieved through a compensatory stepping response (CSR) [17,18].

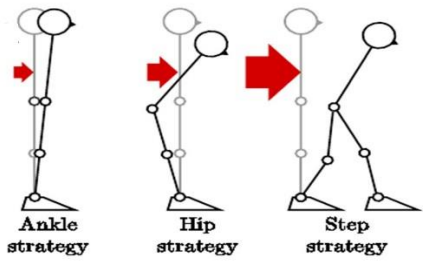

Figure 2: Fixed and Change in Support Strategies: Adapted from Kanamiya et al (2010) [19]

In perturbation situations those with PD require more steps and a greater amount of time to recover balance to prevent a fall in comparison to non-PD [20]. They are also unable to scale their postural response to the size of the perturbation [21] and have difficulty in switching their postural strategy if necessary, such as from an ankle to a stepping strategy or vice versa [22]. Importantly, these postural responses are not improved through dopaminergic therapy [5,20,23].

Muscular Deficits in PD: Do they lead to balance impairments?

Muscle Strength

An increased risk of falls in PD can be explained, in part, by the strong link between muscle weakness and balance deficits, where muscle weakness decreases the ability to create successful responses to balance [24], as the muscles cannot generate adequate force to produce a proficient CSR. Muscle strength and the rate of force development in the muscles, particularly at the ankles [25], are crucial for humans to employ a CSR in order to regain balance during an

external perturbation, or fall-like situation [18,26]. Muscle strength is important to produce sufficient force, as is the rate of force development (the ability to create force in a shorter period of time), thus propelling the stepping limb forward at a faster rate. Taken together this greater loss of muscle strength in the legs and impaired ability to develop force could further explain why individuals with PD are more likely to fall.

Notably, muscle weakness has been identified as one of four independent risk factors for falls in PD, along with freezing of gait, poor co-ordinated stability and previous history of falls [27]. Muscle weakness in PD can be partially attributed to decreased muscle strength [28–31] and a reduced rate of force development [32]. As the basal ganglia are hypothesized to select appropriate muscles for performance and create sufficient force at an adequate rate in muscles [33], it is not surprising that weakness occurs when basal ganglia degenerate (as ensues in PD). Moreover, degenerated basal ganglia cause reductions in excitatory output to the motor cortex, suggesting that the motor cortex is unable to sufficiently excite motoneuron pools [34]. A decreased excitation of motoneurons leads to an inadequate activation of motor units, causing muscles to atrophy [2]. This atrophy seems to be selective to type II fibres in PD [35], which are the fibres that create large amounts of force and generates this force rapidly. In comparison to non-PD, individuals with PD have reduced muscle strength [54], particularly in the lower limbs, which are important to employ a CSR [36].

Muscle Power

Another component of muscle weakness in PD is reduced muscle power [37,38], which can be defined as the product of the force and velocity of a muscle contraction; essentially the ability to rapidly generate a large amount of force [39]. As the limiting factor to recovering balance may be the velocity of the movement, it has been hypothesized that power is more

important to recover from a fall than strength alone [40]. This relationship between muscle power and falls is strengthened from evidence that those with PD displaying decreased muscle power were more likely to have experienced multiple falls in the previous year [38]. Further indicating it could be the velocity component of muscle power that is reducing the ability to rapidly generate a CSR to an external perturbation.

Notably, during power testing individuals with PD demonstrate a reduced ability to activate muscles as movement velocity increases [41]. In normal aging (non-PD), loss of dopaminergic neurons within the basal ganglia is thought to attribute to decreased velocity and power changes in muscles [42]. Given enhanced basal ganglia dysfunction in PD, it is logical that muscle power in PD would be decreased comparatively to non-PD older adults [37]. Specifically, overall maximal power (the highest power output produced from 30-90% of maximal strength), and power at lighter loads (30-60% of maximal strength) are impaired in PD compared to non-PD [37]. As muscle power declines earlier and faster in normal aging (non-PD) than muscular strength [42] (due to atrophy of type II fibres and the associated changes in force generation in the remaining fibres [43]), it is important to identify how improvements in muscle power could enhance muscular outcomes and balance in PD.

Differences in muscle strength and power

It is important to note that both muscle strength and muscle power heavily rely on the rate of force development to create force, however the underlying mechanisms for how they create, and improve the rate of force development differ. The ability of a muscle to create force is modulated by the frequency of stimulation of motoneurons, as well as the amount of type I and type II motor units (motoneuron and all of the fibres innervated) recruited [44]. Type I motor units have a slow contraction speed and do not fatigue as fast, thus they are the first to be

recruited [44]. As a greater amount of force generation is necessary, type II motor units (higher-threshold) are recruited (after type I), they have a higher contraction velocity but fatigue fast [44]. Thereby, the greater the intensity of the stimulus, the greater number of motor units and motoneurons that are required to complete a movement, causing a large increase in muscle force [44]. Muscle strength is the ability to produce force, whereas muscle power is the ability to produce force *rapidly*. An intent to move force fast increases neural drive, which recruits higher frequency motor units, and increases motoneuron firing frequency [45,46]. A larger neural drive causes an increased and earlier recruitment of type II fibres [47], whereas high force but lower velocity training (i.e. strength training) does not provide as much neural drive to recruit as many type II fibres or as rapidly [48]. The rapid rise in muscle force, means power training can generate greater force development earlier in the muscle contraction [46], thus large forces are generated in a shorter time period. Strength training does allow for increased rate of force development to occur, but it does not occur as early in the muscle contraction as power training, as the recruitment of type II fibres is not as rapid, and the decreased neural drive does not activate high-threshold motor units either [48]. Thus, if there is a selective atrophy of type II fibres in PD (likely increasing risk of falls) a program that would require greater neural drive (activating type II fibres faster and bigger motor units), ultimately generating large forces, might allow those with PD to successfully create a step in a timely matter in response to a fall.

Rationale for deficits in muscular strength and power in PD

Overall, it is unclear why these strength and power deficits occur in PD, however there are several explanations that could account for them. Firstly, it is hypothesized that due to functional limitations (i.e. freezing of gait, postural instability, reduced gait speed) that occur with disease progression, this causes individuals to increase sedentary behaviour in order to

reduce the likelihood that a fall will occur [36,49]. General deconditioning occurs as a result of this sedentary behaviour, and ultimately leads to muscular atrophy through disuse, as there is no longer a stimulus (exercise) for neural drive to occur, thus fibres that are no longer activated atrophy and become denervated [43,50]. Secondly, peripheral impairments could be involved as well, although there is a scarcity of literature in PD. However, there is indication that mitochondrial dysfunction occurs in comparison to non-PD age matched controls, whether this causes muscle deficits is controversial [51]. Recently, it has been observed that PD, in comparison to age matched non-PD, had larger type I myofibers, indicating type I fiber hypertrophy, which is hypothesized to be due to a higher amount of type I motor unit activation [52]. Though further research is warranted in this area, authors hypothesized that this increased hypertrophy of type I fibers is a compensatory strategy to restore or retain muscle mass due to a reduction in type II motor unit activation [52]. Finally, as discussed previously, dysfunctional basal ganglia ultimately cause an inability to sufficiently activate adequate motor units leading to muscular atrophy [2,34]. Thus, central changes have been suggested as well to cause these muscular changes [36], particularly increased coactivation of antagonist muscles, as the basal ganglia are responsible for inhibiting inappropriate muscle activation [53,54]. It is unlikely that just one of these rationalizations explain the deficits in strength and power in PD, but rather a combination, due to the complexity of PD.

Consequences of Impaired Strength and Power: Falls

Given the role agonist muscles have for creating force, it is likely that an increased amount of coactivation of antagonist muscles could underlie the causes of strength and power deficits [53,55], as well as a decreased rate of force development [56], which are also present during external perturbations [53]. In non-perturbation situations, an increase in coactivation is

assumed to occur to increase joint stability and thus, reduce disturbances that can occur due to destabilizing forces [57]. However, a large amount of coactivation during perturbation situations has been hypothesized to be detrimental to balance, as in non-PD older adults, a sufficient amount of force is unable to be generated by the agonist muscles to offset the imbalance created [58]. A rapid generation of force from the muscles is required to produce a successful CSR due to an external perturbation [16]. Large coactivation is maladaptive in fall situations as the antagonist muscle group opposes the agonist group force generation [59], thus rendering the agonist groups less capable of accelerated muscle contractions (due to reduced reciprocal inhibition) [60,61]. It is hypothesized that abnormal postural responses occur in PD is due to a large amount of coactivation amongst agonist and antagonist muscle groups [55]. When a movement happens, reciprocal inhibition ensues, where corticospinal projections activate inhibitory interneurons [62,63] on the antagonist muscles. Thus, increasing the inhibition of antagonists muscles would allow the agonist muscle to generate sufficient force [64]. Reciprocal inhibition is hypothesized to be particularly important when fast and powerful movements are required, increasing inhibition of antagonists allows the agonists to accelerate muscle contractions [64]. In non-PD older adults there is a decreased inhibition of the reciprocal pathway due to a central source [65], resulting in increased activation of antagonist muscles, thus a reduction in the ability to fully activate agonist muscles [66]. Ultimately, this causes a reduction in the acceleration of muscle contraction, and decreases rapid force production. Thus, inhibition of reciprocal pathways in older adults, is likely enhanced in PD, given that PD is hypothesized to be a disease of accelerated aging [67,68]. Therefore, an increased amount of coactivation of antagonist muscles in PD means a reduction in force agonist muscles can create

(due to reduced reciprocal inhibition) during an external perturbation, providing an underlying cause for falls in PD.

Taken together, this information suggests that improving muscle strength and power through a rehabilitation strategy, could improve CSRs in PD, through a reduction of coactivation and improving agonist muscle group activation. How strength or power training might cause these changes to occur will be discussed in the subsequent sections.

Fall predictors in PD

To determine if a rehabilitation strategy is promising to reduce risk of falls in PD, it is necessary to improve outcomes that are known risk factors for falls in PD. Decreased muscle strength and power have both been identified as fall risk factors [27,38,69–71]. Thus, attempting to improve muscle strength and power are viable options to reduce risk of falls in PD. Higher motor disease severity, as assessed by the Unified Parkinson's Disease Rating Scale motor subsection (UPDRS-III) [72], is also related to increased fall risk [9,27,73,74], and has been shown to be improved through strength and power training programs [75,76]. Although consistent strategies to investigate if a program was effective at reducing fall risk, these outcomes do not provide a full depiction of changes that could be occurring within the muscles to reduce fall risk.

Thus, there is a need for predictive fall tools in PD, that provide objective information to sufficiently guide assessment of falls and rehabilitation strategies, such as exercise. With the abnormal muscular responses that have been found during an external perturbation in PD (i.e. excessive coactivation and reduced magnitude of activation of muscles [21,53,77,78]), a tool that incorporates electromyography (EMG) would provide data allowing researchers to identify individuals at a greater risk of falling based on objective outcomes. Thus, this was the purpose of

experiment one of this thesis, to attempt to predict PD fallers based on EMG data during an external perturbation, specifically the latency to onset of activation, magnitude of activation and coactivation. Data of this nature would provide further understanding in the effectiveness of rehabilitation strategies aimed at reducing fall risk. If specific muscle parameters were improved, this would provide insight into the utility of a rehabilitation strategy employed to reduce falls, in comparison to basing results on a falls diary alone. In order to determine an appropriate rehabilitation strategy to attempt to improve muscular deficits, a program would have to incorporate strength or power training.

Muscular Strength and Power Training in PD

Overview of Strength and Power Training

Given that impaired strength and power are fall risk factors for PD, it is important to attempt to improve them, thus two current rehabilitation therapies to improve muscular weakness in PD (and ultimately reduce falls), are strength training and power training. Strength training can be defined as a type of physical activity that employs exercising a muscle, or groups of muscles, against an external resistance [79]. Power training for older adults, is also known as high velocity strength training (a form of strength training), and involves completing the concentric part of the movement as fast as possible and the eccentric component within 2-3 seconds [80]. In regards to training in older adults, the only difference between strength and power training is the velocity of the movement. Both forms of training have been used to try to rehabilitate fall risk factors in PD with varying levels of success (see table 1). The rationale for utilizing a strength training program in PD is, in part, due to the theory that there is increased neural activation within the basal ganglia by repetitively generating large forces (in comparison to small forces)[81]. Increased basal ganglia activity as a result of large repetitive force

generation has been demonstrated in a previous neuroimaging study [71], implying that by plasticity could occur within the basal ganglia due to a strength or power training program. Thus, strength and power training are both feasible rehabilitation therapies for PD.

Strength Training

Notably, it has been found that after an eight-week strength training program (targeting lower limbs) individuals with PD have equivalent muscle strength values as non-PD older adults, demonstrating the utility of this type of intervention in PD [30] (*see table 1*). Furthermore, Corcos and colleagues [75] demonstrated that strength training is safe and feasible over two years, with only one adverse event reported (occurring during a maximal voluntary contraction), and with 80% of participants remaining in the study. This study also observed an 8.7 decrease in UPDRS-III scores (from 34.5 to 25.8) while off dopaminergic medication in the strength training group, compared to the control group (PD individuals completing a stretching and flexibility program) whose scores remained the same over two years. Another study found an improvement in UPDRS-III motor scores as well, with an average of a 12 point reduction, after a 12-week program [82]. Further fostering evidence that strength training is capable of improving motor symptoms and a known fall risk factor in PD.

Although there are many positive effects of strength training in PD, to date there has yet to be a studying investigating the effect on reducing falls. However, it should be noted that one study [83] did investigate the effect of strength training on balance measures (i.e. the Equitest; a standardized test assessing postural stability in PD) [24]. Gains in muscle strength (quadriceps, hamstrings and gastrocnemius) were to shown to enhance balance duration before instability occurred, as well as reducing the number of falls recorded. These improvements were still observed at the four-week follow-up, after the intervention was completed. Although this stu1dy

did not measure CSRs, results still demonstrate the critical role that improved muscular strength might have on fall reduction in PD. In fact, strength training has been shown to reduce coactivation in non-PD older adults, specifically while testing rate of force development [84]. Researchers found as the rate of force development increased, the amount of coactivation decreased, likely through improved neural control of reciprocal inhibition. Perhaps indicating that a strength training program may reduce the activation of motoneurons of antagonist muscles, thus allowing the agonist muscles to accelerate contraction.

As mentioned previously, muscle strength is important to be able to produce a CSR to regain balance during a fall-like situation, as is the rate of force development. Power training, as previously described, employs fast velocity movements during training to enhance force development earlier in the muscle contraction. Thus, it could provide added benefits to producing a successful CSR, rather than training strength in isolation. Interestingly, the primary stimuli for neural adaptations to occur (increased rate of force development and motor unit recruitment) are also the key elements involved in a power training program [45]. Based on this assumption, Orr and colleagues (2006) suggested that power training could theoretically enhance neural functioning through reducing the response latency of muscles and effectively improve the recruitment of postural muscle groups [85]. This highlights the need to investigate a power training intervention in PD.

Table 1 Previous research employing strength or power training in PD

Study	Duration (weeks)	Frequency (x/week)	Sets	Repetition	Intensity	Muscle Groups	Control Group	Outcomes
Strength Training								
Hirsh et al, 2003	10	3	1	12	60% of 4 Repetition Maximum	Lower body only	Balance training	Improved balance (reduced falls)
Scandalis et al., 2001	8	2	1	12	60% of 1-RM	Lower body only	Age matched non-PD	Increased muscle strength
Morris et al., 2015	8	2 (one at home)	3	15	Weighted Vests	Full body	Movement strategy training; and life skills group	84.9% fewer falls then non-exercise group
Hass et al, 2012	10	2	2	12-20	70% of 1-RM	Lower body only	Non-exercise PD	Improved muscle strength
Carvalho et al., 2015	12	2	2	8-12	70-80% of 10RM	Full Body	Aerobic and physiotherapy	Decreased motor disease severity
Dibble, et al., 2006	12	3	NA	NA	NA (Eccentric only)	Lower	None	Improved strength
Power Training								
Lima et al., 2013	10	3	3	10	40% of 1RM	Lower	None	Safe, high adherence and attendance
Paul et al., 2014	12	2	3	8	1 set at each-40,50,60%1RM	Lower body	Sham (low intensity)	Improved power and strength Reduced falls
Schilling et al., 2010	8	2	3	5-8	NA	Lower Body	Standard care	Improved strength
Ni et al., 2015	12	2	3	10-12	30-90% of 1-RM	Full Body	Non-exercise PD	Reduced bradykinesia, improved strength and power

Power Training

It has only recently been recognized that muscular power in PD is significantly declined [37], thus the amount of information on the effects of power training is limited. Yet, in non-PD older adults the literature is far more extensive where power training programs have shown enhanced balance [85], muscular strength and power [86], improved contraction speed of muscles and time to complete a movement [85]. Furthermore, an increase in muscle activity during the initial 100 ms of muscle contraction [87] has been observed, likely demonstrating there is an increased neural drive to recruiting more type II fibres in agonist muscles, and earlier in a muscle contraction. However, the effects power training could have on CSR to external perturbations have not been researched in older adults.

The only evidence regarding power training and the role it has on CSR to external perturbations comes from a study of young healthy athletes (with no underlying health conditions) [88]. This study found the power trained athletes were faster and more successful at responding to external perturbations, compared to endurance athletes. Such results indicate that in an otherwise young, healthy population (non-PD), increased muscle power might underlie improved CSRs.

Power training studies in PD have found muscle strength and power to be improved [75,76,89–91], and one study found components of the UPDRS-III improved [76] (researchers were only concerned with bradykinesia outcomes). Importantly, a recent study in PD individuals found that power training is a safe intervention, with no adverse events reported and high attendance rates (88%) over a 10-week period [89]. However, only one study has addressed falls in PD while employing a power training program [90]. Based on fall diaries, researchers found that after the program, 37% of individuals in the power training group experienced a fall

compared to 63% in the control group. These results indicate power training could be a successful program for fall reduction in PD. Yet, it is not clear why or how there was a reduction in falls, if it was due to improvements in compensatory postural responses, changes in behaviour due to knowledge of participation in a fall study, or if there was an improvement in other fall related factors (i.e. freezing of gait). It is important to note that after a power training program in older adults, researchers found that participants had a reduction in antagonist coactivation and an increase in agonist activation [92]. Thus, likely improving reciprocal inhibition, further demonstrating the utility of power training to improve contract the agonist muscle rapidly, enhancing the rate of force development earlier in a muscle contraction. This highlights the need to design an outcome that can measure components of physiological outcomes (coactivation, agonist activation) that are known to be impaired in PD during compensatory postural responses in fall-like situations. This could give a clearer account if a physiological component is contributing to decreased falls after an intervention.

To date there has yet to be a study to attempt to employ objective and physiological outcomes during a fall-like situation in PD, to determine if these muscle responses characteristic in PD, can predict PD fallers from non-fallers, providing the framework for experiment one of thesis. Building on the results of experiment one, experiment two aimed to bridge a gap in the literature to explore potential differences between a power training program and a conventional strength training program in PD. More specifically, to investigate if benefits of either of these programs could improve known risk factors for falls in PD (i.e. activation of agonist muscle groups, amount of coactivation, muscle strength and power, or motor disease severity).

Specific aims and hypotheses

The first experiment of the current thesis (Independent Study) aimed to investigate whether a modified lean-and-release method that induces an external perturbation, whilst employing EMG could predict PD fallers from PD non-fallers. Given that abnormal muscle parameters have been defined in PD in comparison to non-PD controls in response to an external perturbation, it was hypothesized PD fallers would demonstrate unique muscle abnormalities compared to PD non-fallers. Specifically, an increased coactivation, longer latency to muscle onset and decreased magnitude of muscle activation were hypothesized to distinguish fallers from non-fallers.

The second experiment of the thesis aimed to investigate the effects of a strength or power training program on fall risk factors in PD, specifically the muscle parameters that were able to predict fallers from non-fallers in study one (i.e. ankle coactivation). Further goals were to examine the effects of both strength and power training on muscle strength and power, severity of motor symptoms, and falls in PD. It was hypothesized both groups would experience improvements in muscular measures; however those in the power training group would exhibit further improvements in comparison to the conventional strength training group. It was further hypothesized that those in the power training group would demonstrate improved CSRs to an external perturbation (i.e. increased activation, less co-activation). Both groups were hypothesized to demonstrate improvements in muscle strength and power, with the power group experiencing increased muscular power. Finally, it was hypothesized both groups would improve disease severity, as it has previously been demonstrated in the literature. It was contemplated that power training would have further enhancements given the increased neural drive required to complete this form of training, likely stimulating basal ganglia plasticity to a greater extent.

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Chapter 2

A clinical test to detect fallers in Parkinson's with electromyography during a lean-and-release task

Brittany Intzandt, Eric N. Beck, Marcelo P. Pereira PhD, & Quincy J. Almeida PhD

Brittany Intzandt

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Abstract

Introduction: In order to reduce the number of falls individuals with Parkinson's disease (PD) experience, it is first important to identify individuals more likely to fall through fall prediction tools. Current tools in PD lack feasibility in clinics or employ retrospective data. A falls prediction tool should include measures of muscle activity known to be impaired during a fall-like situation in PD such as increased coactivation and reduced magnitude of agonist activation. Thus, the aim of the current study was to design a feasible falls outcome to predict PD fallers (≥2 falls in past year) from non-fallers using muscle activity during a fall-situation. **Methods:** Forty-six individuals with PD (20 fallers) completed a lean-and-release task (fall-like situation). Muscle activity of the tibialis anterior (TA), lateral gastrocnemius (LG), rectus femoris (RF), and biceps femoris (BF) were recorded through electromyography (EMG) equipment on both right and left legs. Muscle activity from both legs were recorded to observe if differences were present in the stepping (leg step was completed with) and the stance limb. A Receiver Operating Characteristic (ROC) Curve was used to predict fallers and non-fallers. **Results:** Longer latency of LG onset (Area Under the Curve [AUC] =0.668, p=0.049) and increased TA activation (AUC= 0.704, p=0.017) in the stepping limb accurately categorized fallers (sensitivity: 73% and 82% respectively). Greater coactivation of LG and TA (AUC=0.696; p=0.023) and activation of TA (AUC=0.722, p=0.01) distinguished fallers from non-fallers in the *stance* limb (sensitivities of 83%). **Conclusion:** Results indicate unique muscle activity during the lean-and-release could predict fall status. This is the first study to identify the importance of the stance limb in current PD fallers. Clinicians could use this method to predict individuals with PD who are more prone to fall.

Introduction

Individuals with Parkinson's disease (PD) experience falls twice as often as non-PD older adults [1], with 13% reporting one or more falls weekly [2]. Falls are the primary reason for hospitalization and injury in PD [3], thus it is important to detect individuals more prone to fall. To date, defining the risk of falls in PD is challenging, as the most common and accurate outcome is previous history of falls [4], which does not prevent a first fall. Therefore, there is a need for objective measures readily available in clinics that are not based solely on retrospective and self-reported data, but rather that include current and objective information to guide assessment (i.e. accurate analysis of fall status) [5].

An objective measure should include examination of an individual's response to a fall-like situation, known as an external perturbation. This would allow for clinicians to identify aspects of a response that increase the likelihood of an individual with PD to fall. A useful behaviour that could be assessed is a compensatory stepping response (CSR), which is defined as a step effectively employed to prevent a fall due to an external perturbation [6]. A successful CSR requires effective communication between skeletal muscle groups, particularly in the lower limbs [7]. An efficient response includes decreased latency to onset of activation of the agonist muscles and an increased amount of activation of agonist muscles (i.e. amplitude) [7,8]. The agonist muscle group is the group that contracts to create force for a movement, whereas the antagonist group opposes the agonist contraction, typically to create stability [9]. Thus, another important feature is successful co-operation between agonist and antagonist muscle groups (i.e. coactivation) [7], where agonist muscles are sufficiently activated, as the antagonist groups are reduced in activation (due to reciprocal inhibition), thereby allowing for generation of force and the rate of force development to create an effective step.

In individuals with PD, successful CSRs are inconsistent due to increased time to complete a step and decreased step length [10], indicating this as an underlying cause of falls [11,12]. This can be explained by a large amount of coactivation in antagonist muscles, such as the tibialis anterior (TA), and a reduced amount of activation in agonist muscle groups. Such as soleus, in PD [8,13–15]. Likely indicating that a reduction in the soleus is caused by increased coactivation of the TA (attributable to decreased reciprocal inhibition[16]), causing the soleus to generate a reduced amount of activation as well as a reduced rapid activation, compared to non-PD older adults. Thus, it is less likely a step is taken. These atypical responses are further characterized by short and sporadic bursts [14], indicating the lower limbs are unable to successfully coordinate together to create a CSR, resulting in a fall.

Differences in muscular activation and coactivation between older adult non-fallers and fallers have been found while employing electromyography (EMG) [17], rendering EMG an attractive option as a feasible fall prediction measure in PD. EMG is particularly desirable as well given its availability in many neurology clinics and multiple uses in a clinic outside of identifying fallers [18,19]. One method to objectively induce a CSR while collecting EMG data is through the employment of a lean-and-release protocol. The lean-and-release measure is a static tool previously used to replicate CSRs in older adults [17,20,21]. Generally, this technique has harnessed participants in a static forward posture, by a horizontal tether cable. After a random time-delay, the tether is released and the participant must respond to the perturbation, with a CSR, to regain balance. As noted above, researchers have quantified muscular aspects involved in CSRs in older adults through EMG, allowing for identification of EMG differences between older adult fallers (self-report ≥2 falls in the previous year) and non-fallers [17]. Specifically, Ochi et al., found non-PD fallers had increased time to maximally activate lateral

gastrocnemius (LG), and an increased coactivation amongst the biceps and rectus femoris. This activity likely accounts for the shorter step length and slower step velocity in fallers compared to non-fallers. The lean-and-release method has yet to be employed in conjunction with EMG in individuals with PD.

Thus, the purpose of this study was to investigate if the lean-and-release method in PD can distinguish fallers from non-fallers with EMG. Although the studies previously discussed induced CSRs through numerous perturbations [10–13,15,17,20,21], it has been suggested that as falls during daily life occur due to a solitary, unexpected perturbation, it is vital to study the first trial in isolation [22]. Thereby, in order to examine muscular characteristics most representative of a fall in daily life in PD, only the *first* trial results are presented here. Furthermore, both limbs' muscle activity were measured to investigate if differences exist, as previous work has identified the role the stance limb (the limb that remains in contact with the ground) has in a tripping perturbation in non-PD older adults and young adults [23]. It was hypothesized that an increased latency to onset of muscle activation, specifically in the LG, and increased coactivation of the TA would distinguish PD fallers from non-fallers during a perturbation.

Methods

Participants

The current study included a total of 46 participants with idiopathic PD (mean age 68.9±8.5 years: 33 male; Unified Parkinson's Disease Rating Scale Motor Subsection (UPDRS-III) 21.1±9.0) after recruitment was completed from the Movement Disorders Research and Rehabilitation Centre at Wilfrid Laurier University in Waterloo, Canada. All participants gave written informed consent prior to participation according to the Declaration of Helsinki. All protocols were approved through the Wilfrid Laurier University Research Ethics Board.

Inclusion criteria consisted of a confirmed diagnosis of idiopathic PD by a neurologist. Participants were excluded if they had vestibular (vertigo, acoustic neuroma), orthopedic (prosthetic limb, fractures or soft tissue injury) or other neurological conditions (i.e. vascular PD, stroke, Parkinson-Plus disorders, or Multiple Sclerosis) that could interfere with the ability to respond to a fall.

Participants were characterized as fallers or non-fallers based on fall history. A fall was defined as an event that caused a participant to involuntarily reside on the ground or a lower surface (regardless of injury) and was not due to a large intrinsic event or hazard [24]. Participants who experienced one fall or less in the previous 12 months were classified as non-fallers [25]. Individuals were defined as fallers if they had experienced two or more falls in the previous 12 months [25]. With these criteria, 20 participants were identified as fallers and 26 as non-fallers. Disease severity was assessed by the UPDRS-III by a movement disorders specialist on a scale of 0-108, where higher scores indicate greater motor disease severity [26]. Cognitive functioning was assessed through the Montreal Cognitive Assessment (MoCA) [27], which was administered through trained personnel. The MoCA is an assessment of global cognitive functioning and is based on a score out of 30, where a higher score indicates better cognitive status, and scores less than 24 out of 30 suggest mild cognitive impairment to be present [27].

Measure of Electromyography

The myoelectric signals of four lower extremity muscle groups were measured using surface bipolar electrodes through the surface EMG (Telemyo 2400 EMG, Noraxon® EMG and Sensor Systems, MyoResearch XP, Scottsdale AZ). The surface electrodes consisted of a pair of two disposable Ag/AgCl electrodes displaced approximately 20 mm center-to-center. Electrodes were placed on both lower limbs of the following muscle groups: lateral gastrocnemius (LG),

tibialis anterior (TA), rectus femoris (RF) and biceps femoris (BF). The LG was selected instead of the soleus for measurement during the lean-and-release task as it is a more superficial muscle compared to the soleus [28], thus reducing possible cross-talk and noise in the EMG signal. The LG is also comprised of a greater amount of type II fibres than the soleus, and therefore contains greater proportions of motor units important for high velocity movements [28,29], such as those required to create a CSR. In regards to selection of RF, the RF is the only quadriceps muscle capable of producing hip flexion [28]. Given that the lean-and-release protocol is in a forward static position, hip flexion is imperative to aid the stepping leg to successfully create force to help propel the leg forward to create a successful CSR. Previous research found that non-PD older adults (during a lean-and-release task) with weak hip flexors, were more likely to require multiple steps to recover balance, due to the inability to generate an effective CSR with a single step [30]. Thus, demonstrating the importance of the measurement of RF, given its role in hip flexion and as a knee flexor.

The superficial skin over these muscle groups was prepared by first shaving any hair, and then applying a mild abrasive gel (NuPrep®) to the skin to reduce impedance. Finally, isopropyl alcohol was used on the skin to remove gel and other substances on the skin. Electrodes were placed according to the Surface ElectroMyography for the Non-Invasive Assessment of Muscles (SENIAM) standardized guidelines [31]. All electrodes were placed over the mid-bellies of the muscles and oriented parallel to the muscle fibres. The data were collected at 3000 Hz and recorded in MyoResearch XP software.

Lean and Release Method

Although not as ideal as capturing a real-life fall, there are multiple techniques to induce a fall-situation within the laboratory that are more feasible to capture. In particular there is the pull-test, and dynamic posturography. There are inherent limitations to each of these methods

however, including a high amount of inter-rater variability [32], and expensive equipment not feasible for many laboratories or clinical settings [33], respectively. Another protocol that induces a fall-like situation involves the lean-and-release protocol which was utilized in this study to induce a fall-like situation.

To complete the lean-and-release task participants wore a fitted harness, attached to a Biodex ™ unweighing harness system through a vertical suspended tether cable (*see figure 3*). The participants stood stationary on an electronic walkway carpet (Zenowalkway- ProtoKinetics, Havertown, PA, USA) and were required to remove footwear. Spatiotemporal gait data were recorded using the ProtoKinetics Movement Analysis Software™ [PKMAS (Zenowalkway- ProtoKinetics, Havertown, PA, USA)]. To begin, all participants were instructed to cross their arms over their chest, and were then lowered to 25 degrees from the vertical, remaining completely straight in a forward leaning posture. The angle of forward lean was measured with a goniometer where a standardized marking midway through the sagittal plane of the right shank was in line with a vertical reference. The lateral malleolus served as the fulcrum mark of the goniometer. Prior to the trial, all participants were instructed to attempt to regain balance by taking a step in response to the perturbation though no instruction was given on what leg to employ for a step. This was explained and demonstrated to ensure participants understood. After a random time delay, tension was released from the vertical tether, by engaging the "trigger" (*see figure 3*). If a step was not taken, the harness prevented the participants from falling to the ground. A total of nine trials were completed with three in each condition: i) no instruction on the leg to employ; ii) regain balance employing left leg; iii) regain balance employing right leg. Trials were completed in random order, with the exception of the first trial, which was always the trial with no instruction on which leg to utilize. As mentioned previously, only the first trial

was included as it was hypothesized to most accurately represent a fall in daily life [22], the other eight trials were completed to answer different research questions.

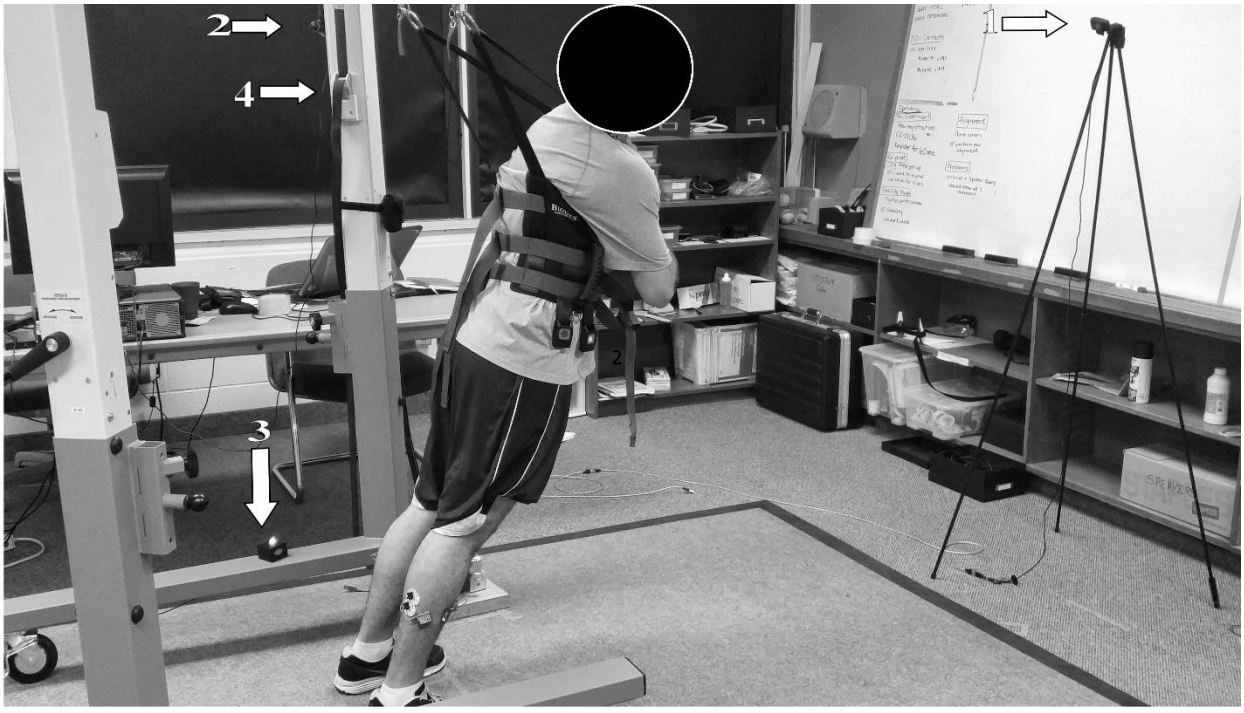


Figure 3: Vertical Lean-and-Release Set-Up: 1.PKMAS Video Camera; 2. EMG Video Camera; 3. Light emitting diode; 4. "Trigger"

Previous research has identified individuals with PD to be more likely to fall due to intrinsic factors, such as impaired mobility and balance, specifically during activities like bending forward or standing up [34]. These occur due to vertical factors, indicating a vertical suspension system would be more authentic to a real fall in PD. Thus, instead of a horizontal cable, as used in previous studies, a vertical cable was employed.

Finally, it should be noted, for the purposes of this study, as the perturbation was in the forward direction, the LG and BF acted as the agonist muscle groups and the TA and RF were the antagonist group.

Data Analysis

A web camera connected to PKMAS™ was placed 1.5 m in front of the participants and 1.8 m above the ground and was used to capture the perturbation, as well as a light emitting diode for time locking the EMG and PKMAS™ data. Another camera, connected to the Myoresearch Software (Noraxon® EMG and Sensor Systems MyoResearch XP, Scottsdale AZ), was placed on the Biodex unweighing system™ immediately above the device that released tension from the harness, for further confirmation of onset of perturbation (see *figure 3*). Two markers were placed in each of the MyoResearch files after the data were collected. Specifically, the onset of the perturbation and automatic postural responses were defined. The onset of the perturbation was defined when researchers released tension from the harness assessed through the two video recordings. Researchers identified participants' "resting" centre of pressure (COP) velocity, with PKMAS, where resting state was defined as the time between when the lean angle was set and the frame prior to the perturbation. The automatic postural response onset time (initial postural response to perturbation [35]) was marked as the time between the perturbation frame and where the COP velocity (average of anteroposterior and mediolateral) exceeded two standard deviations above resting COP velocity (*figure 4*) [36]. If the participant did not complete a CSR in response to the perturbation, the trial was still included, and recorded as a fall. If a step was not completed, a consistent muscle measure was required for all participants to be included in the analysis and to further investigate what occurs in fallers prior to a CSR that disallows a successful step. Accordingly, the onset to the automatic postural response was the phase considered in the analysis. In those who do did not complete a CSR, further analysis was required to determine which leg they might have used. To do so, we utilized the average resting COP displacement (where resting occurred from onset of lean angle to the frame prior to the perturbation) to determine which direction (left or right limb) COP was directed, indicating the

limb that would have completed a step. Since individuals with PD take approximately 200 ms after a perturbation for force changes to occur in their stepping limb [10], the average COP displacement 200 ms after the perturbation was used to compare to the resting COP displacement. All participants were oriented the same on the Zenowalkway. Based on the PKMAS™ coordinate system, any COP displacement to the right was indicated offline by a negative integer, and to the left was positive. In those where a CSR was utilized participants' videos were analyzed to define the stepping and stance limb.

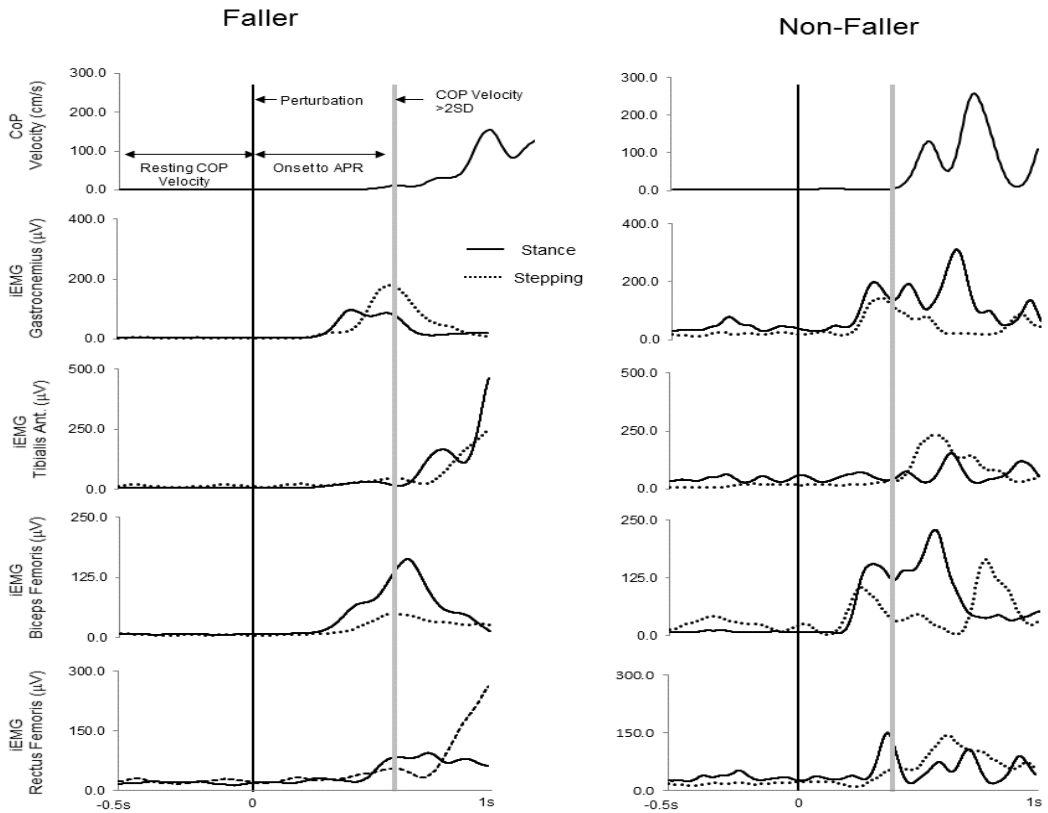


Figure 4: Onset of perturbation and time to Automatic Postural Response (APR) based on COP velocity more than two standard deviations above resting COP velocity. EMG based on onset to APR in stepping and stance limbs. Example of faller and non-faller data

The EMG data were filtered offline by a 20-250Hz by a dual bandpass filter and full wave rectified. The linear envelope was computed by means of a second order Butterworth low-pass filter with a cut-off frequency of 6 Hz to produce a smooth signal [37]. This cut-off frequency was determined through an algorithm for smoothing biomechanical EMG data [52,53]. For the muscle onset time, semi-automatic procedures were adopted [38]: initially, a resting period that muscles were inactive (500 ms) was visually detected and the mean and standard deviation of the signal during this period was calculated for all muscles. The amplitude threshold was set at this baseline mean + 5 standard deviations. To be considered active, the muscle activity had to be above the threshold for at least 20 ms. If this automatic procedure failed to detect muscle onset, this was manually detected. The muscle latency was considered the difference in time between onset of postural perturbation and muscle onset. For analysis of EMG amplitude, signals were integrated over time (iEMG) from perturbation onset until the automatic postural response onset. Finally, using this amplitude, the coactivation index was defined at both knees and ankles, according to the formula [39,40]:

$$Coactivation\ Index\ (CI) = \frac{2\ x\ Antag}{Total\ Activity} x\ 100$$

Where Antag is the iEMG of the antagonistic muscle (lower iEMG value) and Total Activity is the sum of the antagonistic and agonistic (higher iEMG value) activity. The CI was determined in percentage for both knee and ankle joints considering respectively, the RF/BF and LG/TA.

Statistical analysis

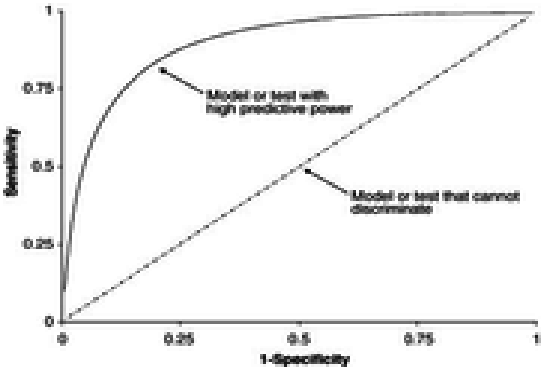
IBM SPSS Statistics for Windows, Version 23 (Armonk, NY, USA: BM Corp) was used for statistical analysis and a significance level was set at $p \leq 0.05$.

Demographics

An independent samples t-test and chi-square were used for all demographic data to identify differences between fallers and non-fallers, as well as to identify potential differences between those who responded with a CSR and those who did not, regardless of fall status.

Receiver Operating Characteristic (ROC) Curve

A receiver operating characteristic curve (ROC Curve) is used as an attempt to quantify the accuracy of a diagnostic test to discriminate dichotomous outcomes, "diseased" and "non-diseased" (i.e. fallers versus non-fallers) [41]. ROC Curves provide Area Under the Curve (AUC), which is a combination of sensitivity and specificity to describing the validity of said test to "diagnose"[41] (*figure 5)*. Figure 3 demonstrates an ideal ROC Curve, as well as criteria for determining the accuracy of the diagnosis based on the AUC results. Thus, in order to determine if EMG measures, specifically the latency of muscle onset, amount of muscle activation (iEMG) and coactivation could correctly distinguish fallers from non-fallers with PD. Furthermore, the ROC curve analysis, provides cut-off values for each significant outcome that are based on sensitivity and specificity. It was determined that sensitivity was of upmost importance compared to specificity, as it would be more appropriate to have a false positive than a false negative. In other words, from a clinical perspective, it would be more acceptable to incorrectly diagnose an individual as a faller, rather than determine a faller to be a non-faller. The AUC represents how well an outcome (i.e. coactivation) is able to predict an individual as a faller. A number of 0.5 or less is considered no greater than chance, whereas an AUC closer to 1 is an excellent predictor of the outcome.



Area Under the Curve (AUC)	Accuracy of diagnostic
0.9-1	Excellent
0.8-0.9	Good
0.7-0.8	Fair
0.6-0.7	Poor
0.5-0.6	Fail

Figure 5: ROC Curve Adapted from Linden 2006

Correlations

Demographic data that were statistically different between fallers and non-fallers were correlated with muscle EMG parameters found to be significant in the ROC analysis.

Results

Demographics

The independent samples t-test analysis revealed fallers were significantly more impaired on the MoCA compared to non-fallers (t= -2.646; p=0.011) though the groups did not differ in age, disease severity or duration (p>0.05). It should be noted that although not statistically different, a difference in scores on the UPDRS-III of five or more is considered clinically different [42]. A chi-square analysis also revealed no differences between fall status and gender (χ^2=2.07, p=.197). All demographics are found in *table 2*. A total of 17 individuals did not complete a CSR (37%), of which 10 were fallers. A chi-square analysis found that the number of non-fallers and fallers that responded with a CSR to the perturbation was not different from the number of non-fallers and fallers who did not respond with a CSR to the perturbation (CSR: Faller 11/ Non-Faller 19, No-CSR: Faller 10/ Non-Faller 7- χ2(1)=2.58, p=.107). An independent samples t-test analysis revealed those who did not complete a CSR had higher disease severity

(CSR: 18.5, No-CSR: 26.7- t=-3.22, p=0.002), and had greater impairments on the MoCA (CSR: 25.7, No-CSR: 21.9- t=3.16, p=0.003), however they were not different in age or duration of disease compared to those who did employ a CSR (p>0.05).

Table 2: Demographics of PD Fallers and PD Non-Fallers

	Fallers n=20	Non-Fallers n=26	p-value
Sex: No. (%)			
Men	12 (60)	21 (80.8)	0.151
Women	8 (40)	5 (19.2)	
Age: Mean±SD, y	68.8 ± 8.5	68.8 ± 8.9	0.999
UPDRS-III (0-108): Mean±SD	23.9 ± 8.3**	18.9 ± 9.9	0.089
Duration of Disease: Mean±SD, y	7.2 ± 5.5	6.0 ± 5.3	0.475
MoCA (0-30): Mean±SD	22.5±5.0*	25.8±3.3	0.010

*p<0.05; ** trend toward statistical significance, but clinically different

Lean-and-Release: Stepping Limb

The ROC curve analysis revealed the following results in the stepping limb: the latency to activation of LG had an AUC of 0.668 (p=0.049; range 0.509-0.827 see *Table 2*); the amount the TA activated had an AUC of 0.704 (p=0.017; range 0.556-0.852). These results indicate increased latency in LG activation and increased amount of TA activation in the stepping limb predicted PD fallers from non-fallers (see *figure 6*). Several outcomes were not statistically significant (see *table 3*; p≥0.05).

Lean-and-Release: Stance Limb

The ROC analysis demonstrated coactivation of the TA and LG, and increased activation of TA distinguished fallers from non-fallers (*see figure 6*). Specifically, an increased amount of coactivation of the TA and LG in the stance limb demonstrated an AUC of 0.696 (p=0.023 range 0.544-0.848) and a larger activation of the TA (AUC= 0.722 (p=0.01) 0.574-0.869).

Table 3: Results of ROC Curve for all outcome measures in both the stepping and the stance limb

	Stepping Limb			Stance Limb		
	AUC	p-value	Range	AUC	p-value	Range
Coactivation (%)						
TA/LG	0.589	0.296	0.424-0.75	***0.696***	***0.023****	***0.544-0.848***
BF/RF	0.496	0.720	0.270-0.663	0.552	0.581	0.368-0.736
Latency (secs)						
Gastrocnemius	***0.668***	***0.049****	***0.509-0.827***	0.640	0.101	0.481-0.799
Tibialis Anterior	0.657	0.065	0.491-0.824	0.580	0.348	0.409-0.751
Biceps Femoris	0.602	0.282	0.406-0.797	0.633	0.159	0.450-0.816
Rectus Femoris	0.682	0.053	0.513-0.852	0.573	0.440	0.375-0.771
iEMG (**µV·ms**)						
Gastrocnemius	0.662	0.058	0.503-0.821	0.584	0.327	0.420-0.748
Tibialis Anterior	***0.704***	***0.017****	***0.556-0.852***	***0.733***	***0.006****	***0.589-0.876***
Biceps Femoris	0.685	0.050	0.515-0.858	0.672	0.068	0.495-0.849
Rectus Femoris	0.582	0.392	0.397-0.766	0.625	0.185	0.451-0.799

*p<0.05

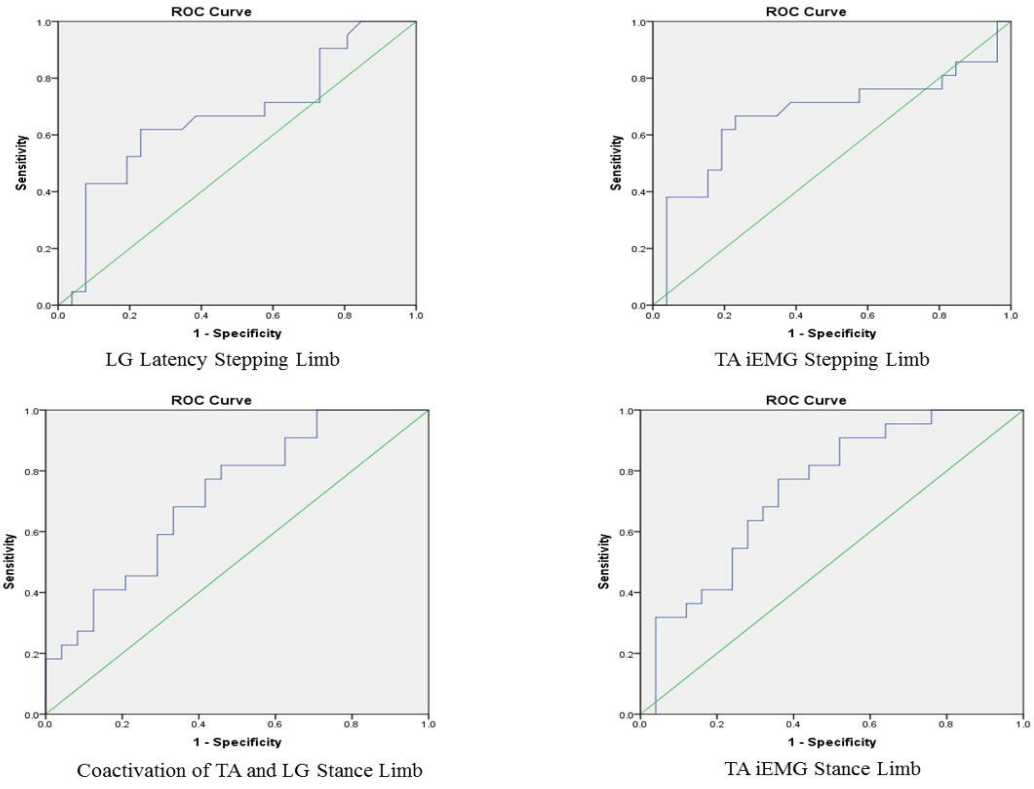


Figure 6: Statistically significant ROC Curves

Correlations for demographics and significant ROC curve outcomes

Correlations were used to investigate relationships between significant EMG data identified through the ROC Curve and demographics that were significantly different between fallers and non-fallers. Thus, correlations were used between the stepping limb LG latency, TA iEMG, stance limb TA iEMG, stance limb TA coactivation and MoCA. The results are as follows: stepping limb LG latency (r=-.087, p=0.561) and TA iEMG (r=-.052, p=0.727); stance limb TA iEMG (r=-.077, p=.609) and TA coactivation (**r=-.305, p=.039**). Results indicated that significantly higher coactivation in the stance limb had a weak positive correlation [43] to lower scores on the MoCA. No other relationships were present between the muscle characteristics and MoCA scores (p>0.05).

Table 4: Suggested cut-offs for muscle characteristics

Muscle Characteristic	Cut-Off	Sensitivity	Specificity
Stance Limb Ankle Coactivation (%)	0.41	81.8%	64.2%
Stance Limb Tibialis Anterior iEMG (µV/ms)	3.16	81.8%	66.0%
Stepping Limb Lateral Gastrocnemius Latency (sec)	0.18	72.7%	46.0%
Stepping Limb Tibialis Anterior iEMG (µV/ms)	3.31	81.8%	40.0%

N.B: Values above these thresholds would indicate a greater risk of falls

Discussion

The objective of this study was to investigate if muscle activation parameters as measured through EMG could predict the fall status of individuals with PD through the lean-and-release method. To the authors' knowledge, this was the first study to investigate whether EMG activity in *both* the stepping and the stance limb could differentiate PD fallers from non-fallers during a perturbation. A longer latency in LG and a larger activation of the TA in the stepping limb was found to distinguish fallers from non-fallers. Increased latency of the agonist muscle groups (soleus) in the stepping limb has not been demonstrated in PD non-fallers when directly

compared to non-PD controls, with no balance impairments [13,15]. However, studies in non-PD populations have found that older adult fallers compared to non-fallers have an increased latency to activation of the LG, in the stepping limb [38]. Therefore, increased latency to activation of LG could be exclusive to fallers, likely explaining the increase chance of falling, as this muscle contributes greatly to initiating the swing-phase through push-off in the stepping limb [21].

Interestingly, results from this study revealed that PD fallers could be accurately categorized by coactivation of the TA in the stance limb. It seems when attempting to employ a CSR, an increased amount of coactivation (or stiffness) might be more detrimental when present in the stance than the stepping limb. These findings align with previous work indicating greater coactivation is present in PD, and supports the increased risk of falling in PD compared to non-PD older adults [8,13–15]. The stance limb is important to accelerate the stepping limb forward relative to the upper body [23] to create a successful CSR. A reduction in coactivation created through a decrease in TA activity, and increase in LG activity would be expected to allow for greater plantar flexion [39] to create forward acceleration from the stance limb [23]. Thus, results from this study indicate increased coactivation of the TA and LG and activation of TA found in the fallers' stance limb, may not allow for sufficient stepping limb acceleration due to a reduction in the force, and the rate of force LG can create [16,39].

Generally, PD fallers have greater disease severity [29], consequently indicating further impairment of the basal ganglia [40]. As, the basal ganglia are important for inhibiting inappropriate antagonist muscle activation [15,41] (i.e. increased coactivation of TA and LG and TA activation), this could justify the increased activation and coactivation of TA observed in the fallers. Although this study did not find a statistically significant difference in disease severity between fallers and non-fallers, a difference of five points on the UPDRS-III is considered

clinically different [36] (see *table 2*). Therefore, excessive dysfunction of the basal ganglia could further explain larger TA and LG coactivation in fallers. It is interesting to note that an increased amount of coactivation in a non-perturbation situation in PD is defined as rigidity [42,43], thus rigidity alone might be a useful marker for fall risk in PD. Future research should further investigate differences in muscle activation characteristics, specifically coactivation, during a fall situation in those with higher compared to lower, or no rigidity.

Results from this study were able to *suggest* cut-off values to differentiate fallers from non-fallers (see *table 4*). Significant AUC and cut-off values are reported in table 2. Previous research that has employed a ROC analysis in PD to predict fallers from non-fallers (with a comparable sample size) have reported an AUC of 0.612 to 0.888 [44] and 0.682 to 0.730 [45] as significant predictors, which are in the same range that results from the current study found. It is important to note that two muscle parameters demonstrated a trend towards significance in the stepping limb, where an increased latency to activation of the RF and greater activation of BF were muscle patterns close to distinguishing fallers from non-fallers (*see Appendix*). These muscle patterns reveal the opposite characteristics as the more distal groups in the stepping limb, increased latency to activation of the antagonists (RF) and greater activation of agonists (BF). Given the opposite behaviour, it could be that these proximal muscles are attempting to compensate in the fallers for the maladaptive behaviour of the distal leg muscles, however it was not statistically significant, thus results must be interpreted with caution.

Conclusion

In conclusion, this study was able to distinguish PD fallers from non-fallers through the use of an objective falls measure. Interestingly, EMG activity in the stance limb may play a key role in further identifying fallers from non-fallers. Since EMG is a standard tool for most neurology clinics [19], it is feasible to suggest using EMG to identify individuals with PD whom are likely to fall by evaluating coactivation of the TA and LG, latency of the LG, and iEMG of the TA. These results are clinically important as this vertically suspended lean-and-release method would allow clinicians to differentiate which individuals with PD are prone to fall. It is however suggested, that future research include more participants to truly determine if these are appropriate and accurate cut-off values in a larger sample of individuals with PD.

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Chapter 3

Power training does not improve electromyographic fall predictors during a fall situation in Parkinson's disease: A single blinded randomized controlled trial

Brittany Intzandt, Eric N. Beck & Quincy Almeida, PhD

Brittany Intzandt

Master's Thesis Document

Abstract

Introduction: Power training (PWR) could reduce frequent falls in Parkinson's disease (PD) by improving muscle parameters that differentiate fallers from non-fallers. PWR involves enhancing the velocity at which force is applied, which could improve ability to regain balance, as muscles contract rapidly. Strength training (ST) does not prioritize velocity as PWR does, and therefore may not allow one to regain balance as rapidly. Therefore, the purpose of this study was to investigate if PWR is more effective than ST at improving muscle parameters that are predictors of fall status (latency to onset of activation, magnitude of activation and coactivation of antagonists) in a fall situation. **Methods:** 44 individuals with PD were randomized to a 12 week PWR or ST program, twice weekly, where PWR completed concentric portion of exercises rapidly. 17 individuals with PD were in a control group. *Primary Outcome:* Electromyography (EMG) on both legs was measured from: lateral gastrocnemius (LG), tibialis anterior (TA), biceps (BF) and rectus femoris (RF) during a lean-and-release protocol. Predictors of fall status in the stance and stepping limb were collected. *Secondary outcomes*: Predicted 1-repetition maximum (1-RM), muscle power at 30, 50 and 70% of 1-RM, disease severity and falls diary. All outcomes were collected at baseline and after training. **Results:** A main effect of time occurred in the stepping limb with decreased latency of activation in LG and TA in all groups at post-testing. No other significant findings in the stepping or stance limb were found. Training significantly improved muscle strength and peak and average power at 50% 1-RM compared to the control group. Disease severity was reduced in PWR post-training. **Conclusion:** PWR and ST were similarly effective at improving fall risk factors in PD, such as muscle power and strength, thus providing feasible and safe rehabilitation strategies to enhance fall risk factors in PD.

Introduction

Falls occur frequently in Parkinson's disease (PD), and are not reduced with the standard PD therapy of dopaminergic replacement medication. In fact, 66% of individuals report falling at the peak of their dopaminergic medication potency [1]. Thus, a rehabilitation strategy, in addition to standard therapy, is necessary and should address potential causes of falls in PD. It has been suggested that the ability of an individual to generate rapid leg muscle power (ability to generate fore rapidly) is a key component to creating a step to recover balance in response to an external perturbation, or fall-like situation [2]. Importantly, it has been determined that individuals with PD that have decreased muscle power were more likely to have experienced multiple falls in the previous year than due to reduced muscle strength [3]. These findings could explain the increased susceptibility to falls in PD, indicating that improving muscle power should be a target of a rehabilitation strategy to reduce falls in PD.

The proficiency to produce a successful step to regain balance is known as a compensatory stepping response (CSR) [4]. In order for a CSR to be successful, recruitment of skeletal muscle groups must be effective [5], including: i) a high amount of activation (to produce sufficient force to complete a step); ii) a short onset latency to muscle activation (to take a step rapidly) [5,6]; and iii) the productive co-operation between agonist and antagonist muscle groups (to reduce co-activation) [5]. In PD, CSRs display a reduction in the amount of agonist activation and an increased coactivation of antagonist muscles [6–9], indicating the ability of agonists to produce force is reduced, thus poor CSRs in PD could underlie increased risk of falls [10]. Moreover, recently we identified muscle parameters that predicted fall status in PD through the use of electromyography (EMG) during a lean-and-release task, inducing a fall-like situation (Intzandt et al, 2016 *under review at Movement Disorders*; chapter 2). Specifically, it was found

that in the stepping limb, longer latency to onset of activation of the lateral gastrocnemius (LG) and increased activation of the tibialis anterior (TA) distinguished fallers from non-fallers. In regards to the stance limb, an increased coactivation of TA and an increased activation of the TA also differentiated fallers from non-fallers. These outcomes provide value to identifying if a rehabilitation strategy is able to improve muscle responses that appear to be impaired in PD fallers.

Conventional strength training has been shown to improve fall risk factors in PD [11–16], indicating it's utility to reduce risk of falls. However, given that muscle power is more impaired than strength in PD [17], it could be hypothesized that power training and its associated improvements in muscle power would have added benefits to reducing falls. Muscle power is muscle's ability to generate force rapidly (force and velocity) [18]. Power training has been argued to increase neural drive [19–22], causing type II fibers to contract prior to or in conjunction with type I fibers [23,24], and to activate higher-threshold motor units, thereby increasing type II motoneuron firing frequency [21,22]. There is also an increase in rate-coding, which is greater recruitment of motor units that are already activated, and stimulates high threshold motor units, thereby increasing muscle force [25,26]. Taken together, these studies suggest power training is able to produce a large amount of force rapidly and earlier in a muscle contraction [22], as the neural drive continues to increase bigger motor units are recruited faster, and even larger units are activated. Conversely, in strength training the peak of the rate of force development occurs later in the muscle contraction than after power training [27] and a decrease in power output is argued to occur due to the nature of a program (repetitions involve deceleration, not acceleration) [28]. The neural drive required in strength training is not as large as in power training, due to the lower velocity that force is produced at, so the cascade of

benefits that power creates (i.e. recruit higher-threshold motor units) does not occur to the same extent. Thus, it could be hypothesized, as power training generates rapid muscle force earlier in a muscle contraction, it is a more appropriate training strategy to prescribe to individuals with PD to allow for a CSR to occur faster and more effectively.

The primary aim of the current study was to investigate if power training would be more effective at improving the previously mentioned muscle parameters that distinguished fall-status (Intzandt, et al 2016), compared to a conventional strength training program. It was hypothesized that the power training would have enhanced improvements in muscle parameters to a fall-like situation, compared to the strength training and control group. Secondary aims of this experiment included investigating other indications of diminished muscle function related to falls in PD: muscle strength, muscle power, disease severity and falls' diaries. It was hypothesized power training would have greater improvements in these outcomes than strength training or the control group.

Methods

Study Design and Participants

The current study was a prospective, single-center randomized controlled trial conducted between August 2015 and May 2016. Participants for this study were recruited from the Movement Disorders Research and Rehabilitation Centre (MDRC) exercise database (Wilfrid Laurier University, Waterloo, Canada). A rolling start protocol was utilized to enrol participants in the study. Specifically, the first phase of recruitment allowed participants to enrol from the beginning of August until mid-September 2015. The second enrolment phase began in early January 2016 and was completed at the end of January 2016. The majority of participants were enrolled and completed baseline testing within the first two to three weeks of recruitment. The

few participants that were not enrolled in this time frame were still randomized by the simple randomization method.

All individuals that expressed interest in participating in an exercise program with PD were contacted by telephone. Inclusion criteria comprised of: a clinical diagnosis of idiopathic PD from a neurologist, either gender, the ability to walk 10 metres, and ability to understand verbal instructions in English. Participants in the exercise groups were required to have a signed Physical Activity Readiness Medical Examination checklist (PARmed-X form) to participate in a resistance training program from a physician. Exclusion criteria included any neurological disease other than PD, uncontrolled hypertension, and physical impairments preventing participation in a muscular strength test such as low back and knee pain. Prior to data collection, ethics approval was obtained through the Wilfrid Laurier University Research Ethics Board. All participants provided informed written consent before commencing the study in accordance with the Declaration of Helsinki. This trial is registered as National Clinical Trial 02476266 (clinicaltrials.gov; NCT02476266).

Power and Strength Training

After baseline testing, individuals were randomized through a simple randomization protocol in SPSS [29] to one of two groups: power training or conventional strength training *(see figure 7*). The strength training group participated in two one-hour exercise sessions per week for a twelve-week period. Participants completed three sets of eight repetitions at 70% of their predicted one repetition maximum (1-RM). When participants classified their rating of perceived exertion (RPE), on the third set, as a 7 or less on the modified Borg Scale (1-10; where higher scores demonstrate increased RPE) [30], weight was increased by 5% the subsequent session [31]. Exercise sessions included: leg press, knee extension, knee flexion, hip abduction, calf

raises, chest press, and latissimus pulldown (Selection Line, Technogym, Gambettola, Italy) and were separated by at least twenty-four hours to reduce risk of injury and to allow for muscle development and recuperation [32]. Individuals in the power training group completed an identical program, with the important exception that when completing the concentric part of a movement, they were instructed to "*attempt* to move as fast as possible". The time of day that training sessions were completed at was kept consistent across participants. All participants received three one-on-one sessions that were the exact program described, in order to become familiarized with equipment and to ensure appropriate technique was learned on all equipment. These three sessions were part of the total 24 sessions. Sessions were led by a certified fitness professional (Certified Exercise Physiologist (CEP), BI), and were supervised by trained personnel, allowing the majority of participants to receive one-on-one sessions throughout the program. It is important to note the CEP was present at all times, and random checks were completed by the CEP to ensure the protocol was followed correctly.

Control Group

A convenience sample control group was included to account for learning effects that could occur during the lean-and-release protocol, as well as to investigate if strength or power training is more beneficial in PD than not participating in a supervised training program. Individuals in the control group were from the MDRC exercise database, however, they identified they were unable to commit to a 12-week program due to planned vacation, personal reasons or lack of transportation. It should be noted that individuals in the control group were used in another exercise study that occurred concurrently. All participants were asked to maintain their daily activity levels while participating in this study, regardless of allocation to group.

Outcome Measures

All of the following measures were completed prior to randomization into groups, and then again within two weeks at the completion of the 12-week program, where the collection occurred at the same time of day at baseline and post-testing for the majority of participants. Outcomes were measured by researchers blinded to group assignment.

Primary Outcome: Modified Lean-and-Release Method

The lean-and-release technique was used to produce a fall-like situation in the anterior direction. All protocols followed for this outcome measure have been previously described (see Intzandt et al, 2016- under review at *Movement Disorders*; Chapter 2). Specifically, it was observed that the stepping limb increased latency to onset of LG activation and magnitude of TA activation, distinguished PD fallers from non-fallers. Moreover, in the stance limb, PD fallers were differentiated by increase magnitude of TA activation and increased coactivation of TA and LG.

In brief, this protocol required individuals leaned 25 degrees from the vertical in a static forward posture and were suspended by an unweighing harness through a vertical suspended tether cable (*see Figure 3: Chapter 2).* Participants were instructed to cross their arms over their chest and to attempt to regain balance by taking a step in response to the perturbation; this was demonstrated and explained to ensure participants understood. No instruction was given in regards to which leg to use to regain balance. After a random time delay, tension on the vertical tether was released, inducing a forward perturbation. The purpose of this outcome was to identify if power training could improve muscle responses in PD, identified in Chapter 2 as predictors of fall status, more than a strength training program. To reiterate, the muscle data captured during this lean-and-release was from the onset of perturbation until 200 ms after the perturbation. This

allowed for *all* participant data to be included, as approximately half of participants did not complete a CSR to the perturbation. Thus, by using this time frame consistent measures for all participants could be used.

Electromyography

Four of the leg muscle groups were measured during the perturbation bilaterally: lateral gastrocnemius (LG), tibialis anterior (TA), biceps (BF), and rectus femoris (RF), which are the same groups utilized in Chapter 2. The LG and the BF were again the agonist muscles and the TA and RF were the antagonist muscle groups. The superficial skin above these four muscles groups were prepared by shaving any hair, and then applying a mild abrasive gel, NuPrep®, to further reduce skin impedance. The final preparation involved isopropyl alcohol to remove any substances or remaining gel from the skin. Surface electrodes were placed according to the Surface ElectroMyography for the Non-Invasive Assessment of Muscles (SENIAM) standardized guidelines [33]. All electrodes were placed over the mid-bellies of the muscles and oriented parallel to the muscle fibres. The surface electrodes were two disposable Ag/AgCl electrodes that were displaced 20 mm center-to-center. Myoelectric signals of these muscles were measured through surface EMG and collected at 3000 HZ (Telemyo 2400 EMG, Noraxon® EMG and Sensor Systems, MyoResearch XP, Scottsdale AZ).

The data were filtered offline by a 20-250 Hz bandpass filter and full wave rectified. A second order Butterworth low-pass filter was employed with a cut-off frequency of 6 Hz to produce a smooth signal and compute a linear envelope [34]. To define muscle onset a semi-automatic procedure was employed [35]: a resting period that muscles were inactive (500ms) was detected visually and the standard deviation and mean of the signal during this time were calculated for all muscles. Threshold amplitude was then set at this baseline mean + 5 standard

deviations. In order to be considered active, muscle activity had to be above the threshold for 20 ms or more. Manual detection of muscle onset occurred if the automatic procedure failed. The difference of time between the onset of postural perturbation and muscle onset was considered to be the latency. In regards to analyzing the EMG amplitude, all the signals were integrated over time from the onset of the perturbation until the automatic postural response began. Using this amplitude, according to the following formula, the coactivation index was defined for the knees and ankles [36,37]:

$$Coactivation\ Index\ (CI) = \frac{2\ x\ Antag}{Total\ Activity} x\ 100$$

In the formula "Antag" is the antagonist muscle group iEMG (lower iEMG value) and total activity is the sum of the agonist and antagonist (higher iEMG) activity. The index was determined in percentage for both the ankle and knee considering, the LG/TA and RF/BF, respectively.

Secondary Outcomes: Submaximal Muscular Strength Testing

All participants underwent a 10 repetition maximum (10-RM) muscle test on the leg press machine, in order to predict a one repetition maximum (1-RM) [38]. The 10-RM was used as a safer estimate of maximal strength (rather than a 1-RM). To estimate the weight used for the 10-RM the participants were asked about their weight lifting history and engaged in two warm-up sets. The initial warm-up weight was based on history of weight lifting, or if not applicable, on the knowledge of the CEP. The first warm-up set was ten repetitions at 50% of their anticipated 10-RM. Participants were asked their rating of perceived exertion (RPE) on the Borg Scale of 0-10 [30], and how many more repetitions they felt they could have completed; the second warm-up was incorporated these answers into the weight chosen. The second warm-up

set was five repetitions, at approximately 70% of their anticipated 10-RM. A two-minute rest period was given between the first and second warm-up sets. After the second warm-up, participants were asked their RPE, and how many more repetitions they felt they could have completed. The weight used in the warm-up, the participant's RPE and feedback from the two warm-up sets helped to estimate the weight used to establish the participant's 10-RM. Once an appropriate weight was established the participant was permitted 5 attempts to reach failure after 10-repetitions. Feedback was received after each attempt to gauge how many more repetitions the participants could complete, and weight was then added to try to have the participant reach failure at 10-repetitions. Participants were given three minutes of rest between each set. All participants were fatigued to failure within one to two attempts.

Table 5: Average Number of Repetitions and %1-RM

Repetitions	%1-RM
1	100
2	95
3	93
4	90
5	87
6	85
7	83
8	80
9	77
10	75
11	71
12	67
15	65

The following equation was used, in conjunction with the numbers in *table 5*, to predict 1-RM from their 10-RM performance: $1\text{-RM}=\frac{weight\ lifted}{corresponding\ \%\ of\ 1-RM}$, where corresponding % of 1-RM is the sum of the number of repetitions completed to failure. For example, if the participant

completed ten repetitions at 50 kg, the equation was: 1-RM=$\frac{50}{0.75}$; where predicted 1-RM was 66.7 kg.

Secondary Outcomes: Muscular Power

On a separate day (at least 24 hours after the 10-RM protocol), participants were asked to complete one repetition on the leg press at 30%, 50% and 70% of predicted 1-RM (randomized in order of completion) as fast as possible. A ChronoJump linear encoder (Boscosystems®, Spain), was attached to the leg press machine during the repetitions to collect the following outcomes: peak muscle power, average muscle power and velocity at each of the three intensities.

Secondary Outcomes: Parkinson's disease Severity

The Unified Parkinson's Disease Rating Scale motor subsection (UPDRS-III) was completed by a movement disorder specialist, blinded to group allocation. This provided a score of motor disease severity, on a scale of 0-108, with higher scores indicating greater disease severity [39]. All participants were tested on dopaminergic medication and at the same time of day for both baseline and post-assessments.

Secondary Outcomes: Falls Diary

Prior to beginning the intervention all participants were asked if they had experienced a fall in the previous 12 months. A fall was defined as an incident (not due to an overwhelming hazard or large internal event) that caused a participant to come to rest on the ground or other lower surface involuntarily [40]. Falls were recorded weekly for the duration of the study.

Statistical Analysis

All outcome measures were analyzed using IBM SPSS Statistics for Windows, Version 23 (Armonk, NY, USA: BM Corp). All data were checked for normality, as confirmed by results of Shapiro-Wilk tests. Data that were not normal were log or rank transformed, where possible. Non-normal data are reported in the results section with the outcomes of tests of normality. If data were not normalized after transformation, they were then analyzed with the appropriate non-parametric tests where indicated. A minimum completion of 80% of all exercise sessions were required to be completed in order to be included the statistical analysis. A value of $p \leq 0.05$ was established for statistical significance.

Primary Outcomes

Given the known variance in EMG outcomes [41] and that non-parametrics analyze based on the mean (not accounting for variance), it was determined to be more appropriate to transform all the data in an attempt to normalize. A 2 x 3 (time x group) repeated measured analysis of variance (ANOVA) was used to investigate differences in muscle parameters (magnitude of activation, latency to onset of activation, co-activation). Significant outcomes were further examined with Tukey's HSD post-hoc procedure.

Secondary Outcomes

Baseline differences in muscle strength and a few power outcomes existed at baseline thus, it was determined that change from baseline to post-testing would be measured between groups. Although disease severity was not statistically significant amongst groups at baseline, the difference between the power training and control group was greater than five points, which is considered clinically significant for the UPDRS-III [42]. This was employed across all muscular strength, power and disease severity measures to remain consistent. Specifically,

relative change ($\frac{(post-baseline)}{baseline}$) was used, as it was determined to be a more accurate representation of all individuals from baseline to post-testing, while including baseline differences. Differences among power, strength, and control groups across the intervention period (12-weeks) were analyzed using a 1 (change in outcome from baseline to post-testing) x 3 (group: power, strength and control), one way ANOVA to investigate differences in muscle strength (1-RM), peak power, average power and velocity at 30, 50 and 70% of 1-RM, as well as disease severity. Significant outcomes were further analyzed with a Tukey-HSD post-hoc. Muscle strength, peak power at 50% 1-RM, average power at 50% and 70% 1-RM, and velocity at 30, 50, and 70% 1-RM were not normal at baseline and as transformations were unable to normalize these parameters, a Kruskal-Wallis test was used. Significant outcomes were further examined by Mann-Whitney test. Finally, the number of falls reported from baseline to post-testing was investigated with a one-way ANOVA, amongst the power training, strength training and control group.

Results

The number of participants recruited and the flow of participants through this study are presented in *Figure 7*. There were significant differences between groups at baseline in muscle strength, peak power and average power at 50% 1-RM. No other significant differences were observed at baseline between groups. All demographic information is found in table 1. Four participants dropped out of the power training program, two were due to injuries sustained during falls that occurred outside of the study, and two due to poor attendance early in the program. Attendance in power and strength training was high (>95%; see *table 6*). No injuries were reported in either training group.

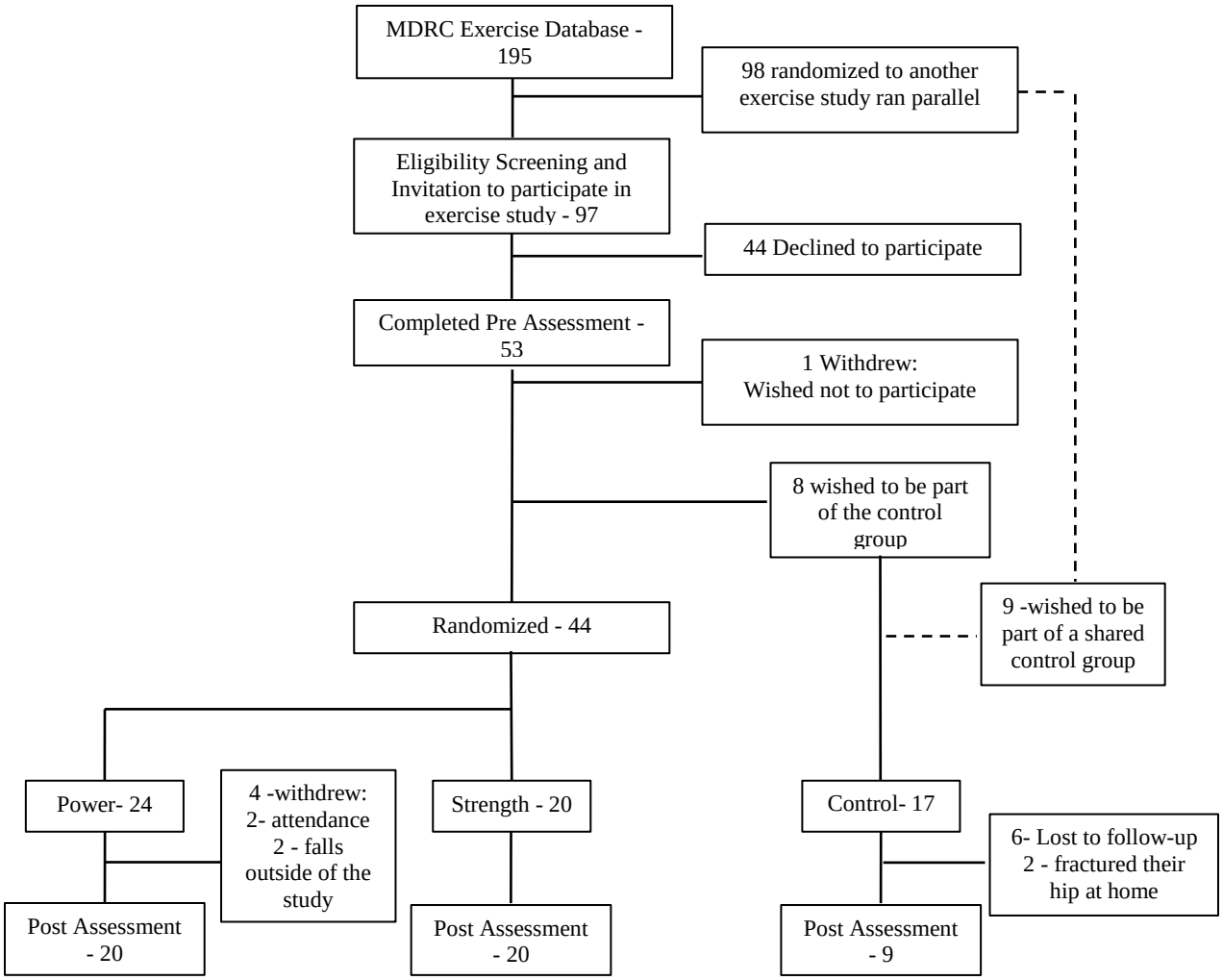


Figure 7 Participant flow through the study

Electromyography data during Lean and Release Task

In the stepping limb there was a significant main effect of time in the lateral gastrocnemius (LG) ($F_{(1, 36)}$ =11.728; p=0.002). All groups reduced onset to activation of the LG at post-test from baseline. A main effect of time was demonstrated in the tibialis anterior (TA) of the stepping limb as well ($F_{(1, 36)}$ =4.836; p=0.034). Onset to latency of TA activation was faster at post-test from baseline. No other significant differences were found in the stepping limb for: latency to onset of activation in the rectus femoris (RF) or biceps femoris (BF; p>0.05); magnitude of activation of the TA, LG, RF or BF (p>0.05); coactivation of the TA or BF (p

>0.05). No significant differences were found in any EMG measures for the stance limb (p>0.05).

Table 6: Demographics

Variable	Power Training (n=20)	Strength Training (n=20)	Control (n=9)	p-value
Age (years)	69.6 ± 8.8	68.1 ± 10.1	69.7 ± 6.9	0.77
Gender (female/total)	7/20	7/20	1/10	0.34
Height (cm)	162.2 ± 9.6	173.0 ± 9.1	174.2 ± 9.8	0.49
Weight (kg)	74.5 ± 11.5	78.0 ± 6.1	79.7 ± 12.8	0.57
MoCA (0-30)	25 ± 3.2	24.7 ± 3.3	22.1 ± 6.7	0.35
Disease Duration (years)	6.8 ± 5.4	6.1 ± 4.4	7.0 ± 6.2	0.94
UPDRS-III (0-108)	24.6 ± 10.0	20.3 ± 8.1	17.4 ± 9.8	0.11
1-Repetition Maximum (kg)	68.7 ± 31.0	73.5 ± 31.3	78.8 ± 73.5	0.81
Fallers In Past Year (n/total)	9/20	8/20	2/10	0.40
Attendance (%)	97.5 ± 3.4	95.8 ± 6.5	---	
Side Affected (Left [L], Right [R] or Both [B])	12:L, 7:R, 1:B	7:L, 10:R, 3:B	6:L 3:R	0.33
Dominant Limb	3: L, 17:R	1:L, 19:R	2:L 7:R	0.58

Given that the onset of motor symptoms is unilateral, the sides that individuals were most and least affected were defined based on the UPDRS-III and the guidelines of Foster and colleagues [43]. In some cases participants were affected by PD motor symptoms equally on both sides, without unilaterality. Participants were also asked about their lower limb dominance, using the following question: “If you were to kick a soccer ball or take a step up a set of stairs, which leg would you use most often?” Chi-square analyses were utilized to investigate if there were differences among the three groups for most affected side and the limb dominance. There were no statistically significant differences uncovered.

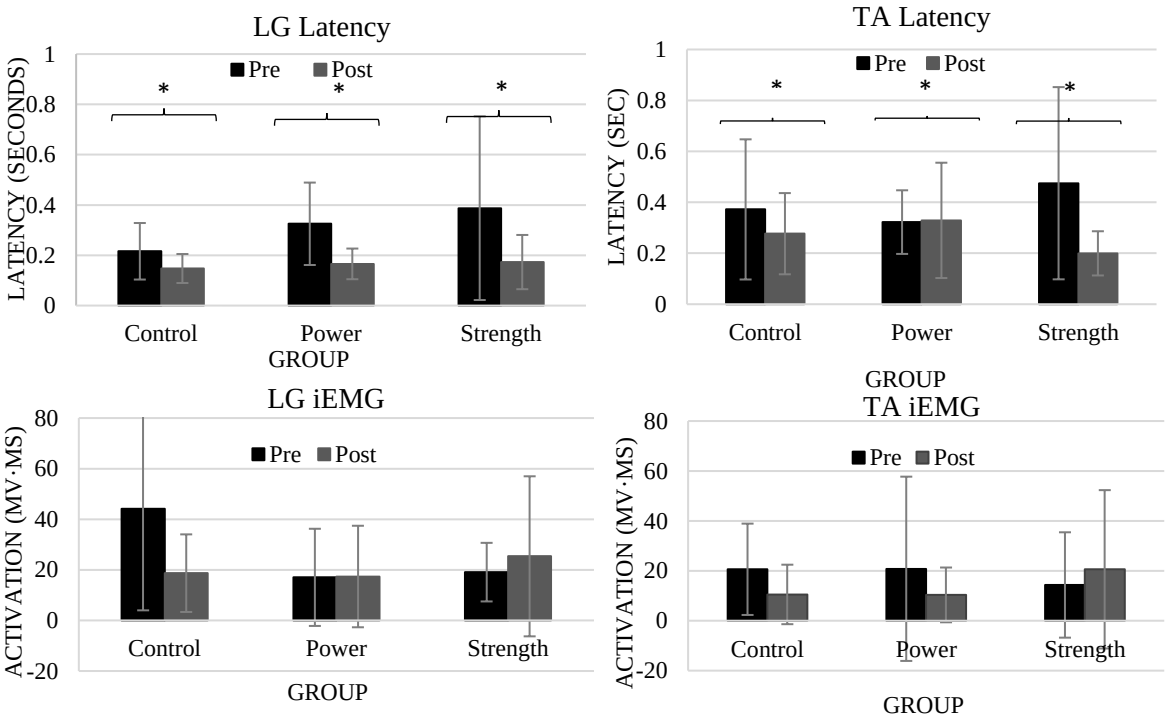


Figure 8: Muscle parameters in the stepping limb

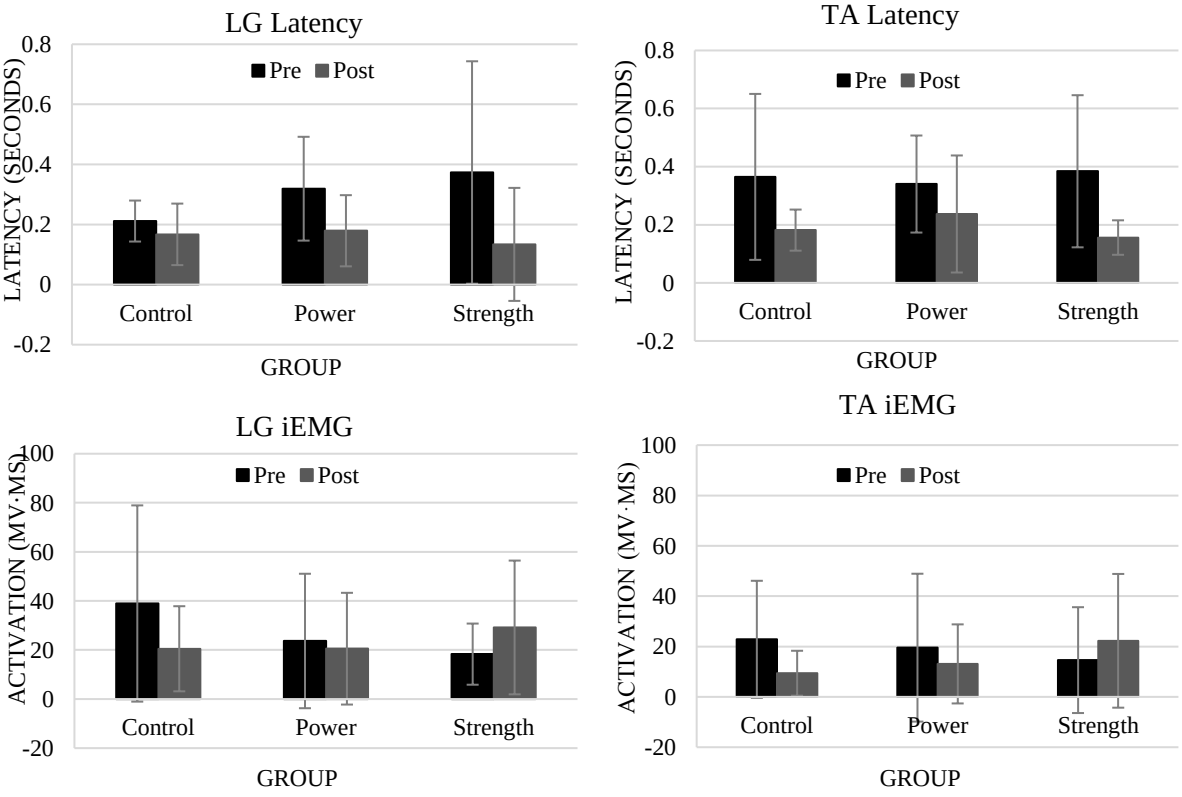
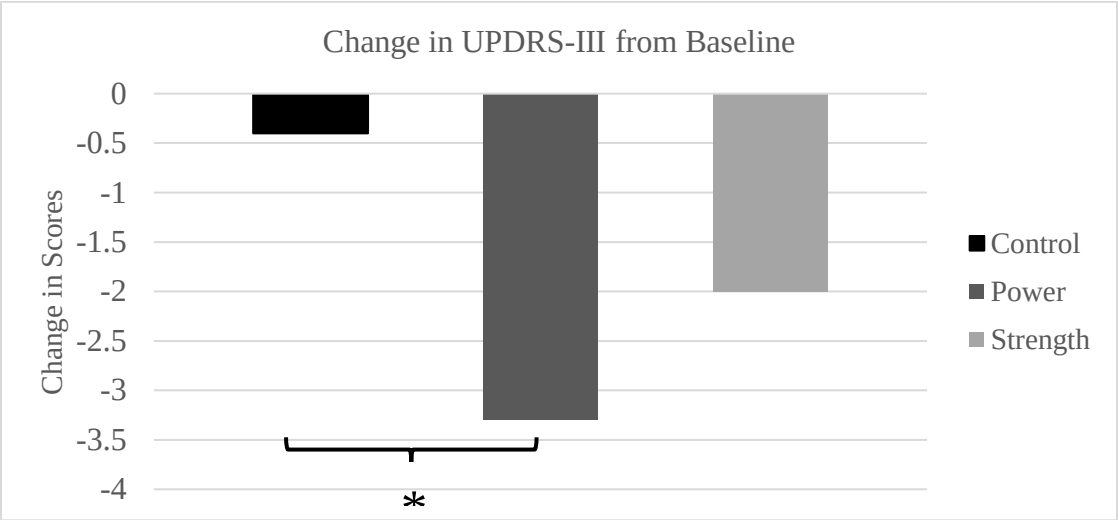


Figure 9: Muscle parameters in the stance limb

Secondary Outcomes

For muscle strength, both power (*U*=10; p=0.001) and strength (*U*=10; p=0.003) groups significantly increased strength compared to the control group from baseline. There was a significant difference for peak power at 50% of 1-RM (χ^2=7.82 (2); p=0.02), where the Mann-Whitney analysis demonstrated the power group (*U*=3.0; p=0.004) and strength groups (*U*=10; p=0.039) had significantly higher change in power than the control group from baseline. Average power at 50% 1-RM was significantly different across groups (χ^2=8.67 (2); p=0.013); wherein increased change in muscle power occurred in the power (*U*=0.00; p=0.001) and strength (*U*=6.0; p=0.011) compared to controls. The change in UPDRS-III scores from baseline to post-testing revealed power training demonstrated significant reductions in scores compared to the control group (p=0.012). No other differences were significant in muscle power outcomes (p >0.05). For the number of falls reported during the study, there were no significant differences from baseline to post-testing amongst the groups ($F_{(2,46)}$=0.005; p=0.995), where power and strength training both reported a mean of 1.8 falls and control group reported a mean of 2.0. *Table 6* includes results of the falls diaries, broken down by number of fallers and non-fallers at baseline and post-testing. *Table 7* includes all muscular outcomes at baseline and post-testing.



*p ≤0.05 significant differences between control and power training

Figure 10: Change in UPDRS-III scores from baseline to post-testing

Table 7: Fall status based on falls diaries at baseline and post-testing

Fall Status		Non-Fallers (<2)	Fallers(≥2)	Reported Average Falls During 12-weeks
Power Training (n=20)	Baseline (n)	11	9	1.8
	Post (n)	15	5	
Strength Training (n=20)	Baseline (n)	12	8	1.8
	Post (n)	13	7	
Control group (n=9)	Baseline (n)	7	2	2.0
	Post (n)	7	2	

Non-fallers experienced less than two falls, fallers reported two or more. No significant differences between groups. Should be noted power training group had 4 individuals drop-out, not included here.

Table 8: Muscle strength and power outcomes from baseline to post-testing

Measure	Power			Strength			Control		
	Pre	Post	Relative Change	Pre	Post	Relative Change	Pre	Post	Relative Change
Muscle Strength (1-RM)	68.7 ±31.0	115.1 ±44.9	67.5 ±79.0*	72.9 ±31.9	115.5 ±36.2	58.4 ±98.5*	82.3 ±74.1	87.4 ±76.8	6.2 ±16.9
Peak Power 30% 1-RM	328.6 ±158.2	426.6 ±214.3	39.9 ±37.5	353.2 ±195.9	437.4 ±226.1	36.7 ±50.2	644.1 ±343.8	527.8 ±344.1	-17.0 ±26.4
Peak Power 50% 1-RM	334.0 ±160.9	462.4 ±252.5	50.0 ±66.9*	350.9 ±158.2	437.5 ±197.2	22.0 ±47.1*	585.2 ±279.9	468.0 ±264.3	-21.6 ±14.1
Peak Power 70% 1-RM	368.2 ±199.8	322.8 ±193.2	-4.7 ±36.2	361.0 ±158.4	359.4 ±194.3	12.5 ±62.3	537.0 ±247.0	318.2 ±73.0	-32.5 ±29
Average Power 30% 1-RM	143.6 ±69.7	166.2 ±83.8	20.4 ±40.2	146.0 ±73.1	180.0 ±80.2	35.5 ±45.7	277.1 ±130.1	198.2 ±71.7	-22.0 ±24.7
Average Power 50% 1-RM	139.0 ±65.6	170.8 ±97.2	29.9 ±51.2*	151.0 ±75.7	184.5 ±81.2	26.4 ±58.3*	295.2 ±103.1	183.9 ±101.8	-37.0 ±22.3
Average Power 70% 1-RM	158.5 ±97.3	118.6 ±76.3	-15.4 ±35.3	165.6 ±77.3	165.5 ±78.2	14.2 ±66.5	180.3 ±35.0	117.8 ±13.5	-33.6 ±11.4
Average Velocity 30% 1-RM	0.38 ±0.13	0.31 ±0.08	-3.1 ±45.5	0.36 ±0.13	0.34 ±0.12	0.1 ±36.9	0.36 ±0.09	0.35 ±0.06	-2.6 ±10.2
Average Velocity 50% 1-RM	0.29 ±0.10	0.23 ±0.07	-8.3 ±30.6	0.27 ±0.09	0.25 ±0.13	-10.1 ±39.8	0.30 ±0.07	0.20 ±0.07	-33.21 ±20.7
Average Velocity 70% 1-RM	0.25 ±0.11	0.12 ±0.05	-43.0 ±25.7	0.22 ±0.09	0.18 ± 0.12	-13.9 ±54.3	0.20 ±0.01	0.14 ±0.04	-31.4 ±19.2

* $p \leq 0.05$; significantly different than control. All values reported as mean ± SD .Relative change is reported as percentages. Muscle strength is in kg, peak and average power are in watts and velocity is m/s.

Discussion

The purpose of the present study was to investigate the effects of a power and strength training program on muscle parameters found to distinguish PD fallers from non-fallers, in a fall-like situation (Intzandt, et al 2016-*Chapter 2*), which to the authors' knowledge is the first study to do so. Results from the muscle parameters from baseline to post-testing demonstrated no differences between groups though muscle strength and several muscle power outcomes were significantly increased with both training protocols compared to control. Finally, power training also improved disease severity (UPDRS-III scores) compared to the control group.

Results of the muscle parameters from the EMG during the lean-and-release protocol demonstrated no differences from baseline to post-testing between groups. However, there was a main effect of time, where all groups decreased onset latency to activation of the LG and TA at post-testing. These changes are likely due to a practice effect, as all participants displayed this change, regardless of group. Additionally, previous studies have not found latency to activation of agonists in PD to be different from non-PD controls (unlike coactivation of antagonists and magnitude of activation) [7,9]. Importantly, changes that accompany strength training (neural and muscular) are affected by all components of a program, such as frequency, intensity and volume [43]. It is possible that the frequency, intensity, or progression of the strength and power programs were not sufficient to reduce falls, as there was a lack of change in muscle parameters that distinguish fallers. Significant hypertrophy of type II fibres has been observed after 12-weeks of strength training, performed three times a week at 80% 1-RM [44]. Thus, increasing the frequency (muscles stimulated more often by neural drive) and intensity (increased neural drive) may have provided ample neural input to observe improvements in PD, to overcome existing neuromuscular deficits [45]. Finally, it possible that the EMG parameters used as the

primary measure were not sensitive enough to detect changes from baseline to post-testing, given the variability that accompanies this measure [41]. However, it is more likely that insufficient training frequency and intensity are the underlying factors.

In regards to muscle strength and power, both the power and strength training groups had significantly greater improvements in strength, peak and average power at 50% 1-RM, from baseline to post-testing, compared to controls. These results are similar to or greater than previous research investigating power training in PD, where muscle strength increased ~12% and muscle power increased ~25% [31,46], demonstrating training was as effective as previous work. The frequency, volume and duration used in this study was the same as in previous studies, furthermore the minimum time between training sessions was 24 hours [31], equivalent to our study. Unfortunately, Ni and colleagues did not report time between training sessions [46]. There was a difference in the intensity and progression of training (*see table 1 from Chapter 1),* which could explain why our subjects demonstrated a larger magnitude of improvement in muscle strength, but a comparable increase in muscle power. As these previous studies only measured muscle strength and power with 1-RM and average peak power of 30-90% of 1-RM respectively, it is unknown if differences in intensity and progression would demonstrate improvements at other intensities of power (i.e. 70% 1-RM) or if they would translate to enhanced recruitment of type II fibers. However, this is unlikely, given the program from the present study demonstrated superior muscle strength and similar power improvements. Power training is argued to stimulate the large neural drive required [47] to activate type II motor units which are responsible for generating a large and rapid amount of force early in a muscle contraction [48]. Thus, a power training program with increased frequency and intensity, may have provided greater neural drive and been able to demonstrate improved muscle power at 70% 1-RM as well, as hypertrophy of

type II fibres has been shown to increase with the relative intensity of 1-RM [49]. It has been demonstrated that if training intensity is not large enough, decreased neural activation occurs [50]. As the progression of weight in the program was based on RPE, instead of when individuals were capable of completing all eight repetitions in the final set [18], participants may have reported higher RPE during the final set, perhaps not progressing the load sufficiently to receive increased neural drive. Consequently, augmenting the frequency and intensity (particularly in regards to the progression of weight) of the program may have provided a more frequent and stronger neural stimulus to increase the force production of type II fibres [51]. Furthermore, given that no injuries were reported in this study, it is likely that increasing intensity and/or frequency would prove to be safe in PD. Regardless, enhancement of two risk factors for falls in PD (muscle strength and power [3,17,52–54]) is promising and suggests that either form of training could be utilized to reduce fall risk factors in PD.

The power training group demonstrated a significantly greater improvement in disease severity as evidenced by a change in UPDRS-III scores compared to the control group from baseline to post-testing (-3.3 versus -0.5 points). There was no difference between the power and strength training group in change of score (-3.3 versus -2.0 points). An improvement in disease severity in the power training group could be due to baseline scores that were clinically different than those in the control group (7.2 points) [42], therefore had greater room for improvement. However, results from this study are in line with a recent meta-analysis investigating resistance training in PD, where an average improvement of 3.6 points (range 2.3-5.1) in the studies was significant in improving motor symptoms compared to a non-exercise group [55]. While this review only focused on strength training, there has yet to be a study that investigated disease severity (UPDRS-III) in its entirety from baseline to post-testing in regards to power training.

Thereby, it can only be postulated that this change in disease severity in the power training group could indicate power training improved motor symptoms (another fall risk factor for PD [52,56,57]). It is important to note a five point change on the UPDRS-III is required to be considered clinically important [42]. Finally, falls data tracked over the duration of this study did not demonstrate significant differences amongst groups in the number of falls reported. Moreover, randomization did not account for fall status, however there were no differences in the number of fallers in each group at baseline, indicating baseline fall status did not negatively influence results. The only study that has investigated the effects of power training on falls in PD (prior to this study) did not find a significant reduction in falls six-months follow-up, however, they did observe a trend, where only 37% in the power group reported a fall compared to 63% in the control group. Thus, to investigate if falls are reduced due to an intervention, it is likely the duration of tracking needs to be longer than 12-weeks.

Lastly, it is possible that changes were not observed between the power and strength training groups due to level of basal ganglia degeneration in PD. The basal ganglia are responsible for the amount of excitation from the motor cortex, ultimately to the muscles [58], helping to create the neural drive necessary to activate the appropriate muscles, and the amount of force necessary from muscles for movement. Thus, in PD, the added neural drive required in power training (due to the intent to move rapidly) to activate motor units [21,22], may not be possible given the amount of degeneration present in the basal ganglia of PD [59]. This could in part, explain why the power and strength training groups demonstrated similar results.

A few additional limitations exist in the current study, notably, the randomization procedure likely led to some of the changes that were observed and may also account for a lack of change in other outcomes. Groups were not matched for disease severity or fall status (based

on self-report or muscle parameters) in this study. Although not statistically significant at baseline, seven points is a clinically meaningful difference in disease severity as measured by the UPDRS-III [42], indicating that improvements in disease severity demonstrated in the power group may have been due to greater disease severity at baseline compared to the controls. Moreover, given the primary outcome was based on muscle parameters able to define fallers, it is likely that defining and then randomizing individuals to the strength or power training, based on these parameters would have been more appropriate. Furthermore, the frequency of training, twice weekly, created a situation where some participants went almost five days without a training stimulus, or only 24 hours occurred between training sessions. As previously discussed, individuals with PD may require a more frequent neural stimulus to overcome neuromuscular deficits. Finally, the lack of changes in other muscle parameters could be further explained by the variability in EMG [41], and the known heterogeneity of PD [60], which likely introduced even further variability.

Conclusion

Overall, this is the first study to investigate if power training could improve upon muscle parameters found to distinguish PD fallers during a fall-like situation. The present study observed that neither the power nor the strength training improved muscle parameters that differentiated fall status. However, as decreased muscle strength and power have been reported by multiple studies as predictors of falls in PD [3,52–54,56,61], it is important that both the power and strength training groups were similarly effective at improving muscle strength and power, particularly compared to the non-exercise control group. This indicates that both forms of training could be used to improve fall risk factors and thus, possibly reduce risk of falls. However, a longer follow-up period would be required to determine this. Moreover, only the

power training group demonstrated improvement in changes to disease severity at post-testing and as increased disease severity is another risk factors for falls in PD, power training is a viable option to improve fall risk factors in PD.

Future research should employ interventions with a higher exercise intensity that continuously increases weight so that participants complete repetitions to failure, as well as more frequent training sessions to discover if improvements can occur in muscle parameters measured by EMG in PD. Moreover, future research should concentrate on continuing to employ these rehabilitation strategies with fall predictors that have consistently demonstrated to be accurate in assessing future fall risk.

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Summary Discussion

Given the heightened risk of falls in Parkinson's disease (PD) [1–4], in part due to muscular weakness [5,6], two forms of resistance training (power training and conventional strength training) were utilized in this thesis to assess the effectiveness of each to reduce fall risk. Two experiments were conducted, where the first was designed to develop a feasible fall prediction tool that would provide viable outcomes to distinguish PD fallers from non-fallers. Primary results of experiment one indicated that individuals with PD could be distinguished as fallers (from PD non-fallers) when they presented with the following muscle parameters: i) in the stepping limb an increased latency to onset of activation of the lateral gastrocnemius (LG) and an enhanced activation of tibialis anterior (TA), ii) in the stance limb an increased coactivation of the TA as well as larger activation of the TA. Results from experiment one provided the primary outcome for experiment two, which was designed to assess if a high-velocity strength training program (power training) would be more effective at improving these muscle parameters, than a conventional strength training or non-exercise control group, thus reducing fall risk.

After the 12-week training period, neither the power nor strength training groups improved muscle parameters found to differentiate fall status. Although differences were observed at post-testing (for all groups) in reduced onset to activation of the LG and TA in the stepping limb, it could be attributed to a learning effect, as the lean-and-release protocol may have no longer been novel at post-testing, thus participants were aware of what to expect. Notably, lack of change in muscle parameters in the power training group was surprising, given that greater activation of type II fibers [7–9], and greater rate of force development is generated early in a muscle contraction [9] due to the increased neural drive required in power training [7,9–11]. However, a few methodological issues could account for this. First and most simply, electromyography (EMG) data were not normalized with the maximal voluntary contraction

(MVC) of each participant for experiment one or two. Given the variability of surface EMG within individuals, and over multiple testing periods [12], including the MVC of each participant would have further normalized the data by reducing variance, as demonstrated by previous research, where the variance of EMG was decreased in a lean-and-release task in older adults utilizing MVCs [13]. Thus, including MVCs may have provided more accurate and reliable results in experiment one and two. Furthermore, regarding the analysis of the EMG signal, only one investigator (BI) completed the identification of markers to label time points in the EMG data (i.e. onset of perturbation and automatic postural responses). Even with strict criterion for the classification, completing intra-rater and inter-rater measures would have been warranted to ensure reliability and validity of time points, given the extreme sensitivity of the data to time (max 200 ms). Finally, greater variability might have been introduced when using EMG [12], in conjunction with a heterogeneous population like PD [14], where participants with tremor, and dyskinesia's (involuntary movements due to overmedication) were included. For example, some participant data were too noisy to be analyzed, either at baseline or post-testing, and could not be included in the final analysis, reducing the final sample size and statistical power. It should be noted that although the EMG from study one was not transformed in order to be normalized, as was done in study two, the ROC Curve analysis that was utilized in SPSS assumed data to be non-parametric and analyzed the data based on this.

As the rationale for a power training program included the greater neural input required [7,9], which activates more type II fibres [15] and larger motor units [9,16] to create a large rapid generation of muscle force, it is surprising no significant differences in any of the outcomes between the power and strength training existed at post-testing. Furthermore, power training is argued to increase the firing frequency of type II motoneurons due to a greater activation of

higher frequency motor units [7,9], consequently creating rapid force development early in a muscle contraction [9], which is crucial in a fall situation, where time is limited to step. It was hypothesized given these properties, those in power training would demonstrate increased activation of agonists, and decreased latency to onset agonist activation. It was further argued that increased activation of agonist groups would be a consequence of reciprocal inhibition, where a reduction in antagonist coactivation would be present due to improved neural control inhibiting antagonists. Previous researchers have observed after a six-months of power training in non-PD older adults, participants increased agonist activation and reduced antagonist coactivation [17]. However, in that study coactivation was measured during an isometric MVC while performing a leg extension, which is a single-joint movement, contrary to a fall-like situation which requires complex multi-joint movements. It is speculated due to greater intermuscular coordination required for motor units to learn, multi-joint movements require a greater amount of time and effort for muscular gains to translate to a multi-joint improvement [18]. As our power training groups did demonstrate enhanced muscle strength and aspects of power, it may be in order to translate to a fall-like situation, a longer period of time would be required to allow for the type II fibers to learn and create appropriate coordination between muscles. Though, it is more likely changes in muscle parameters did not occur due to the prescribed exercises in the training program.

As discussed in chapter 3, it is possible the intensity, frequency, and progression of the power and strength training programs may not have been sufficient to improve responses to a fall-like situation. Changes that occur in the first eight weeks of strength training are due to neuromuscular changes [19]. If neural drive was not large enough during this time, type II fibers and higher-threshold motor units may not been recruited as much, therefore not hypertrophying

as much. Furthermore, rate-coding may not have occurred due to an insufficient intensity or frequency of training, thus further activation of large motor units already activated would not occur. Thereby, the typical consequences of a power training program (rapid and early force development during a muscle contraction), may not have transpired during this critical period of the training.

Due to the pathology of PD, neuromuscular changes may not have ensued, or not occurred to the extent possible in non-PD. The slow movement that occurs in PD, known as bradykinesia, has been suggested to occur due to a higher sensitivity of energy cost [20]. Thus, when asking individuals with PD to intend to move as rapidly as possible, due to reduced implicit motivation, they move slower than they are capable of, to reduce the energy cost. With this information, it could be argued that the power training group may not have been performing the movements as fast as possible, and perhaps had the potential to move more rapidly, but did not. If this were the case, there would have been no difference in the prescribed training between the power and the strength training groups, which could explain lack of distinctions between the two post-testing. Without implicit motivation to move fast, the increased neural input that is characteristic of power training, leading to the cascade of effects in the neuromuscular system, may not have taken place. As the power training group did observe enhancements in muscle strength, it is likely that motor unit recruitment was improved, however likely not to the extent characteristic of increased neural drive due to power training, thus increased rate of force development early in a muscle contraction may not have occurred.

Finally, it could also be stipulated, that as a greater number of individuals in experiment two were non-fallers (62%), benefits to the muscle parameters that fallers may have experienced could have been weakened due to non-fallers experiencing no changes, as these are parameters

that distinguish fallers only. Given this, it is likely that non-fallers likely do not need to improve muscle parameters compared to fallers, as they are successful at producing a proficient step in a fall-situation, likely indicating normal muscle parameters compared to fallers. Thus, to investigate if a rehabilitation strategy is effective at reducing falls, the population examined may need to be only be fallers, or fallers with a matched non-faller, for disease severity and age, to create a more homogenous comparison.

Another limitation to this study includes the "control" group that was included in study two, which although not statistically different at baseline from the other two groups, they were clinically less severe than the power group, and there were less fallers (2 out of 10 versus 9 out of 20). The control group were also not true non-exercise controls, as they were less severe at baseline, they were participating in programs outside of the laboratory environment and completing physiotherapy or physical activity programs on their own. Given that they were part of the Movement Disorders Research and Rehabilitation Centre exercise database, it was determined that they would have similar characteristics to the interventional groups, however because they opted to participate in the control group they, may have had unique characteristics to the other two exercise groups. Future research should attempt to randomize individuals to an intervention or a control group.

Future directions

It is suggested, that future research employ the lean-and-release technique with EMG, in a larger population of individuals with PD. As previously discussed, the variability is large in EMG as well as within PD, indicating that a larger sample would be required to further validate the muscle parameters from Chapter 2 (Intzandt et al, 2016) as able to distinguish PD fallers from non-fallers. Moreover, it would be warranted to employ this protocol in individuals who are

not fallers (less than 2 falls in the previous year), and track these individuals over an extended period of time (more than one year) to investigate if the same muscle parameters could identify fallers at the follow-up. This would further demonstrate if the muscle parameters identified in Chapter 2 (Intzandt et al, 2016) were truly able to predict individuals with PD more prone to falling.

Furthermore, in regards to the rehabilitation strategy, it is suggested that future studies employ a more frequent program, with a greater intensity, and follow ACSM guidelines for progression of load used [21,22], to identify if those with PD could demonstrate further muscle gains, both in power and muscle parameters from Chapter 2. The employment of exercises that require more multi-joint movements should also be investigated to observe if this would translate more effectively to muscle parameters necessary during a fall-like situation, as compensatory stepping responses (CSR) require complex multi-joint movements. Finally, future work should investigate if individuals with PD are able to overcome reduced implicit motivation that is likely demonstrate during training. Thereby, providing future rehabilitation studies with the insight to power training as a feasible program to attempt to improve muscle parameters to reduce fall risk. If individuals with PD are unable to overcome implicit motivation, then power training may not be a well-suited program, as the intent to move rapidly is the defining feature for the neural, neuromuscular and muscular benefits to occur [7].

Conclusions

Overall, this thesis was able to distinguish PD fallers from non-fallers during a fall-like situation through the use of EMG. Specifically, four muscle parameters were found to define individuals more prone to falling: i) in the stepping limb an increased onset latency to activation of the lateral gastrocnemius, and larger amount of activation of the tibialis anterior; ii) in the

stance limb a greater amount of tibialis anterior coactivation, and a larger activation of the tibialis anterior overall. Importantly, this experiment is the first to identify that abnormal muscle activity in the stance limb is present in PD fallers, not just in the stepping limb. The second experiment demonstrated that power and strength training improve fall risk factors similarly in individuals with PD. Findings reveal that both forms of training are effective at improving several fall risk factors, thus providing individuals with PD with two rehabilitation options to reduce risk of falls.

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Appendix

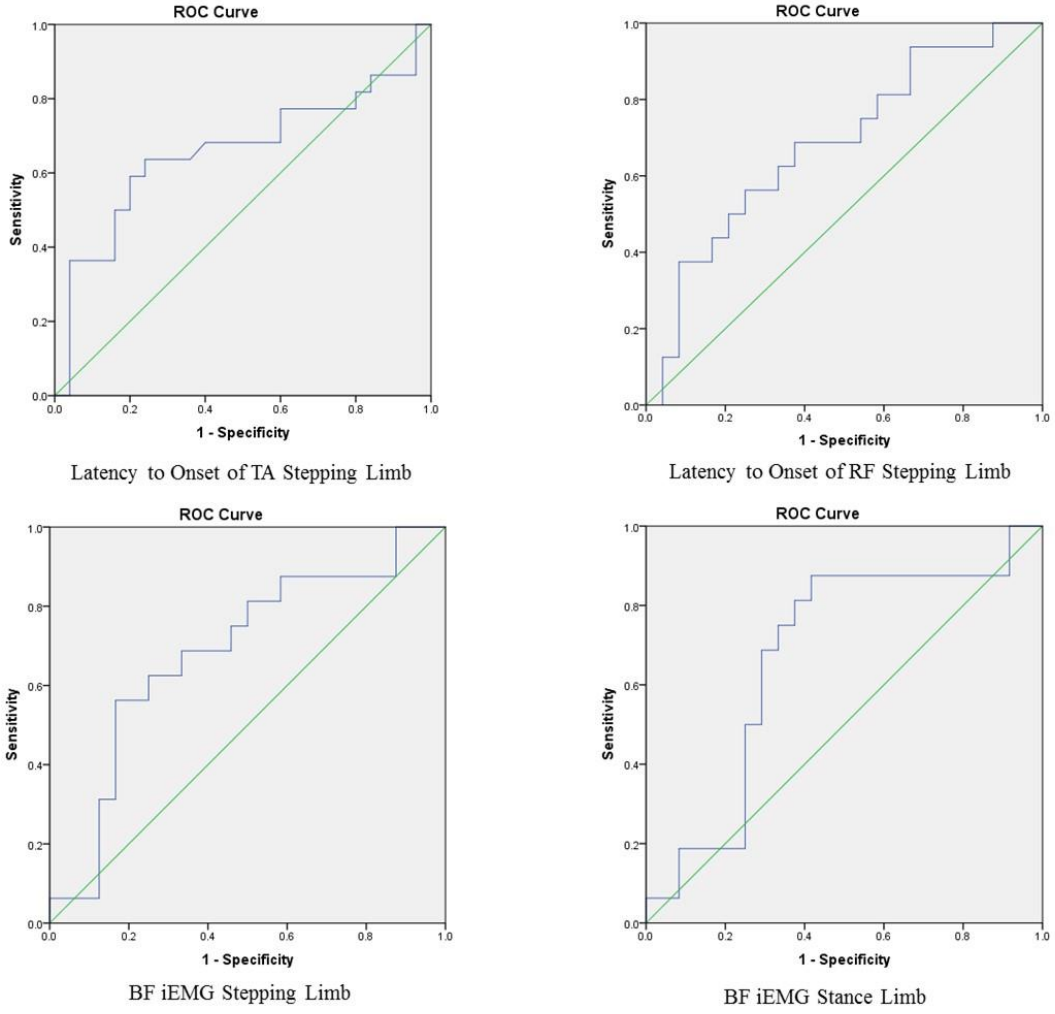

Figure 11: ROC Curves Approaching Significance from Chapter 2

Figure 11 demonstrates four muscle parameters form chapter two that demonstrated trends for distinguishing fallers from non-fallers. Given this data, three occurred in the stepping limb, where increased latency to activation of TA and RF, and increased activation of BF could be more likely to distinguish fallers. In the stance limb, larger activation of the BF could also be likely to differentiate fallers from non-fallers as a parameter.