Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature:

_____ _____

Kimberly C. Lang Date

Abnormal muscle activity during balance before and after an exercise-based balance rehabilitation in people with Parkinson's disease

By

Kimberly Carol Lang
Doctor of Philosophy

Graduate Division of Biological and Biomedical Science
Neuroscience

Dr. Lena H. Ting Advisor	Dr. Thomas Wichmann Committee Member
Dr. Madeleine E. Hackney Committee Member	Dr. Steven L. Wolf Committee Member
Dr. J. Lucas McKay Committee Member	

Accepted:

Lisa A. Tedesco, Ph.D.
Dean of the James T. Laney School of Graduate Studies

Date

Abnormal muscle activity during balance before and after an exercise-based balance rehabilitation in people with Parkinson's disease

By

Kimberly Carol Lang
B.S., Davidson College, 2009

Advisor: Dr. Lena H. Ting, Ph.D.

An abstract of
A dissertation submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
in partial fulfillment of the requirements for the degree of
Doctor of Philosophy
in Graduate Division of Biological and Biomedical Science
Neuroscience
2019

Abstract

Abnormal muscle activity during balance before and after an exercise-based balance rehabilitation in people with Parkinson's disease
By Kimberly C. Lang

BACKGROUND: Abnormal muscle activity during reactive balance may cause balance impairments in Parkinson's disease (PD) and may be a potential mechanism by which Adapted Tango (AT), an exercise-based balance rehabilitation intervention, improves clinical balance measures. Here, a multidirectional perturbation paradigm was used to quantify how antagonist muscle activity during reactive balance is influenced by 1) PD and impaired balance assessed by standardized behavioral scales and 2) AT. METHODS: Antagonist activation during reactive balance responses to multidirectional support-surface translation perturbations was compared between 1) 31 participants with PD and 13 participants without PD and 2) 30 participants with PD who did (16) or did not (14) participate in AT. Muscle modulation (the ability to activate and inhibit muscles appropriately according to perturbation direction) was quantified using modulation indices (MI, MI180) derived from minimum and maximum EMG activation levels observed across perturbation directions. Modulation was quantified for 100-175 ms (APR1), 70-450 ms (APRX), and 175-250 ms (APRY) after perturbation onset. Clinical measures quantified balance (Berg Balance Scale, BBS; Fullerton Advanced Balance scale, FAB) and gait (Dynamic Gait Index, DGI) performance. RESULTS: In cross-sectional comparisons using MI and APRX, antagonist leg muscle activity was abnormal in participants with PD compared to participants without PD. Linear mixed models identified significant associations between impaired modulation and PD ($P<0.05$), PD severity ($P<0.01$), and balance ability ($P<0.05$), but not age ($P=0.10$). In the longitudinal examination of AT or Control participants with PD, there was a significant group by time interaction effect on DGI performance, but not on BBS or FAB. Neither the group, time, nor group by time interaction effects were significant for MI in either APRX or APRY. Individual cases showed relationships between FAB and MI changes differing with baseline balance ability. CONCLUSION: This dissertation 1) presents a new method to quantify co-contraction, 2) shows that reduced modulation is associated with PD severity and across PD phenotypes, and with clinical quantifications of balance, and 3) provides evidence suggesting that baseline functional balance ability may be more important to rehabilitation outcomes than age or PD phenotype, with those who stand to benefit most having lower balance ability.

Abnormal muscle activity during balance before and after an exercise-based balance rehabilitation in people with Parkinson's disease

By

Kimberly Carol Lang
B.S., Davidson College, 2009

Advisor: Dr. Lena H. Ting, Ph.D.

A dissertation submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
in partial fulfillment of the requirements for the degree of
Doctor of Philosophy
in Graduate Division of Biological and Biomedical Science
Neuroscience
2019

Acknowledgements

I would like to acknowledge the years of support from my PI, Dr. Lena Ting, without whom none of this would be possible. Over the course of my time in her Neuromechanics Lab, she provided the resources and training for me to succeed in this area of research and supported my pursuit of a Master of Science in Clinical Research degree. She provided copious lessons about both science and life and sculpted me to be a better scientist.

Similarly, I would like to thank Dr. J. Lucas McKay for his patient technical support in coding and statistics and moral support during tough times. I greatly appreciate Dr. Madeleine Hackney for sharing her expertise and for her tutelage in conducting all phases of our translational study, from recruitment to publishing, and for her encouragement and enthusiastic support.

In addition, many thanks are due to Dr. Steven Wolf and Dr. Thomas Wichmann for generously providing their expertise and invaluable feedback to help shape and interpret this dissertation.

I am grateful to the members of the Neuromechanics Lab, past and present, who offered technical, conceptual, and moral support throughout my time here. In particular, I would like to thank Dr. Andrew Sawers, Dr. Jessica Allen, Dr. Brian Horslen, Dr. Kyle Blum, Dr. Aiden Payne, and Sistania Bong. They generously shared their time, expertise, technical assistance, thoughtful feedback, revisions, critiques, and good humor.

I would like to thank my fiancé, Aaron Robinson, and family, Paul Lang, Carol Lang, and Alison Lang, for their unwavering love and support through this process, especially during the challenging times.

Finally, I am tremendously thankful for the friends I made during my time at Emory, in particular, Dr. Kristen Thomas, Dr. Amy Dunn, Dr. Laura Scorr, Dr. Nisha Raj, and Amielle Moreno. Their friendship provided support and assistance during my work at Emory and enriched my time in Atlanta with fun adventures and good times.

Table of Contents

Figures and Tables

List of Abbreviations

APR	Automatic postural response
APR1	Time bin from 100-175 ms after perturbation onset
APRX	Time bin from 70-450 ms after perturbation onset
APRY	Time bin from 175-250 ms after perturbation onset
AT	Adapted Tango
BBS	Berg Balance Scale
BFLH	Biceps femoris long head
CoM	Center of mass
DGI	Dynamic Gait Index
EMG	Electromyography, electromyographic
FAB	Fullerton Advanced Balance scale
FOGQ-B	Freezing of Gait Questionnaire B
ID	Indeterminate
L-DOPA	Levodopa
MCID	Minimally clinically important difference
MGAS	Medial gastrocnemius
MI	Modulation Index calculated from maximum and minimum levels of EMG activity across perturbation directions; reflects the greatest amount of modulation across perturbation directions
MI180	Modulation Index calculated from maximum and minimum levels of EMG activity across ranges of 3 perturbation directions; reflects more physiologically-relevant modulation
OR	Odds ratio
PD	Parkinson's disease
PIGD	Postural instability and gait difficulty
PRET-PD	Progressive Resistance Exercise Training in Parkinson's Disease trial
RFEM	Rectus femoris
SOL	Soleus
TA	Tibialis anterior
TD	Tremor dominant
UPDRS	Unified Parkinson's Disease Rating Scale
VMED	Vastus medialis

1. Introduction

1.1. Parkinson's disease impairs balance

Parkinson's disease (PD), first described in 1817 by James Parkinson (Parkinson, 1817), is the second most common neurodegenerative disease (Nussbaum & Ellis, 2003). In the United States alone, there will be an estimated 930,000 individuals aged ≥45 years with PD in 2020; this number is expected to rise to 1,238,000 by 2030 (Marras et al., 2018). PD is a progressive disease characterized by loss of dopaminergic cells in the substantia nigra pars compacta and presence of intracellular α-synuclein Lewy bodies in specific brain stem, spinal cord, and cortical regions (Lees, Hardy, & Revesz, 2009), although involvement of other neurotransmitter systems (catecholaminergic, cholinergic, serotonergic) is also recognized (Espay, LeWitt, & Kaufmann, 2014; Huot & Fox, 2013; Muller & Bohnen, 2013). The four cardinal symptoms (bradykinesia, tremor, rigidity, and postural instability) do not occur until 50-60% of nigral neurons and 80-85% of striatum dopamine are lost (Marsden, 1996; Wirdefeldt, Adami, Cole, Trichopoulos, & Mandel, 2011). Non-motor symptoms, including autonomic dysfunction, sleep disorders, mood disorders, cognitive abnormalities, and pain and sensory disorders, are also recognized and often precede motor symptoms (Lee & Gilbert, 2016).

Of the motor symptoms, postural instability has a particularly negative impact on mobility and quality of life. Postural instability is associated with increased falls and fear of falling, which contribute to low health-related quality of life scores (Grimbergen, Schrag, Mazibrada, Borm, & Bloem, 2013) and may reduce physical activity (Bloem, Grimbergen, Cramer, Willemsen, & Zwinderman, 2001). While PD treatments, including pharmacotherapy and surgical interventions, successfully mitigate some motor signs (e.g., reduction of tremor and rigidity, restoration of more normal muscle activity patterns) and assist with mobility, balance

remains an important, but difficult, domain to treat successfully (Bloem et al., 2001; Melton et al., 2006; Schoneburg, Mancini, Horak, & Nutt, 2013). Physical therapy rehabilitation interventions targeting balance and gait have shown efficacy in improving clinical measures of gait and balance, but greater understanding of the mechanisms of improvement is needed to enhance the clinical use of these interventions (N. E. Allen, Sherrington, Paul, & Canning, 2011; Speelman et al., 2011).

1.2. Multiple mechanisms contribute to successful balance and are affected by Parkinson's disease

Successful balance control is the ability to maintain an upright body orientation with respect to gravity, requiring maintenance of the position of the center of mass (CoM) over the base of support. The CoM is the average position of the body's mass and thus changes with body position. The CoM is also the point at which the net effect of gravity acts on the body. To maintain balance, this gravity effect must be opposed by another force (ground reaction force), which occurs when the downward projection of the CoM remains within the base of support, an area defined by the contact points between the body and environment (e.g., the area between two feet on the ground or between feet on the ground and the point where a hand grasps a railing). Through this broad strategy of controlling the position and motion of the body's center of mass (keeping it within the base of support) and the body's rotation around its CoM, the nervous system maintains balance through both static positions and dynamic movements, and during both steady state and perturbations (internal and external) (Macpherson & Horak, 2013).

Appropriately activating muscles to control CoM and maintain balance requires sensation, neural processing, and motor output. Even in quiet standing, the body is constantly in motion with some amount of sway. To maintain balance, the body actively counteracts this sway

by contracting muscles. Contracted muscles increase muscle and limb stiffness, which reduces sway. However, further control is necessary and occurs in the form of complex patterns of muscle contraction generating direction-specific forces to move the CoM. This postural equilibrium can be perturbed by voluntary movement such as reaching or turning or by unexpected perturbations like a push or the floor sliding underfoot as a train starts to move. Because voluntary movement is expected, its impact on the CoM can be offset by anticipatory feed-forward motor responses, which are muscle activations that precede a movement to counteract the expected and potentially destabilizing forces. These anticipatory responses must be learned and are adaptable. In contrast, responding to unexpected perturbations is reactive and involves organized response patterns driven by visual, vestibular, and somatosensory information (Jones, 2000; Macpherson & Horak, 2013). These patterns are called automatic postural responses (APRs) and are the focus of this work.

Sensation, neural processing, and motor output for maintaining balance are affected by PD. Impaired sensation is evident with reduced proprioception (Teasdale, Preston, & Waddington, 2017). Processing challenges are seen with 1) difficulty rapidly changing the weighting of sensory inputs (e.g., difficulty standing on unstable surface with eyes closed) (Schlenstedt et al., 2016), 2) switching between strategies when biomechanical contexts change (e.g., standing to sitting) (Horak, Nutt, & Nashner, 1992), and 3) difficulty scaling postural responses to the appropriate size (e.g., muscle activation for feet-in-place responses or too-small step size in stepping responses, leading to festination or retropulsion) (Horak, Frank, & Nutt, 1996; Jacobs, Horak, Van Tran, & Nutt, 2006). Impacts to motor output include bradykinetic reactive balance responses to perturbations (Horak et al., 1996). These PD-associated changes lead to impairments in multiple balance domains: quiet stance (flexed posture), postural sway

(higher velocity, higher frequency, larger in the lateral direction), smaller perceived limits of stability, and impaired stepping responses (Schoneburg et al., 2013). Some of these abnormalities occur at early stages of PD; abnormal posture has been reported at Hoehn and Yahr Stage 1-1.5 (Khallaf & Fayed, 2015) and altered postural sway has been seen in recently diagnosed PD patients who were not yet taking medication (Mancini et al., 2011). Other abnormalities are reported later in the disease progression, with reduced limits of stability and impaired stepping responses seen in groups of PD participants with mean Unified Parkinson's Disease Rating Scale (UPDRS, (Fahn & Elton, 1987)) motor scores of 48 (Mancini, Rocchi, Horak, & Chiari, 2008) and 24 (Jacobs et al., 2006), respectively. However, the limits of stability and stepping abnormalities may arise earlier in the disease, as these studies were not examining when the abnormalities first arose. In sum, these impairments degrade the ability of people with PD to keep their CoM over the base of support, leading to falls. The gold standards for PD symptom treatment, levodopa (L-DOPA) and deep brain stimulation, have variable effects on reactive postural adjustments (Bloem et al., 1996; St George et al., 2012).

1.3. Impaired balance is tested with perturbations in both the clinic and laboratory

Impaired balance is tested by perturbing an individual, which displaces their CoM and allows the examiner to see their motor response as they attempt to control their CoM and keep it within the base of support. Strategies to maintain standing balance can include controlling the CoM by rotating about the ankle or moving about the hips (ankle or hip strategy, both of which involve keeping feet in place) or increasing the base of the support (e.g., taking a step or grabbing a stable nearby object). In clinical settings, balance is tested with assessments such as 1) the backward pull test of the UPDRS, in which a participant receives a sharp backward pull on the shoulders, or 2) the Push and Release Test (Jacobs et al., 2006) or the reactive postural

control item on the Fullerton Advanced Balance scale (FAB, (Klein, Fiedler, & Rose, 2011)), in which support to the back is suddenly withdrawn from a participant pushing or leaning backward into the assessor's hands. To maintain balance, participants must take a step and extend the base of support under the CoM. As PD severity increases, the ability to generate large enough steps declines, and the perturbed person must take additional small steps, which is a less effective response (Jacobs et al., 2006). At the most extreme, there is no observable attempt to step.

In the laboratory, similar perturbations are applied in a more standardized fashion, generally using a perturbation platform that translates or rotates underfoot as participants stand on the platform. The precise control over the displacement, velocity, and acceleration of these perturbations allows researchers to standardize the balance challenge and provide an opportunity to examine the motor output that comprises reactive balance control. Based on the timing of an examined response, investigators infer which levels of neural processing contributed to the motor outputs.

1.4. Perturbation-induced reactive balance responses allow quantification of muscle coordination during automatic postural responses

This work features an experimental perturbation paradigm to evoke APRs within reactive balance responses; APRs allow testing of the organization of the muscle activity used in reactive balance. The standardized perturbations reduce the variability of sensory inputs to the nervous system by providing consistent levels of perturbation displacement, velocity, and acceleration (perturbation direction is systemically varied). Selecting trials with feet-in-place responses excludes stepping responses, further controlling variability. Examining APRs allows researchers to focus on brainstem-level processing. These specifications allow the motor output component of balance control to be examined in a standardized fashion.

APRs are “highly organized, flexible, and adaptive patterns of muscle activation” in which a characteristic sequence of multiple muscles’ activation is used to maintain equilibrium after a sudden disturbance causes the body to sway (Macpherson & Horak, 2013). In the case of a perturbation to standing balance in which the support surface translates forward (similar to a bus starting to move or a rug being pulled underfoot), the body sways backward and must coordinate a multiple-muscle response that generates torque about the ankle and force against the ground to return the CoM to its position above the base of support. This response can be characterized by ground reaction force vectors, center of pressure motion, body segment movement, and electromyographic (EMG) activity from muscles (which can allow inferences about neural processes of balance control).

Muscle activity associated with APRs occurs after the initial influence of spinal reflexes and before cortical influences can affect reactive balance responses. APRs reflect the requirements to restore equilibrium, and are driven by CoM movement, in contrast to reflexes, which are driven by muscle stretch. For example, the gastrocnemius is lengthened during both a toes-up rotation of the support surface and a backward translation of the support surface. A small stretch reflex may occur in both situations, but in the rotation, subsequent activation of the gastrocnemius (which further destabilizes the person) is reduced while in the translation, there is a second burst of EMG activity after the stretch reflex to restore equilibrium. APRs are also distinct from voluntary reactions, occurring at shorter latencies than voluntary reactions. More complex responses such as stepping generally occur at longer latencies than less complex responses such as feet-in-place balance maintenance, suggesting more processing within the nervous system (Macpherson & Horak, 2013). By examining muscle coordination within APRs

during feet-in-place responses to perturbations, this work assesses the basic patterns of motor output underlying balance.

The activity of each muscle during an APR has characteristic temporal and spatial patterns. In humans, postural response muscle activation occurs at a latency of 80-120 ms after the perturbation, due to signal conduction from sensory receptors to the central nervous system to leg muscles. The initial activity increases quickly after onset and can be divided into initial burst and plateau regions of the APR muscle activity (Diener, Horak, & Nashner, 1988; Welch & Ting, 2009). Muscles typically show directional tuning, in which they respond to a limited set of perturbation directions. EMG activity amplitude of a given muscle depends on the speed and direction of the perturbation. When a muscle is activated in response to a certain perturbation direction, the response amplitude in the initial burst scales linearly with peak perturbation acceleration, and the amplitude in the plateau region scales with peak perturbation velocity (Welch & Ting, 2009). APRs also show adaptability to changes in support, recruiting different sets of muscles as appropriate based on postural orientation (e.g., arm muscles if holding onto a support) and prior experience (e.g., changing from ankle to hip strategy (Horak & Nashner, 1986) or decreasing the response size over several trials (Dimitrova, Horak, & Nutt, 2004)).

Individuals with PD exhibit abnormal muscle activity (Dimitrova et al., 2004; Hallett & Khoshbin, 1980; Horak et al., 1996; Pfann, Buchman, Comella, & Corcos, 2001; Vaillancourt et al., 2006) with alterations of the timing and magnitude of agonist and antagonist muscles. More specifically, abnormal antagonist activity in leg muscles results in muscle co-contraction or co-activation. Co-contraction is a phenomenon in which paired opposing muscles (termed agonist and antagonist) are activated concurrently, thus counteracting each other to some extent, reducing the resulting force needed to maintain the CoM within the base of support, and leading

to responses that are less effective in restoring balance. Co-contraction also causes joint stiffening (Cenciarini, Loughlin, Sparto, & Redfern, 2010; Hortobagyi & DeVita, 2000; Melzer, Benjuya, & Kaplanski, 2001; Tucker, Kavanagh, Barrett, & Morrison, 2008), which may impair the efficacy of reactive balance responses to restore balance (Bingham, Choi, & Ting, 2011; Tucker et al., 2008).

1.5. Automatic postural responses offer a probe into the neural substrates of balance

A reactive balance response begins with peripheral inputs providing crucial information about the body's position and movement in space. APRs depend heavily on sensory afferents, which impact the timing and directional tuning of the response. While the exact somatosensory afferents that cause an APR are not known, Ia afferents from muscle spindles, Ib afferents from Golgi tendon organs, and cutaneous afferents provide key proprioceptive and pressure information for timing and directional tuning of APRs (Jacobs & Horak, 2007). Vestibular and visual signals are less important for APRs. Vestibular signals are not necessary for the timing of balance reactions, although damage can result in oversized responses. Visual processing is too slow to contribute significantly to the involuntary portion of APRs (Macpherson & Horak, 2013).

The sensory inputs triggered by a sudden perturbation travel to supraspinal balance centers, which produce outputs that descend along the medial and lateral vestibulospinal and reticulospinal tracts to the spinal cord to trigger APRs. Exactly which centers are involved is not known, but the brain stem and cerebellum are prominent candidates. Both sites integrate multisensory inputs (vestibular, visual, and somatosensory in brainstem; vestibular, visual, proprioceptive, and cutaneous in cerebellum), which could account for the integrated internal model or schema of the body that is key to postural control (a single sensory modality can be

misleading) (Deliagina, Beloozerova, Orlovsky, & Zelenin, 2014). The weights of individual modalities can be updated based on the demands and limitations of a given situation and the model is used to calculate the appropriate APRs (Macpherson & Horak, 2013).

1.6. Parkinson's disease may impair balance-restoring automatic postural responses through muscle co-contraction

Co-contraction is the concurrent activation of opposing muscles, which can occur when muscles serving as antagonists are abnormally activated. Higher levels of co-contraction or co-activation of agonist and antagonist muscles were found in PD patients during reactive balance compared to controls (Carpenter, Allum, Honegger, Adkin, & Bloem, 2004; Dimitrova et al., 2004; Horak et al., 1996; St George et al., 2012), due to earlier, longer, and larger antagonist muscle activation. However, the generalizability of these findings is limited by participants being selected for postural difficulties and minimal tremor (Dimitrova et al., 2004; Horak et al., 1996) or small sets of muscles and perturbation directions (2 bilateral muscles, 1 perturbation direction (St George et al., 2012); 8 muscles [3 bilaterally], 6 rotational perturbation directions (Carpenter et al., 2004)). Recent work from the Ting Neuromechanics Lab reported delayed onset and decreased magnitude in antagonist activation in PD participants' responses to perturbations after completing an Adapted Tango (AT) intervention (McKay, Ting, & Hackney, 2016). That work was similarly limited in muscle and perturbation number and by the lack of a control group. It is unclear whether the wider population of PD patients demonstrates abnormal antagonist activation across perturbation directions and muscles. In addition, previous work did not examine the relationship between antagonist activation and PD clinical features, age, or balance ability. This dissertation examines these features and uses multiple clinical balance measures to assess balance ability independent from the APR analysis.

While co-contraction is not a PD-specific phenomenon (Damiano, 1993; Hortobagyi & Devita, 2006), it is relevant to understanding balance impairment in PD, given that co-contraction is elevated during postural tasks with age (Allum 1998; Laughton 2003; Benjuya 2004; Nagai 2013; Nelson-Wong 2012) and PD (Carpenter et al., 2004; Dimitrova et al., 2004; Horak et al., 1996; St George et al., 2012) and affects functional balance. Co-contraction generally increases when control becomes more important than efficiency and is inversely associated with postural control ability in older adults (Nagai et al., 2011). In adults without PD, muscle co-contraction is associated with functional changes in behavior, including increased sway (Laughton et al., 2003; Nagai et al., 2013; Nagai et al., 2011; Warnica, Weaver, Prentice, & Laing, 2014), increased risk of falls (Ho & Bendrups, 2002; Nelson-Wong et al., 2012), and decreased functional reach distance and functional stability boundaries (Nagai et al., 2013). In PD, co-contraction is increased compared to older adults (Carpenter et al., 2004) and is not significantly affected by deep-brain stimulation or L-DOPA therapy (Kelly & Bastian, 2005; St George et al., 2012). Notably, in people without PD, co-contraction is reduced with 4 or 8 weeks of biweekly balance training (Freyler, Weltin, Gollhofer, & Ritzmann, 2014; Nagai, Yamada, Tanaka, et al., 2012) or 6 months of biweekly strength training (Hakkinen et al., 1998).

Whether co-contraction is "good" or "bad" for balance depends on the situation and it should be considered a strategy that may be appropriately or inappropriately employed. It is unclear whether co-contraction is part of the PD disease process or a compensatory mechanism for impairments resulting from PD. On one hand, co-contraction before a perturbation may be helpful in maintaining balance, as it 1) maintains some level of muscle activation, thereby reducing the amount of time necessary for a muscle to activate and build force and 2) stiffens joints, which may be an attempt to minimize postural sway (Benjuya, Melzer, & Kaplanski,

2004; Engelhart et al., 2016; Hortobagyi & DeVita, 2000). However, co-contraction after a perturbation and during the APR reduces the efficacy of the response and is detrimental to balance. Pre-perturbation co-contraction facilitates reflex antagonist activation after a perturbation (Lewis, MacKinnon, Trumbower, & Perreault, 2010), though it remains to be seen whether similar increases are seen in the APR. Given that co-contraction in healthy populations decreases as skill develops (Damiano, 1993) and increases with fear (e.g., of falling) (Cleworth, Chua, Inglis, & Carpenter, 2016; Nagai, Yamada, Uemura, et al., 2012), I hypothesized that balance ability improvements would be seen with co-contraction reductions in people with PD.

1.7. Rehabilitation interventions have been shown to improve balance in Parkinson's disease

Exercise interventions are an established rehabilitation for mitigating the gait and balance impairments seen in PD. Interventions include strength training, treadmill walking, step training, boxing, dancing, tai chi, among others and their effects on PD symptom severity, muscle strength, balance, gait, and even cognition have been investigated (N. E. Allen et al., 2011; Hackney & Earhart, 2009a, 2010; Hirsch, Toole, Maitland, & Rider, 2003; Keus, Munneke, Nijkrake, Kwakkel, & Bloem, 2009; McKee & Hackney, 2013; Shen, Wong-Yu, & Mak, 2016). Interventions targeting balance typically use clinical measures of balance, in which participants' performance of a series of tasks is scored and summed. Overall, exercise and motor training improved balance activity performance in people with PD (N. E. Allen et al., 2011).

AT is one such dance-based exercise intervention effectively targeting balance. AT is a program comprised of tango dance lessons adjusted to accommodate mobility impairments associated with PD. A professional dance instructor leads the classes, which progress in difficulty over time. Classes are typically 60-90 minutes and include a standing warm-up with postural stretches, rhythmic entrainment and partnering enhancement, learning a new step, and

amalgamating previously learned steps. Participants switch partners every 10-15 minutes and dance both leading and following roles, regardless of gender, to commercial musical recordings (Argentine tango, milongas, vals, etc.). Partnering with non-impaired individuals (loved ones, caregivers, pre-health undergraduate and graduate student volunteers) using an adjusted ballroom frame provides a safe environment for participants with PD to practice balance exercises, regulating stride length and gait speed, turning, multitasking, and initiating movement, all of which can be impaired by PD (Hackney, 2015; Hackney & McKee, 2014).

AT interventions improve clinical measures of PD symptoms, including balance, but the mechanisms of balance improvement remain unclear (and whether they constitute repair or compensation is yet to be determined). Several studies have found AT yielded improvements in balance as quantified by the Berg Balance Scale (BBS, (Hackney & Earhart, 2009a, 2009b, 2010; Hackney, Kantorovich, Levin, & Earhart, 2007)), FAB (McKee & Hackney, 2013), and miniBESTest (Duncan & Earhart, 2012, 2014; McNeely, Mai, Duncan, & Earhart, 2015). These balance scales are clinical assessments used frequently and internationally to quantify functional balance abilities. Each scale has 10-14 tasks that challenge balance, such as standing from a chair, standing on one leg, reaching, turning, stepping over an object, walking or standing in tandem stance, and reactive postural control in which participants must step to restore balance after a support is removed. Performance on each item is rated; the rating of each item is summed to provide an overall score and measure of balance performance (Berg, Wood-Dauphinee, & Williams, 1995; Franchignoni, Horak, Godi, Nardone, & Giordano, 2010; Klein et al., 2011). The physiologic changes underlying these functional improvements are unknown but are key to being able to prescribe the appropriate intervention and dose to individuals, thereby improving outcomes.

1.8. Rehabilitation interventions have been shown to improve muscle activity patterns in Parkinson's disease

Recent work suggests that exercise interventions may improve abnormal aspects of muscle activity in PD. The Progressive Resistance Exercise Training in Parkinson's disease trial (PRET-PD) reported increases in agonist duration and magnitude and decreases in the number of agonist bursts in the upper limb (David et al., 2016). A recent pilot study found results that suggest reduced abnormal muscle activation as a potential mechanism of improvement with AT (McKay et al., 2016). Specifically, significant delays in antagonist onset time and reduction in antagonist duration were seen during reactive balance after an AT intervention. However, the study was limited by: the lack of a nonPD control group, the collection of data in the ON medication state, the difference in perturbation levels used across participants, and the small number of muscles (bilateral TA and MGAS) and perturbation directions examined (2), which may result in missing the peak activity of a given muscle.

1.9. This work uses electromyography to probe mechanisms of balance impairment and improvement

This work first investigates whether co-contraction during reactive balance is elevated in a broader selection of people with PD and across a wider selection of muscles and perturbation directions, and how co-contraction is related to PD severity and balance ability. Second, this work investigates whether completion of an AT intervention reduces co-contraction in reactive balance in people with PD. This information contributes to the understanding of mechanisms underlying balance impairment and improvement in people with mild to moderate PD.

The current work uses both clinical measures of balance to quantify balance performance and EMG recordings to quantify the underlying muscle activity patterns and infer the amount of

co-contraction. EMG offers insight into the output of the nervous system, allowing inferences about the upstream processing and providing information about the resulting signals at the muscle level.

1.10. This work presents a new method for assessing muscle modulation

Expanding the analysis of abnormal antagonist activation to multiple muscles and perturbation directions in a group of people with PD requires modifying methods to capture co-contraction. Commonly used methods of assessing co-contraction quantify either the time or magnitude of the overlapping activation of two opposing muscles (Rosa, Marques, Demain, Metcalf, & Rodrigues, 2014; St George et al., 2012). Approaches quantifying magnitude range from simply calculating the difference between the maximum and minimum activation of the opposing muscles or the mean value of the area of overlap to more complex indices such as those used by Falconer and Winter (Falconer & Winter, 1985), Hortobagyi (Hortobagyi & DeVita, 2000), Lewek (Lewek, Rudolph, & Snyder-Mackler, 2004), and Kelly (Kelly & Bastian, 2005). These methods are problematic when examining a range of muscles, some of which lack a clear opposing antagonist, and when considering a given muscle across multiple perturbation directions in which its classification as an agonist or antagonist is unclear. Additionally, EMG normalization typically requires a maximum voluntary contraction, which can be problematic to obtain in a group of people with a voluntary movement disorder such as PD. Thus, it was necessary to adapt an existing modulation index to apply in this study. Kelly and Bastian (Kelly & Bastian, 2005) use a modulation index that quantifies the activity of one muscle as it serves as both an agonist and antagonist. Here, low modulation can indicate low agonist activity, high antagonist activity or both, all three of which have the same functional result of a comparatively elevated antagonist activity.

I adapted the modulation index to work with more than two perturbation directions by using criteria (maximum or minimum activity) to select which EMG values to use instead of pre-specifying directions. This approach was used first in the cross-sectional comparison of people with PD to nonPD controls and again in the longitudinal comparison of people with PD before and after either AT participation or no AT participation. Incorporating clinical measures of balance and PD severity for consideration with modulation allowed this work a fairly unique opportunity to examine the relationship between modulation and clinical measures. These experiments demonstrated that co-contraction is associated with PD, PD severity, and balance impairment. The association with PD was true across different PD phenotypes (tremor dominant, TD; indeterminate, ID; postural instability and gait difficulty, PIGD). While I did not observe a co-contraction change with AT participation in this study, study limitations may explain the null results and are discussed to inform future work.

2. Antagonist muscle activity during reactive balance responses is elevated in Parkinson's disease and in balance impairment

A version of this chapter was published by PLoS ONE and can be read at https://doi.org/10.1371/journal.pone.0211137.

Kimberly C. Lang, Madeleine E. Hackney, Lena H. Ting, J. Lucas McKay. 2019. Antagonist muscle activity during reactive balance responses is elevated in Parkinson's disease and in balance impairment. PLoS ONE 14(1): e0211137.

My contributions were: protocol development, study recruitment and coordination, data collection, management, and analysis, manuscript writing.

2.1. Abstract

BACKGROUND: Abnormal muscle activity may cause balance impairments in Parkinson's disease (PD). Prior studies have described earlier, longer, and larger activation of antagonist muscles in the lower limbs during balance tasks in individuals with PD. Here, I used a multidirectional perturbation paradigm to quantify how antagonist muscle activity during balance tasks is influenced by 1) the presence of PD and 2) the presence of impaired balance as assessed by standardized behavioral scales. METHODS: I compared antagonist activation during reactive balance responses to multidirectional support-surface translation perturbations in 31 participants with PD (age 68±9; OFF-medication Hoehn & Yahr 1-3 and UPDRS-III 32±10) and 13 matched individuals without PD (age 65±9). I quantified modulation of muscle activity (i.e., the ability to activate and inhibit muscles appropriately according to the perturbation direction) using modulation indices (MI) derived from minimum and maximum EMG activation levels observed across perturbation directions. RESULTS: Antagonist leg muscle activity was abnormal in participants with PD compared to participants without PD. Linear mixed models identified significant associations between impaired modulation and PD ($P<0.05$), PD severity ($P<0.01$), and balance ability ($P<0.05$), but not age ($P=0.10$). CONCLUSION: Antagonist activity is

abnormally increased during reactive balance tasks in people with PD as well as in neurotypical individuals with impaired balance. Abnormal antagonist activity may contribute to balance impairments in PD and in neurotypical aging and be a potential rehabilitation target or outcome measure.

2.2. Introduction

Abnormal antagonist muscle activity can cause joint stiffening by concurrently activating paired agonist and antagonist muscles ("co-contraction" or "co-activation") (Cenciarini et al., 2010; Hortobagyi & DeVita, 2000, 2006; Melzer et al., 2001), which may contribute to balance impairment in people with PD. Prior studies in individuals with PD carefully selected for postural difficulties and minimal tremor (Dimitrova et al., 2004; Horak et al., 1996) demonstrate earlier, longer, and larger antagonist muscle activation during reactive balance responses to support surface perturbations compared to controls (Carpenter et al., 2004; Dimitrova et al., 2004; Horak et al., 1996; St George et al., 2012). Evaluation of antagonist muscle activation during balance could therefore potentially inform improved rehabilitative outcome measures (e.g., (McKay et al., 2016)). However, it is unclear whether antagonist muscle activity during reactive balance responses is abnormal in individuals with PD who are not selected by phenotype and are candidates for exercise-based rehabilitation.

While co-contraction is not a PD-specific phenomenon (Damiano, 1993), its elevation with age and PD and its effects on functional balance make it relevant to understanding balance impairment in PD. In adults without PD, muscle co-contraction is associated with functional changes in behavior, including increased sway (Laughton et al., 2003; Nagai et al., 2013; Nagai et al., 2011; Warnica et al., 2014), increased risk of falls (Ho & Bendrups, 2002; Nelson-Wong et

al., 2012), and decreased functional reach distance and functional stability boundaries (Nagai et al., 2013).

Here, the objective was to determine whether antagonist muscle activity during balance responses was increased across leg muscles in participants with PD who were not selected by phenotype. I recorded automatic postural responses induced by multidirectional translational support surface perturbations and examined subsequent muscle activation (Falconer & Winter, 1985; Kelly & Bastian, 2005) in participants with PD and matched participants without PD. As an assay of abnormal antagonist activity, I quantified the ability to activate and inhibit muscles appropriately according to the perturbation direction using modulation indices (MI) derived from minimum and maximum EMG levels observed across directions. Primary analyses examined associations between the presence of PD and decreased modulation. To clarify the role of other predictors, I also performed secondary analyses to assess the associations between decreased muscle modulation and 1) age, 2) interaction between PD and age, 3) balance ability, 4) PD phenotype, and 5) PD severity.

2.3. Methods

2.3.1 Participants

I performed a cross-sectional observational study using baseline measures from a longitudinal study of exercise-based rehabilitation. Participants with PD (n=34) and age-matched individuals without PD ("nonPD," n=16) were recruited from the Atlanta area from December 2013 through May 2017. Among participants with PD, the majority (21/34) were enrolled into a two-arm randomized trial with dance-based exercise rehabilitation and non-contact control arms; the remaining participants and all matched individuals were allocated directly to the non-contact

control arm. No screening on symptom phenotype was performed. Participants provided written consent according to protocols approved by the Institutional Review Boards of Emory University (IRB00083425) and/or the Georgia Institute of Technology (H11159).

Inclusion criteria were: age ≥ 35, vision corrected if necessary, ability to walk ≥ 10 feet with or without an assistive device, normal perception of vibration and light touch on feet, no dance class participation within the previous 6 months, and demonstrated response to levodopa (PD only). Exclusion criteria were: significant musculoskeletal, cognitive, or neurological impairments other than PD as determined by the investigators.

After enrollment, participants were excluded from analysis for the following reasons: neurological diagnosis other than PD disclosed after study entry (N=1 PD, N=1 nonPD), non-compliance with OFF medication state (N=1 PD), inability to complete reactive balance protocol (N=1 PD), suspected undiagnosed cognitive impairment (N=1 nonPD), and technical difficulties in data processing (N=1 nonPD).

2.3.2 Assessment protocol

All participants were assessed according to a standardized protocol that spanned 3-4 hours including informed consent, collection of clinical and demographic information, and assessment of clinical and reactive balance. PD symptom severity was assessed by the Unified Parkinson's Disease Rating Scale III (UPDRS-III) (Fahn & Elton, 1987), by a Movement Disorders Society-certified rater (MEH) either in-person or on video. PD phenotype (tremor dominant, TD; indeterminate, ID; postural instability and gait difficulty, PIGD) was calculated from UPDRS subscores using standard formulae (Stebbins et al., 2013). Balance ability was assessed with the Fullerton Advanced Balance Scale (FAB) (Klein et al., 2011) and Berg Balance Scale (BBS) (Berg et al., 1995). Gait was assessed with the Dynamic Gait Index (DGI)

(Shumway-Cook & Woollacott, 1995). Freezing of gait was assessed with the Freezing of Gait Questionnaire B (FOGQ-B) (Giladi et al., 2000). All participants with PD were assessed in the 12-hour OFF anti-parkinsonian medication state.

2.3.3 Reactive balance assessments

Participants stood on a custom perturbation platform that produced ramp-and-hold support-surface translations (7.5 cm peak displacement, 15 cm/s peak velocity, 0.1 g peak acceleration) (McKay et al., 2016). Feet were positioned parallel with medial aspects 28 cm apart and arms were crossed across the chest. Participants experienced 3 forward perturbations of the support surface to reduce startle (or "first-trial") effects before being tested with a set of 36 randomized perturbations in 12 evenly distributed horizontal-plane directions (Figure 1). Perturbation trials that elicited stepping responses were repeated at the end of the randomized block if possible.

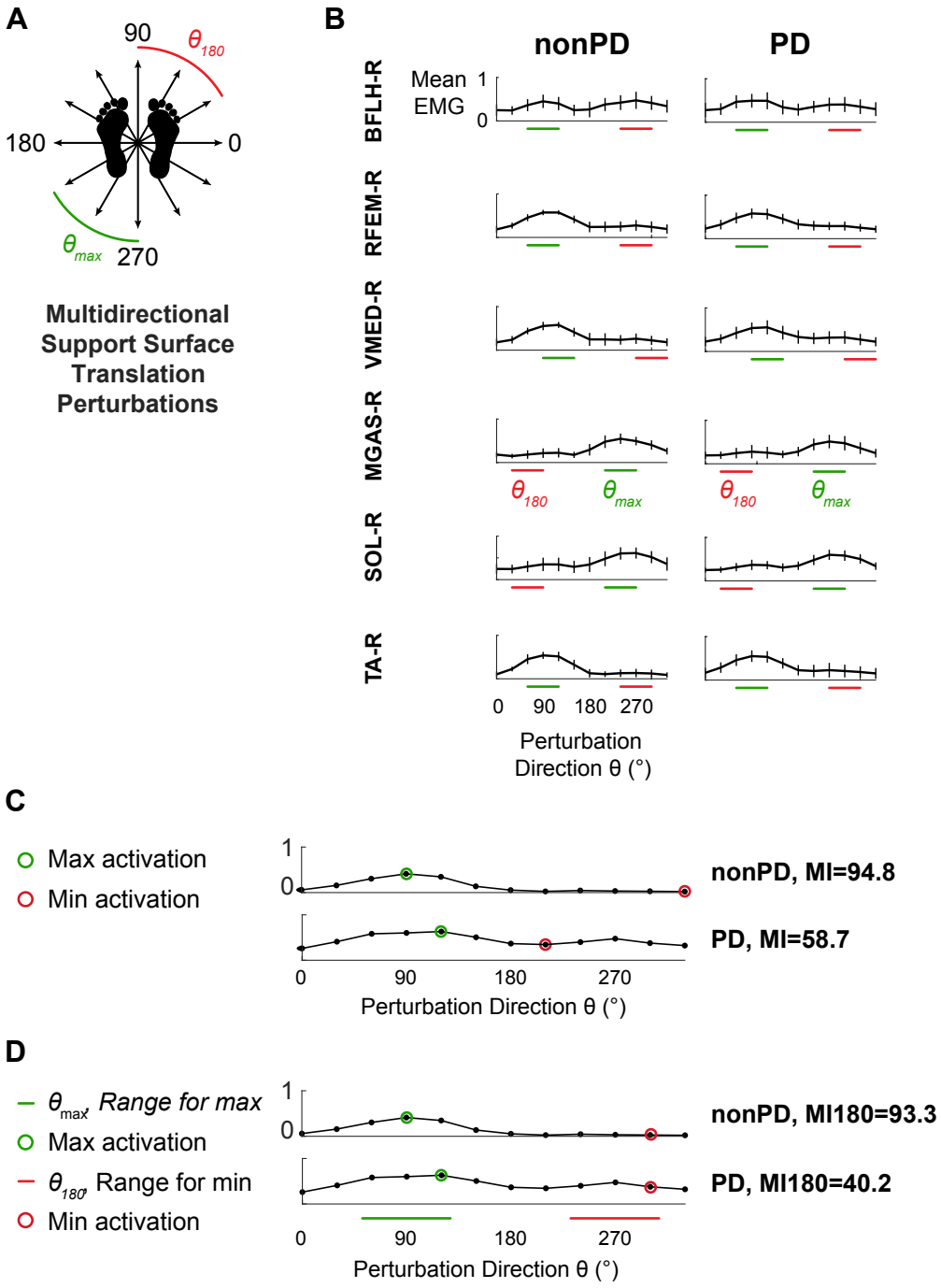

Figure 1. Examples of tuning curves and modulation indices used to quantify muscle activity as a function of perturbation direction.
A: Schematic depiction of multidirectional support surface translation perturbations. Green and red perturbation directions correspond to those for which maximum values were observed most frequently for MGAS-R and those directly opposite (see D). B: Tuning curves from the nonPD and PD groups depicting mean EMG activity during the APRX time bin (70-450 ms after perturbation onset). Horizontal bars indicate perturbation direction ranges θ_{max} and θ_{180} used for

calculation of modulation index MI180. C/D:. Examples of calculation of MI (C, Equation 1) and MI180 (D, Equation 2) for TA from two different participants.

2.3.4 EMG processing

Surface EMG activity was collected from 11 lower limb muscles: bilateral *soleus* (left, SOL-L; right, SOL-R), *medial gastrocnemius* (MGAS-L, MGAS-R), *tibialis anterior* (TA-L, TA-R), *biceps femoris long head* (BFLH-L, BFLH-R), *rectus femoris* (RFEM-L, RFEM-R) and right *vastus medialis* (VMED-R). Silver/silver chloride disc electrodes were placed 2 cm apart at the motor point, over the neuromuscular junction, where the greatest EMG signal has been reported (Basmajian & Blumenstein, 1980). EMG data were recorded using telemetered EMG (Konigsberg, Pasadena, CA) and synchronized to kinematic data (120 Hz) using Vicon motion capture equipment (Oxford Metrics, Denver, CO). EMG data were recorded at either 1080 or 1200 Hz depending on the equipment version. EMG recordings were processed offline (high-pass, 35 Hz, de-mean, rectify, low-pass, 40 Hz) (McKay et al., 2016). Trials eliciting stepping responses or spotter intervention were identified in video records and excluded from analyses. Trials with significant EMG motion artifacts were identified by visual inspection and excluded from analyses. After exclusions due to steps or EMG quality concerns, the number of trials available per perturbation direction per participant ranged from 0 to 5 with an average and standard deviation of 3.0 ± 0.3.

2.3.5 Muscle activity modulation indices: MI and MI180

In order to assess modulation of muscle activity during reactive balance, I computed a muscle "modulation index" that described the ability to activate and inhibit each muscle appropriately according to the perturbation direction. Because of the increased number of experimental conditions compared to previous studies, I developed two extensions of an existing modulation index that was initially developed to assess antagonist activity in only two movement

directions (Kelly & Bastian, 2005). In previous work, the movement directions that require each muscle to be activated (as an agonist) or inhibited (as an antagonist) were obvious from the biomechanical constraints of the task. In the multidirectional perturbation protocol used here, each muscle exhibits a continuum of activity from agonist to antagonist as a function of perturbation direction.

Therefore, I calculated mean EMG levels during two time bins within each trial that encompassed the medium- and medium- and long-latency automatic postural response: 100-175 ms (APR1) and 70-450 ms (APRX) after perturbation onset (Dimitrova et al., 2004), and subsequently assembled mean APR1 and APRX EMG levels into tuning curves that described muscle activity as a function of perturbation direction (Figure 1). Then, I used the maximum and minimum values of each tuning curve for each muscle for each participant to compute the modulation index (MI) using the following equation (Figure 1):

$$MI = 100 \cdot \frac{\max\left(\overline{EMG}(\theta)\right) - \min\left(\overline{EMG}(\theta)\right)}{\max\left(\overline{EMG}(\theta)\right)} \quad (1)$$

where $\overline{EMG}(\theta)$ indicates the vector of 12 mean EMG values for the 12 perturbation directions.

While the MI value reflects the greatest amount of modulation across the 12 perturbation directions, in some cases, it did not capture abnormally elevated activity 180° from the perturbation direction for which the muscles were maximally activated, and in which the muscles could reasonably be assumed to be antagonists due to the biomechanical constraints of the task. Therefore, I developed a similar formula to calculate a more physiologically-relevant index (MI180), in which the maximum value of each tuning curve was identified within the range θ_{max} of the 3 perturbation directions for which maximum EMG values were observed most frequently (Figure 1) and the minimum value was identified within the range θ_{180} directly opposite θ_{max}:

$$MI180 = 100 \cdot \frac{\max\left(\overline{EMG}(\theta_{max})\right) - \min\left(\overline{EMG}(\theta_{180})\right)}{\max\left(\overline{EMG}(\theta_{max})\right)} \quad (2)$$

where $\overline{EMG}(\theta_{max})$ indicates the vector of 3 mean EMG values for the 3 perturbation directions included in θ_{max}, and $\overline{EMG}(\theta_{180})$ corresponds similarly to the vector of 3 mean EMG values for θ_{180}.

2.3.6 Statistical Analysis

Differences between the PD and nonPD groups in demographic and clinical variables were assessed with chi-square tests and independent samples *t*-tests as appropriate.

For each muscle recorded, separate chi-square tests of homogeneity were performed to assess crude differences in modulation between participants with vs. without PD, between participants above vs. below the sample median in age, and between participants above vs. below the sample median in balance ability, as assessed by FAB. For these tests, modulation indices (MI and MI180 in both APR1 and APRX) were dichotomized about median values. Associations between predictors (PD, age above the sample median, and balance ability below the sample median) and the presence of MI below the median were expressed as odds ratios (OR) ± 95% CI. OR>1 indicate strong associations between the presence of a given predictor and the presence of low modulation. Primary analyses were conducted with MI in APRX (detailed below) and repeated with MI in APR1 and MI180 in APR1 and APRX.

To estimate the association between study variables and modulation across muscles, multivariate linear regression analyses were used to examine the effects of predictors of interest, including PD, age, balance, PD severity, PD phenotype, and the interaction between PD and age.

To test whether the presence of PD was associated with muscle modulation, I fit the following linear mixed model:

$$\begin{aligned} MI_{ijk} =& \beta_0 + \beta_{PD} \cdot PD \\ &+ \sum_{i=1}^{N_m-1} \beta_{1i} \cdot Muscle_i \\ &+ \sum_{j=1}^{N_p-1} \beta_{2j} \cdot Participant_j \\ &+ \epsilon_{ijk} \end{aligned} \tag{3}$$

in order to evaluate the following null hypothesis with an *F* test:

$$H_{01} : \beta_{PD} = 0$$

In Equation 3, the indicator variable *PD* is 1 for participants with PD and 0 otherwise, β_{1i} is the beta coefficient for the fixed effect of muscle *i* (with TA as the reference group) and β_{2j} is the beta coefficient for the random effect of participant *j*.

To test whether age was associated with muscle modulation, I fit the following model:

$$\begin{aligned} MI_{ijk} =& \beta_0 + \beta_{Age} \cdot Age_c \\ &+ \sum_{i=1}^{N_m-1} \beta_{1i} \cdot Muscle_i \\ &+ \sum_{j=1}^{N_p-1} \beta_{2j} \cdot Participant_j \\ &+ \epsilon_{ijk} \end{aligned} \tag{4}$$

where Age_c designates participant age centered about the sample median, and evaluated the null hypothesis:

$$H_{02} : \beta_{Age} = 0$$

Similarly, to test whether balance ability as measured by FAB was associated with muscle modulation, I fit the following linear mixed model:

$$
\begin{aligned}
MI_{ijk} = & \beta_0 + \beta_{FAB} \cdot FAB \\
& + \sum_{i=1}^{N_m - 1} \beta_{1i} \cdot Muscle_i \\
& + \sum_{j=1}^{N_p - 1} \beta_{2j} \cdot Participant_j \\
& + \beta_{3j} \cdot Age_c \\
& + \epsilon_{ijk}
\end{aligned} \tag{5}
$$

where *FAB* designates total FAB score, and the following null hypothesis was evaluated with an *F* test:

$$H_{03} : \beta_{FAB} = 0$$

Additional linear mixed models evaluating associations between additional candidate predictor variables and modulation are presented in the Appendix.

2.4. Results

2.4.1 Participant characteristics

Demographic and clinical characteristics of the study participants are presented in Table 1. No significant differences were observed between the PD and nonPD groups in sex, age, or BMI. Compared to nonPD, the PD group had significantly poorer balance performance on FAB, BBS, and DGI (all P values<0.01), and significantly increased prevalence of previous falls (P=0.03).

Table 1. Demographic and clinical characteristics of study participants with and without Parkinson's disease (PD).

	PD (N=31)	nonPD (N=13)	P Value
Sex (N, %)			0.60
Male	17, 55%	6, 46%	
Female	14, 45%	7, 54%	
Age, y, mean±SD	67.6 ± 8.8	64.5 ± 8.8	0.28
BMI, kg/m^2, mean±SD	25.6 ± 4.0	26.0 ± 3.8	0.76
Behavioral balance measures			
BBS (0-56), mean±SD	52.2 ± 4.4	55.1 ± 1.3	<0.01*
FAB (0-40), mean±SD	29.2 ± 5.7	33.1 ± 3.1	<0.01*
DGI (0-24), mean±SD [a]	20.0 ± 3.5	22.5 ± 1.3	<0.01*
Fall History			0.03*
0 falls in previous 12 months, (N, %)	13, 42%	10, 77%	
≥1 fall in previous 12 months, (N, %)	18, 58%	3, 23%	
PD clinical features			
PD duration, y, mean±SD	7.5 ± 5.9	-	
UPDRS-III (0-108), mean±SD	31.7 ± 9.5	-	
UPDRS items, mean±SD		-	
Leg rigidity (III.22, 0-8)	1.9 ± 2.0	-	
Posture (III.28, 0-4)	1.0 ± 1.0	-	
Gait (III.29, 0-4)	1.1 ± 0.6	-	
Postural stability (III.30, 0-4)	0.8 ± 0.7	-	
Modified Hoehn & Yahr Stage, (N, %)		-	
1	1, 3%	-	
1.5	5, 16%	-	
2	13, 42%	-	
2.5	4, 13%	-	
3	8, 26%	-	
PD phenotype, (N, %)		-	
Postural Instability and Gait Disability (PIGD)	19, 61%	-	
Indeterminate (ID)	3, 10%	-	
Tremor-Dominant (TD)	9, 29%	-	
Freezing of Gait, (N, %)[b]		-	
Freezer	14, 45%	-	
Non-freezer	15, 48%	-	

Abbreviations: BBS, Berg Balance Scale; FAB, Fullerton Advanced Balance Scale; DGI, Dynamic Gait Index. [a]PD N=29. [b]PD N=29. *P<0.05.

2.4.2 Description of muscle activity across perturbation directions

Tuning curves exhibited clear cosine tuning (Figure 1) consistent with those reported previously in the literature (Dimitrova et al., 2004; Torres-Oviedo & Ting, 2007). Average APRX tuning curve widths at half maximum (McKay & Ting, 2012) were 115±7° and 111±11° for the nonPD and PD groups, respectively. Across all subjects and muscles, modulation indices in APRX had a mean ± SD value of 71.9±12.9 and a range of 36.4-96.6 for MI. For MI180, the mean ± SD was 59.4±31.8, with a range of -301.6-94.8. In APR1, the MI mean ± SD was 70.8±15.2, with a range of 20.7-98.4 and the MI180 mean ± SD was 63.1±24.2, with a range of -160.3-98.4. Negative values observed in MI180 corresponded to tuning curves in which muscles were more strongly activated in the θ_{180} range of perturbation directions and accounted for a small percentage of tuning curves in both the PD (2.4% in APRX, 1.2% in APR1) and nonPD groups (3.5% in APRX, 0.7% in APR1).

2.4.3 PD, age, and impaired balance ability were associated with impaired modulation in some individual muscles

Univariate analyses showed that PD was associated with lower MI for each muscle analyzed during the APRX time window (Figure 2A, filled circles; note that all Odds Ratios [OR] >1). This association was statistically significant for TA (OR=4.02, P<0.01). PD was associated with lower MI180 in 4/6 muscles analyzed during APRX (Figure 2A, unfilled circles). Age was also associated with lower MI in APRX (OR: 2.79±1.67, range 1.21-5.69), particularly for BFLH (P<0.01), SOL (P<0.05), and TA (P<0.001) (Figure 2B). Low FAB score was associated with lower MI for both BFLH (OR: 2.52, 95% CL: 1.07-5.95, P=0.03) and TA (OR: 4.59, 95% CL: 1.87-11.26, P<0.001) during APRX. Analyses during APR1 showed inconsistent

associations between PD and impaired modulation (significant in SOL with MI180 (OR: 3.12 [1.18-8.25], P=0.02); Figure 2A).

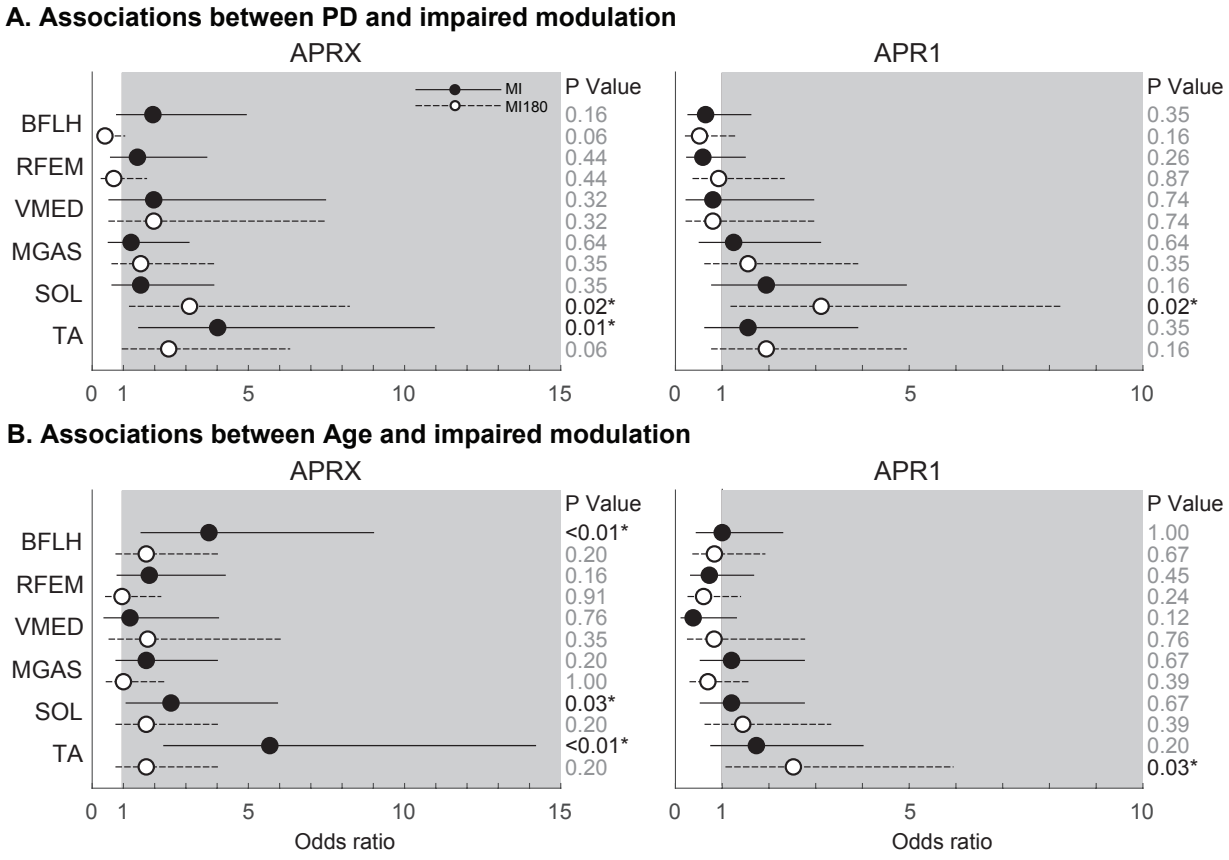

Figure 2. Associations between PD (A) and Age (B) and impaired modulation in analyses of individual muscles.
Associations are described as Odds Ratios (OR) calculated separately using both MI and MI180 modulation indices derived from both APR1 and APRX time bins. Solid lines and filled dots represent the OR and 95% confidence limits for modulation index MI; dashed lines and open dots represent modulation index MI180. Odds ratios > 1 (shaded area) indicate that the presence of the risk factor (PD or Age) is strongly associated with the presence of impaired modulation for that muscle.

2.4.4 PD, PD severity, and impaired balance ability were associated with impaired modulation across muscles

Across muscles, linear mixed models identified significant associations between PD ($P<0.05$) and PD severity ($P<0.01$) and decreased MI during APRX (Table 2). Higher FAB score was significantly associated with increased MI during APRX ($P<0.05$). There was only marginal evidence of an association between increased age and decreased MI ($P=0.10$), or, similarly, for interaction between PD and age in the effect on MI ($P=0.13$). Linear mixed models that stratified the PD group by PD phenotype identified strong associations between each phenotype (TD, ID, and PIGD) and decreased MI although identified parameters were only marginally significant ($P=0.06$, TD; 0.05, ID; 0.15, PIGD). Associations between these predictor variables and MI180 were the same in direction but decreased in magnitude by ≈34%. The only exception to this pattern was that no association was identified between FAB score and MI180. No significant associations between predictors and modulation indices were identified in analyses of APR1 (Table A1).

Table 2. Associations between predictors of interest and muscle modulation indices MI and MI180.

	MI			MI180		
Predictor	*β*	95% CI	P Value	*β*	95% CI	P Value
PD	-4.26	-8.31, -0.21	0.04*	-3.34	-11.66, 4.98	0.43
Age	-0.18	-0.40, 0.03	0.10	-0.14	-0.58, 0.30	0.53
FAB	0.38	0.005, 0.75	<0.05*	-0.04	-0.83, 0.74	0.91
PD Severity	-0.16	-0.26, -0.05	<0.01*	-0.06	-0.29, 0.18	0.64
PD Phenotype						
PIGD	-3.25	-7.67, 1.18	0.15	-2.41	-11.64, 6.82	0.61
TD	-5.22	-10.55, 0.12	0.06	-3.85	-15.00, 7.29	0.50
ID	-7.82	-15.69, 0.04	0.05	-7.70	-24.11, 8.71	0.36
PD•Age	-0.36	-0.83, 0.10	0.13	-0.09	-1.09, 0.91	0.86

*p<0.05. Abbreviations: FAB, Fullerton Advanced Balance Scale; PIGD, Postural Instability and Gait Difficulty; TD, Tremor-Dominant; ID, Indeterminate. Mixed model results reflect the APRX time window.

2.5. Discussion

This study's main result was that leg muscle activity during reactive balance was abnormal in a group of participants with mild-moderate PD and a range of symptom phenotypes. Lower muscle modulation across perturbation directions – an estimate of an impaired ability to appropriately inhibit muscles according to the biomechanical requirements of the balance task – was predicted by the presence of PD and by PD severity. These findings were common across the TD, PIGD, and ID phenotypes, indicating that modulation is affected in all three phenotypes. Overall, these results extend previous seminal studies in carefully selected participants with PD and provide additional evidence that antagonist muscle activation is impaired in PD and could be a useful rehabilitative target.

This study expanded foundational work reporting increased co-contraction in people with PD during reactive balance by demonstrating that the results generalize to a broader selection of PD phenotypes and muscles, and to participants with PD who were representative of those

interested in rehabilitation and not selected on phenotype (Dimitrova et al., 2004; Horak et al., 1996). First, since PD participants were not selected by phenotype (e.g., "gait and postural abnormalities" with Hoehn and Yahr stages 3-4 (Horak et al., 1996) or "axial and/or postural problems and minimal tremor" with Hoehn and Yahr 1-4 (Dimitrova et al., 2004)), this study includes a broader representation of the PD population. While carefully selecting participants decreases variability and is clearly appropriate for foundational research, I propose that it is critical to establish that the results generalize to rehabilitation, where restricting enrollment to certain patient subgroups is typically impractical and uncommon. Second, I examined 11 muscles (5 bilateral) across 12 perturbation directions, in contrast to earlier work that examined 4 lower limb muscles (left tibialis anterior, left soleus, and bilateral gluteus medius) in 6 perturbation directions (Carpenter et al., 2004), 4 muscles (bilateral tibialis anterior and gastrocnemius) in 1 perturbation direction (St George et al., 2012), or 4 muscles (bilateral tibialis anterior and medial gastrocnemius) in 2 perturbation directions (McKay et al., 2016). Third, I examined a larger group of PD participants (n=31) than most earlier studies, which studied groups of 13 (Dimitrova et al., 2004; Horak et al., 1996), 10 (Carpenter et al., 2004), or 9 (McKay et al., 2016) people with PD. St George and colleagues examined 33 participants with PD, but 24 had deep brain stimulation and only 9 did not (St George et al., 2012).

Importantly, while I anticipated differences between the PIGD and TD phenotypes on the balance task (e.g., potentially no association between TD parkinsonism and abnormal balance muscle activity), I found that compared to the overall PD effect on MI (β=-4.26), the effects of each particular PD phenotype on MI were relatively similar, ranging from only moderate attenuation (PIGD, β=-3.25, attenuation of overall PD effect of -24%) to substantial strengthening (ID, β=-7.82, +84%) of the overall PD effect. These effects of all three phenotypes

on MI suggest that modulation is reduced in each of the phenotypes. This overlap between phenotype groups has also been reported in objective measures of balance and gait (e.g., time to complete Timed Up and Go) (Herman, Weiss, Brozgol, Giladi, & Hausdorff, 2014).

While comparing the nonPD group to those of previous studies is difficult – there are no obvious clinical variables to use – it is encouraging that the prevalence of previous falls in this nonPD group recruited from the metro Atlanta area (23%) was similar to that reported among the spouses of participants with PD in the Netherlands (27% (Bloem et al., 2001)). This provides some evidence that the neurotypical nonPD group here is comparable to those recruited from other geographic regions (e.g., Washington and Oregon (Dimitrova et al., 2004; Horak et al., 1996; St George et al., 2012), Western Europe (Carpenter et al., 2004)) with different sociodemographic profiles.

One important limitation to note is that although I examined a larger sample of participants with PD (n=31) than many studies (n=9-13 patients (Carpenter et al., 2004; Dimitrova et al., 2004; Horak et al., 1996; McKay et al., 2016)), sample size limitations prevented me from imposing the most stringent phenotype classification criteria that are currently recommended (Herman et al., 2014). It remains to be seen whether the associations between phenotypes and modulation reported here would be affected by the use of more stringent criteria. However, based on the strong associations with impaired modulation observed in all phenotype groups, I believe it to be unlikely.

I was surprised that age was not significantly associated with muscle modulation here, given that co-contraction is elevated in neurotypical older adults compared to young adults (Damiano, 1993). I speculate that including college-aged participants would probably have

resulted in a clear age effect, although potentially one that was nonlinear with time, given that I did not observe a strong effect of age in this sample, which ranged from 39-86.

The presence of a significant association between FAB score and muscle modulation supports the idea that outcome measures derived from antagonist muscle activation could be useful in the general geriatric population, although more studies are required to confirm this. Reports suggest that training may reduce co-contraction during postural control in neurotypical older adults (Nagai, Yamada, Tanaka, et al., 2012) and PD (McKay et al., 2016). However, in the linear mixed model used here (Equation 5) sample size prevented me from controlling for the presence of PD. The identified association may in part reflect a PD effect rather than a balance effect per se.

From a methodological perspective, the modulation indices developed here may be useful in contexts other than reactive balance for capturing muscle modulation without requiring pre-specified directions of agonist and antagonist activity. These results offer a measure of the greatest possible amount of modulation (MI) and a measure of the amount of modulation that occurs when effective agonist activity is important for reactive balance (MI180). MI180 also captures instances of antagonist activity that are greater than agonist activity, which were infrequent here.

In summary, I found evidence that the presence of PD, PD severity, and reduced balance ability were related to a measure of elevated leg muscle antagonist activity during reactive balance. It remains to be seen whether abnormal muscle activity results from primary PD disease processes or represents a compensatory strategy (adaptive or maladaptive). However, my findings suggest that there is a relationship between antagonist activity and balance impairment in PD that generally holds for the TD and PIGD phenotypes. Consequently, elevated antagonist

activity and the resulting co-contraction could be a useful target or outcome measure for balance rehabilitation.

2.6. Appendix: Antagonist muscle activity during reactive balance responses is elevated in Parkinson's disease and in balance impairment.

2.6.1 Additional linear mixed models

In addition to the linear mixed models described in the main text, I fit the following linear mixed models in order to evaluate associations between additional candidate predictor variables and muscle modulation.

2.6.2 Interaction between PD and age

To test whether associations between PD and modulation were modified by age, I fit the following linear mixed model with an interaction term:

$$\begin{aligned} MI_{ijk} = & \beta_0 + \beta_{PD\cdot Age} \cdot PD \cdot Age_c \\ & + \sum_{i=1}^{N_m-1} \beta_{1i} \cdot Muscle_i \\ & + \sum_{j=1}^{N_p-1} \beta_{2j} \cdot Participant_j \\ & + \beta_{3j} \cdot PD \\ & + \beta_{4j} \cdot Age_c \\ & + \epsilon_{ijk} \end{aligned} \tag{A1}$$

with the following null hypothesis:

$$H_{04} : \beta_{PD\cdot Age} = 0$$

2.6.3 PD phenotype

To test whether phenotype (TD, ID, PIGD, nonPD) was associated with MI modulation during APRX across all muscles, I fit the following linear mixed model, with variables as defined in the main text:

$$\begin{aligned} MI_{ijk} =& \beta_0 + \sum_{l=1}^{N_{Pheno}-1} \beta_{Pheno} \cdot Pheno \\ &+ \sum_{i=1}^{N_m-1} \beta_{1i} \cdot Muscle_i \\ &+ \sum_{j=1}^{N_p-1} \beta_{2j} \cdot Participant_j \\ &+ \epsilon_{ijk} \end{aligned} \tag{A2}$$

where β_{Pheno} refers to the beta coefficient for phenotype l, with nonPD as the reference group. The following null hypothesis was evaluated with a Type III F-test:

$$H_{05} : \beta_{Pheno} = 0$$

2.6.4 PD severity

To test whether PD severity (UPDRS-III score) was associated with MI modulation during APRX across all muscles, I fit the following linear mixed model:

$$\begin{aligned} MI_{ijk} =& \beta_0 + \beta_{PD\,Severity} \cdot UPDRSIII \\ &+ \sum_{i=1}^{N_m-1} \beta_{1i} \cdot Muscle_i \\ &+ \sum_{j=1}^{N_p-1} \beta_{2j} \cdot Participant_j \\ &+ \epsilon_{ijk} \end{aligned} \tag{A3}$$

where $\beta_{PDSeverity}$ refers to the beta coefficient for UPDRS-III score. The following null hypothesis was evaluated with a Type III F-test:

$$H_{06} : \beta_{PD\,Severity} = 0$$

2.6.5 Associations between study variables and modulation indices in APR1.

Across muscles, linear mixed models identified no significant associations between predictors and either modulation index in the APR1 time bin (Table A1).

Table A1. Associations between predictors of interest and muscle modulation indices MI and MI180 calculated during the APR1 time window.

	MI			MI180		
Predictor	β	95% CI	P Value	β	95% CI	P Value
PD	0.31	-4.21, 4.83	0.89	-1.37	-9.35, 6.61	0.74
Age	-0.06	-0.30, 0.17	0.61	-0.02	-0.44, 0.40	0.93
FAB	0.29	-0.13, 0.71	0.17	0.31	-0.44, 1.06	0.42
PD Severity	-0.02	-0.15, 0.10	0.72	-0.01	-0.23, 0.22	0.96
PD Phenotype						
PIGD	-0.55	-5.55, 4.45	0.83	-3.48	-12.23, 5.27	0.44
TD	1.92	-4.10, 7.95	0.53	2.30	-8.25, 12.86	0.67
ID	0.99	-7.90, 9.88	0.83	1.04	-14.52, 16.60	0.90
PD•Age	-0.03	-0.58, 0.51	0.90	-0.10	-1.06, 0.86	0.84

*p<0.05. Abbreviations: FAB, Fullerton Advanced Balance Scale; PIGD, Postural Instability and Gait Difficulty; TD, Tremor-Dominant; ID, Indeterminate.

3. People with PD and high baseline balance function do not improve on clinical measures of balance or abnormal antagonist muscle activity after completion of an Adapted Tango intervention.

3.1. Abstract

BACKGROUND: Antagonist leg muscle activity is increased during reactive balance responses in people with Parkinson's disease (PD). Abnormal antagonist activity is associated with and may contribute to balance impairments in PD and thus could be a potential rehabilitation target. However, it is not known whether antagonist activity is reduced with improvements in balance ability after exercise-based balance rehabilitation interventions. RESEARCH QUESTION: Are improvements in balance ability after completion of an Adapted Tango (AT) intervention (30 hours within 12 weeks) associated with reduced leg muscle antagonist activity? Specifically, is the change in antagonist activity associated with metrics of balance frequently used in physical therapy clinics to quantify performance on balance-challenging tasks (Fullerton Advanced Balance Scale)? METHODS: Antagonist muscle activation during reactive balance responses to multidirectional support-surface translation perturbations in 30 participants with mild-moderate PD was assessed at baseline, 12 week, and 16 week time points. Participants were assigned to an AT intervention or control group. Participants in the intervention group attended 20 AT lessons between baseline and the 12 week time point, and then returned at 16 weeks for a final assessment. The ability to activate and inhibit muscles appropriately according to the perturbation direction was quantified using a muscle modulation index (MI) derived from minimum and maximum EMG activation levels observed across perturbation directions. RESULTS: There was a significant group by time interaction effect on Dynamic Gait Index performance, but not on the Berg Balance or Fullerton

Advanced Balance Scales. For MI, neither the group, time, nor group by time interaction effects were significant. CONCLUSION: After AT, participants showed improvement in gait but not balance tests. While there was neither a significant effect of group nor time in MI during reactive balance, it is possible that a larger sample size or a sample of participants with lower baseline clinical balance performance would show an association between improvements in clinical balance measures and changes in MI after completion of AT. Future studies should include people of lower baseline ability and consider examining MI during a clinical balance task such as the Pull Test to clarify whether changes in MI are associated with balance improvement and impairment.

3.2. Introduction

Interventions designed to mitigate balance and gait deficits in people with PD, such as AT, improve clinical measures of gait and balance, but the mechanisms underlying these improvements remain unclear (Duncan & Earhart, 2012, 2014; Hackney & Earhart, 2009a, 2009b, 2010; Hackney et al., 2007; Kim, Allen, Canning, & Fung, 2013; Schoneburg et al., 2013). Typically, studies investigating improved gait and balance performance focus on clinical assessments of that performance and not the potential physiological changes accompanying those improvements. However, improved understanding of the physiological mechanisms would facilitate intervention development and prescription. Understanding how various interventions mitigate balance impairments would allow the treatments to be more accurately targeted to individual needs and tracked to determine when an individual has attained the maximum benefit. Likewise, understanding the motor control impairments associated with illness and injury (e.g., stroke, PD) can predict differences in the functional challenges faced by individuals. Elucidating

the mechanisms of effective rehabilitation interventions may improve clinical outcomes and guide rehabilitation development.

Abnormal antagonist activity is a candidate mechanism of AT-associated balance improvement. While muscle activity can be impaired in multiple ways, antagonist activity is a promising aspect to examine, as it is both functionally relevant to balance control and can be measured non-invasively. Antagonist activity is increased in people with PD, which can reduce the effectiveness of balance-restoring responses such as the APR. As discussed in Chapter 2, previous studies reported earlier, longer, and larger antagonist muscle activation during reactive balance responses to support surface perturbations compared to controls (Carpenter et al., 2004; Dimitrova et al., 2004; Horak et al., 1996; St George et al., 2012). This increased antagonist activity results in increased co-contraction of muscles during the reactive balance response, impairing its effectiveness in restoring balance. The investigation detailed in Chapter 2 found similar results across a wider selection of participants, muscles, and perturbation directions, and expanded the findings to reveal associations between antagonist activity and PD severity and balance performance.

Abnormal antagonist activity can be altered with rehabilitation interventions. Training healthy older adults increases balance performance and decreases co-contraction (Nagai, Yamada, Tanaka, et al., 2012). More importantly, this decrease is still possible in people with PD. Pilot work in people with mild-moderate PD tested ON medication (McKay et al., 2016) found delayed antagonist onset and reduced duration during reactive standing balance after participating in AT. This result, coupled with the association between antagonist activity and PD, PD severity, and balance (detailed in Chapter 2), suggests that antagonist muscle activity is a potential mechanism by which AT may improve balance.

To test whether abnormal antagonist activation decreases with completion of an AT intervention, my collaborators (L.H. Ting, J.L. McKay, M.E. Hackney) and I performed a randomized trial with AT and Control arms. I hypothesized that abnormal muscle activation in lower leg muscles during standing balance after translational support-surface perturbations would decrease in participants who completed a 30 hour dose of AT over 12 weeks compared to those who did not participate.

3.3. Methods

The Institutional Review Boards of Emory University and/or the Georgia Institute of Technology approved the protocols used for this work and all participants provided written informed consent.

3.3.1 Study design

This work reports the results of a randomized trial with an AT rehabilitation intervention group (AT) and a non-contact Control group. Participants were assessed three times: 1) at baseline, 2) after completion of 30 hours of biweekly AT classes (AT group) or 12 weeks (Control group), and 3) 4 weeks after the second assessment (16 weeks).

3.3.2 Participants

People with PD were recruited from the metro Atlanta area through PD outreach events, PD exercise classes, and PD support groups between December 2013 and June 2015. Thirty-three people were enrolled, with the majority (20/33) randomized into either the AT or Control arm and the remaining participants assigned directly to the non-contact Control arm after randomization to AT was closed. This randomization approach was necessary because all AT participants had to be enrolled and assessed prior to taking one series of AT classes together

(details in 3.3.3). This group comprised the PD participants in the cross-sectional investigation discussed in Chapter 2 (K. C. Lang, Hackney, Ting, & McKay, 2019).

Inclusion criteria were: age ≥ 35, vision corrected if necessary, ability to walk ≥ 10 feet with or without an assistive device, normal perception of vibration and light touch on feet, no dance class participation within the previous 6 months, and demonstrated response to levodopa. Exclusion criteria were: significant musculoskeletal, cognitive, or neurological impairments other than PD as determined by the investigators.

A diagram describing the flow of participants through the study is depicted in Figure 3.

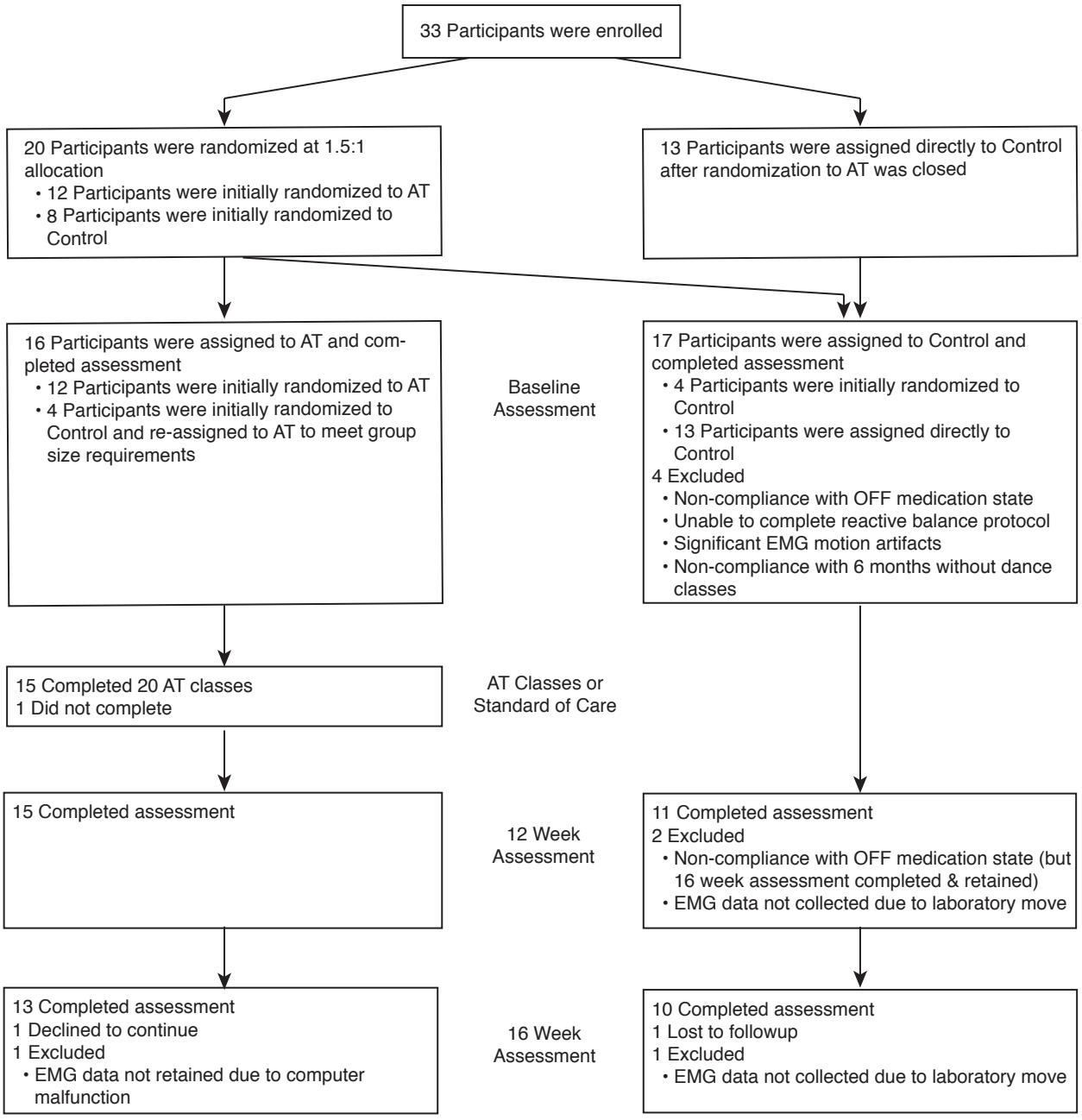

Figure 3. Consort diagram of participation.

3.3.3 Adapted Tango Intervention

Participants completed twenty 90-minute moderate-intensity AT classes in 10-12 weeks. Classes were taught by a professional dance instructor with many years of experience working

with older adults with mobility impairments. Four class sessions were offered each week and participants were expected to attend two. Attendance was tracked to ensure participants received the appropriate dose (quantified as time at class). Participants with PD partnered with individuals without PD, holding forearms in the adapted ballroom frame, and spent an equal time leading and following. Participants also switched partners frequently. In each class, participants completed standing warm-ups to upbeat music, followed by dancing to music. Skills included rhythmic entrainment to the beat (e.g., tapping toes or heels or opening and closing hands), walking to various tango rhythms (more complex than typical gait), learning new steps, and completing sequences of steps to the beat. Difficulty progressed over time. Participants could take breaks as needed, as in previous studies (Hackney & Earhart, 2009a, 2010; Hackney et al., 2007; McKee & Hackney, 2013).

3.3.4 Outcome measure assessment

At each of the three assessments, participants were in the 12-hour OFF medication state and completed a 3-4 hour standardized protocol featuring clinical information collection and clinical and reactive balance assessment, as previously described (K. C. Lang et al., 2019). At the baseline visit, informed consent, demographic information, and information related to inclusion/exclusion criteria that could not be assessed by phone were also obtained.

The following clinical measures were collected: UPDRS-III, by a Movement Disorders Society-certified rater (MEH) either in-person or on video (Fahn & Elton, 1987); PD phenotype (TD; ID; PIGD; calculated using standard formulae) (Stebbins et al., 2013); FAB (Klein et al., 2011); BBS (Berg et al., 1995); DGI (Shumway-Cook & Woollacott, 1995); FOGQ-B (Giladi et al., 2000).

3.3.5 Reactive balance assessment

As previously reported, participants experienced ramp-and-hold support-surface translation perturbations generated by a custom platform (7.5 cm peak displacement, 15 cm/s peak velocity, 0.1 g peak acceleration) (K. C. Lang et al., 2019; McKay et al., 2016). Participants stood on the platform with arms crossed and feet parallel to each other (28 cm between medial aspects). They were instructed to gaze at a landscape photograph on the wall in front of them and to keep their balance with feet in place if possible. To reduce startle or "first-trial" effects, 3 forward perturbations preceded the set of multidirectional perturbations. This set featured 36 perturbations in 12 randomized horizontal directions. If possible, trials with a stepping response were repeated at the end of the block.

3.3.6 EMG collection and processing

As previously reported in Chapter 2, surface EMG activity was collected during reactive balance from 11 leg muscles: bilateral SOL, MGAS, TA, BFLH, RFEM, and right VMED (K. C. Lang et al., 2019). EMG data were collected from silver/silver chloride disc electrodes placed 2 cm apart at the motor point (Basmajian & Blumenstein, 1980) with telemetered EMG (Konigsberg, Pasadena, CA) at 1080 Hz. Vicon motion capture equipment (Oxford Metrics, Denver, CO) synchronized EMG data to kinematic data (120 Hz). EMG data were processed offline (high-pass filter at 35 Hz, de-mean, rectify, low-pass filter at 40 Hz) (K. C. Lang et al., 2019; McKay et al., 2016). Trials were visually inspected for significant EMG motion artifacts.

3.3.7 Muscle activity modulation index (MI)

To examine muscle activity modulation, I calculated a muscle modulation index describing the ability to activate and inhibit each muscle appropriately according to perturbation direction (K. C. Lang et al., 2019). In the multidirectional perturbation protocol used here, each

muscle exhibits a continuum of activity from agonist to antagonist as a function of perturbation direction. To quantify this modulation, I calculated mean EMG levels during three time bins within each trial that encompassed the medium- and long-latency APR: 70-450 ms (APRX) and 175-250 (APRY) after perturbation onset (Dimitrova et al., 2004), and subsequently assembled mean APRX and APRY EMG levels into tuning curves that described muscle activity as a function of perturbation direction. Then, I used the maximum and minimum values of each tuning curve for each muscle for each participant to compute the modulation index (MI) using the following equation:

$$MI = 100 \cdot \frac{\max\left(\overline{EMG}(\theta)\right) - \min\left(\overline{EMG}(\theta)\right)}{\max\left(\overline{EMG}(\theta)\right)} \tag{1}$$

where $\overline{EMG}(\theta)$ indicates the vector of 12 mean EMG values for the 12 perturbation directions.

3.3.8 Statistical analysis

Baseline differences between the AT and Control groups in demographic and clinical variables were assessed with chi-square tests, Fisher's Exact tests, and independent samples *t*-tests as appropriate. To test whether the effect of time on muscle modulation was modified by participation in AT, I fit the following linear mixed model:

$$\begin{aligned} MI_{ijk} = &\beta_0 + \beta_{Group} \cdot Group \\ &+ \beta_{Time} \cdot TimePoint \\ &+ \beta_{Group \cdot Time} \cdot Group \cdot TimePoint \\ &+ \sum_{i=1}^{N_m - 1} \beta_{1i} \cdot Muscle_i \\ &+ \sum_{j=1}^{N_p - 1} \beta_{2j} \cdot Participant_j \\ &+ \epsilon_{ijk} \end{aligned} \tag{6}$$

and evaluated the following null hypothesis with an *F* test:

$$H_{07} : \beta_{Group \cdot Time} = 0$$

In Equation 6, β_{Group} is the beta coefficient for the fixed effect of Group (the indicator variable *Group* is 1 for the AT group and 0 for the Control group), β_{Time} is the beta coefficient for the fixed effect of TimePoint (0, 12, or 16, with 0 as the reference group), $\beta_{Group*Time}$ is the beta coefficient for the interaction between study group and time point, β_{1i} is the beta coefficient for the fixed effect of muscle *i* (with TA as the reference group) and β_{2j} is the beta coefficient for the random effect of participant *j*. This approach was repeated to assess the effect of time on clinical outcome measures, with FAB, BBS, or DGI replacing MI as the outcome variable.

3.4. Results

3.4.1 Baseline participant characteristics

Overall, the AT and Control groups had similar demographic and clinical characteristics at baseline, with the Control group's slightly higher BMI as the only significant difference (Table 3). Though not statistically different from the Control group at baseline, the AT group performance was higher on FAB (2 point difference, p=0.31) and DGI (1.6 point difference, p=0.21). The AT group had a shorter mean PD duration but a higher UPDRS-III symptom severity.

Table 3. Demographic and clinical characteristics of the study population at baseline. Values presented reflect participants available for analysis at baseline, including participants who were later excluded due to incomplete assessments or technical issues with EMG data but excluding 3 Control participants who were noncompliant or could not complete the reactive balance protocol.

	AT	Control	P Value
N	16	14	
Demographic			
Sex (N, %)			0.43
Male	8, 50%	9, 64%	
Female	8, 50%	5, 36%	
Age, y, mean ± SD	66.9±11.3	68.6±5.5	0.61
BMI, kg/m^2, mean ± SD	24.1±3.8	27.3±3.8	0.03*
Behavioral			
Fullerton Advanced Balance Scale (FAB, 0-40), mean ± SD	30.6±6.0	28.6±4.7	0.31
Berg Balance Scale (BBS, 0-56), mean ± SD	52.8±4.3	52.4±4.0	0.80
Dynamic Gait Index (DGI, 0-24), mean ± SD[a]	21.1±3.0	19.5±3.4	0.21
Fall History (N, %)			0.67
0 falls in prev. 12 months	8, 50%	5, 36%	
1 fall in prev. 12 months	1, 6%	2, 14%	
≥2 falls in prev. 12 months	7, 44%	7, 50%	
PD clinical features			
PD duration, y, mean ± SD	5.8±4.7	9.4±6.9	0.11
UPDRS-III (0-108), mean ± SD	32.8±8.5	30.5±11.0	0.53
Modified Hoehn & Yahr Stage, (N, %)			0.85
1	0, 0%	1, 7%	
1.5	2, 12%	3, 21.5%	
2	7, 44%	6, 43%	
2.5	3, 19%	1, 7%	
3	4, 25%	3, 21.5%	
PD phenotype, (N, %)			0.65
Postural Instability and Gait Disability (PIGD)	9, 56%	9, 64%	
Indeterminate (ID)	1, 6%	2, 14%	
Tremor-Dominant (TD)	6, 38%	3, 22%	
Freezing of Gait, (N, %)[b]			1.0
Freezer	8, 50%	7, 50%	
Non-freezer	8, 50%	7, 50%	

*$p<0.05$. [a]DGI was not completed for 2 AT participants. [b]If FOGQ-B data was not available, Freezing of Gait status was based on a participant's response to UPDRS II Question 14.

Of the 30 participants present at baseline, all but 3 (1 AT participant, 2 Control participants) had at least 2 time points with EMG data and were therefore available for longitudinal analysis. Between these AT and Control groups used for longitudinal analysis, there were no significant differences in the characteristics listed in Table 3 ($p=0.06$ for BMI).

3.4.2 Adapted Tango participation and assessment timing

Fifteen AT participants completed 20 classes (<7% attrition rate) and 14 completed all 3 assessments.

3.4.3 Effect of Adapted Tango on clinical outcome measures

Performance on BBS was high in both AT and Control groups over time. On FAB and DGI, the AT group performed better than the Control group and showed a slight trend of improvement over time. Over 16 weeks, the AT group mean improved approximately 2 points on FAB and 1 point on DGI. However, only DGI had significant group by time interaction ($p=0.001$) (Figure 4 and Table 4).

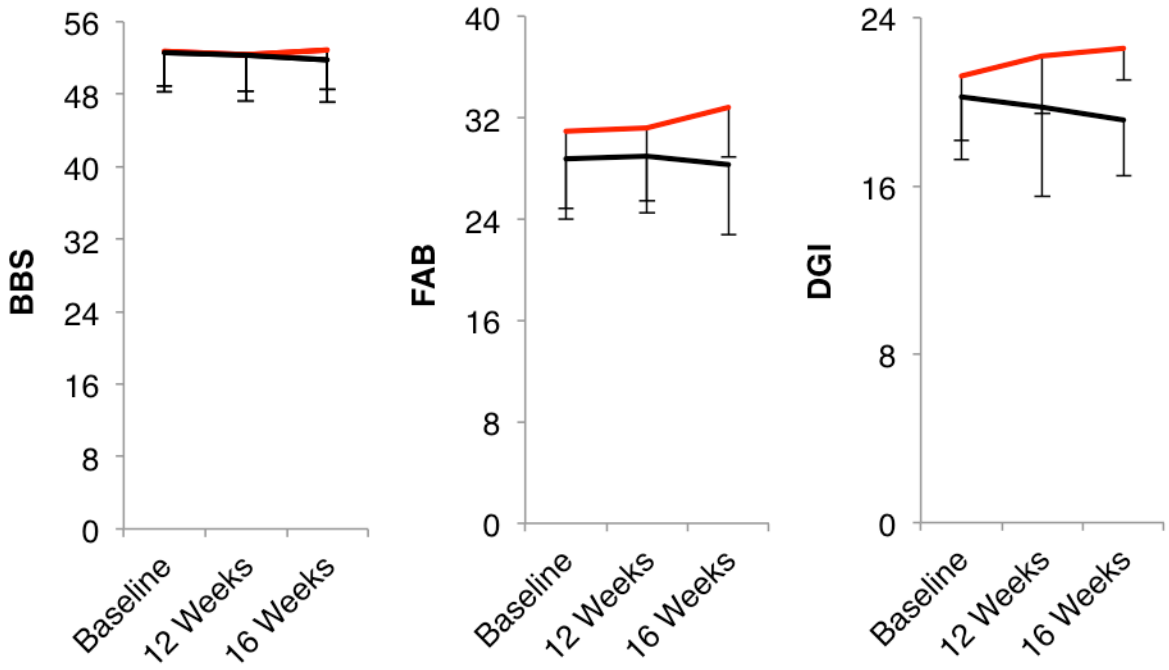

Figure 4. Balance and gait performance was higher in the AT group (red line), across time points.

Table 4. Associations between group and time and clinical measures of balance and gait.

	Group			Time			Group By Time		
Out-come	*β*	95% CI	P Value	*β*	95% CI	P Value	*β*	95% CI	P Value
FAB	2.06	-2.00, 6.11	0.32	-0.06	-0.17, 0.05	0.88	0.13	-0.01, 0.26	0.06
BBS	0.06	-3.02, 3.14	0.97	-0.08	-0.20, 0.03	0.15	0.06	-0.09, 0.20	0.45
DGI	0.89	-1.44, 3.22	0.45	-0.11	-0.19, -0.03	0.34	0.17	0.07, 0.27	0.001*

*p<0.05. Abbreviations: FAB, Fullerton Advanced Balance Scale; BBS, Berg Balance Scale; DGI, Dynamic Gait Index.

3.4.4 Effect of Adapted Tango on muscle modulation

The MI values in both APRX and APRY were similar between the AT and Control groups (Figure 5) and did not change significantly over time; there was no significant group, time or group by time effects on MI (Table 5). MGAS depicted in the graphs showed a slight

difference between groups, with a decrease over time in the AT group, but this was not significant in the linear mixed model (Figure 5, Table 5).

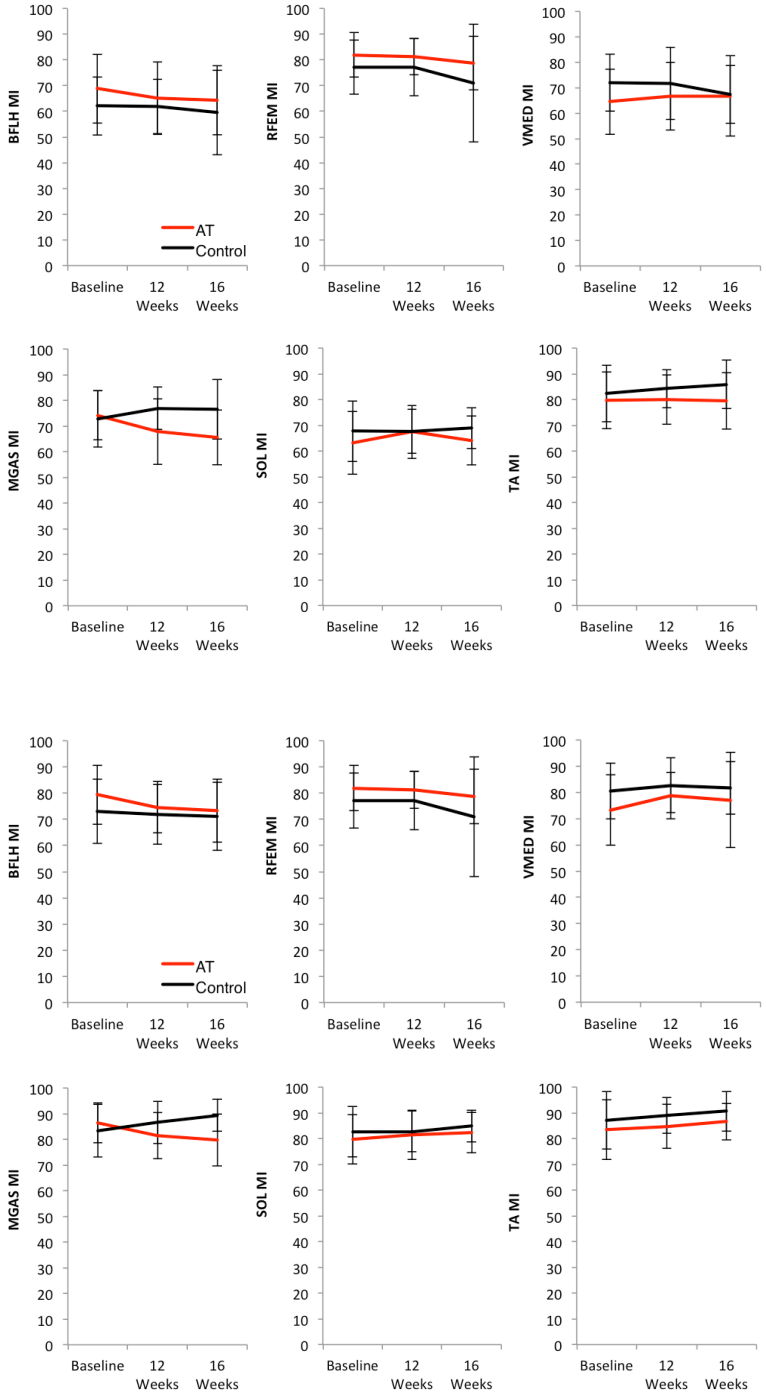

Figure 5. MI values in both APRX (top rows) and APRY (bottom rows) are similar in AT and Control groups and across time in this study.

Table 5. Associations between group and time and MI across muscles.

Out-come	Group			Time			Group*Time		
	β	95% CI	P Value	*β*	95% CI	P Value	*β*	95% CI	P Value
MI, APRX	0.79	-3.91, 5.50	0.74	0.002	-0.17, 0.18	0.17	-0.16	-0.38, 0.06	0.15
MI, APRY	0.86	-3.69, 5.41	0.71	0.009	-0.15, 0.16	0.33	-0.12	-0.31, 0.08	0.23

*p<0.05.

3.5. Discussion

AT participants in this study showed improvement in DGI, but not in MI during reactive balance. This lack of significant group by time interaction effect on MI may be due to a limitation in participants' capacity for improvement with AT from a high baseline balance ability or to the fact that the reactive balance task in the laboratory is not identical to items in the balance and gait scales. Additionally, the fact that MI is a recently developed measure means that 1) this study could not be powered to detect MI change and 2) the level of balance impairment or amount of change in balance impairment associated with a detectable change in muscle modulation is not yet clear. Despite the lack of a robust group result, MI remains a viable research target. Selecting participants to prevent limited potential functional improvement and adding an instrumented clinical balance measure would facilitate examining the associations between change in balance and change in muscle modulation.

I hypothesized that AT might yield balance improvements by decreasing co-contraction, given the reported improvements in clinical measures of balance (BBS, FAB) (Hackney & Earhart, 2009a, 2009b, 2010; Hackney et al., 2007; McKee & Hackney, 2013), and association between impaired balance and decreased modulation (Chapter 2). This effort was one of the first to examine a physiological mechanism underlying functional balance improvements after AT,

expanding upon a pilot study reporting changes in antagonist activation duration and magnitude consistent with decreased co-contraction (McKay et al., 2016). While the current study featured an AT intervention of 20 1.5-hour classes within 10-12 weeks, which differed slightly from the structure of AT in most previous studies (Lotzke, Ostermann, & Bussing, 2015), the total dose was the same or larger, suggesting that the difference in AT program weeks does not explain the differing results.

The lack of anticipated differences between groups over time in FAB and MI measures may be due to a limited ability of AT to improve balance beyond a certain level. This group of AT participants began at a higher baseline level of balance ability compared to previous reports (McKay et al., 2016). McKay et al. reported mean FAB scores of approximately 27 at baseline and 32 at follow-up and of mean DGI scores of 19 (baseline) and 21 (follow-up). In contrast, the AT group examined here began with a mean score of 31 on the FAB and 21 on the DGI at baseline. Thus, this AT group began the study with balance and gait abilities very close to those seen after AT participation in another study. It may be that AT is not able to improve balance performance beyond this level on FAB (although improvement on DGI was seen). Given that performance on these clinical measures was not maximal and FAB is used to avoid ceiling effects, the potential limitation appears to be due to the capacity for functional balance improvement and not due to the scales used. Additionally, the scale that did show group differences over time (DGI) assesses gait performance and its subitems require different motor function than that tested in the laboratory reactive balance task. The expected relationship between AT and modulation may be more clear in a group of participants with lower baseline ability and when considering more similar laboratory and clinical tasks.

Given that MI was a recently developed metric and this investigation is the first to examine how the MI metric changes over time, it is not known where in the spectrum of balance ability or MI values one should expect a possible change in muscle modulation or how much modulation change is possible with training or associated with improved balance. Modulation is known to be reduced in PD compared with controls and associated with balance ability (Carpenter et al., 2004; Dimitrova et al., 2004; Horak et al., 1996; K. C. Lang et al., 2019; St George et al., 2012), but the MI "cutoff score" below which one would expect impaired balance, or vice versa, is unknown. Similarly, the amount of modulation change that would be associated with the minimally clinically important difference (MCID) in balance scale scores is unknown. Additionally, the newness of the measure means that the current study could not be powered to detect a difference in MI (the study was powered to detect a difference in BBS score after an AT intervention).

To further understand the relationship between muscle modulation and balance ability, recruiting participants with lower baseline balance scale scores would reduce potential limitations in balance improvement and adding an instrumented version of a clinical balance task (e.g., UPDRS Pull Test) would reduce heterogeneity between the compared clinical and laboratory balance tasks. Participants with lower baseline balance ability have greater capacity for improvement in balance performance. Given that mean MI values for the AT and Control groups here were below 80 (with the exception of TA), ceiling effects in MI appear to be less of a concern. Additionally, adding a clinical balance task that is more similar to the laboratory task during which EMGs are recorded would further clarify the relationship between motor performance and muscle modulation. Comparing MI during reactive balance to clinical measures of balance (which are composite scores of performance on multiple functional tasks) is not a

direct comparison. That is, the reactive balance recordings are not simply an instrumented version of clinical tests, which introduces additional heterogeneity. An instrumented version of the clinical tests might yield stronger associations, but at the cost of being able to examine a well-characterized response with certain portions associated with different levels of control (e.g., brainstem-mediated, cortical involvement, etc.). Thus, adding rather than substituting an instrumented clinical task such as the Pull Test may be most useful.

Finally, future work might clarify the value of modulation changes in functional balance, both alone and in context with other mechanisms of balance improvement. Depending on contexts such as disease progression and severity, the same direction and magnitude of change might be associated with functional impairment or improvement via compensation. It may be useful to consider the effect of MI changes in the context of impairments, including proprioception (Teasdale et al., 2017), rigidity (Wirdefeldt et al., 2011), processing and adaptation to new biomechanical contexts (Horak et al., 1996; Horak et al., 1992; Jacobs et al., 2006; Schlenstedt et al., 2016), dual tasking (Strouwen et al., 2015), and generating internally-guided or externally-guided movements (Hackney, Lee, Battisto, Crosson, & McGregor, 2015). Capabilities and changes in these other aspects that keenly affect balance control (e.g., cognitive ability, muscle strength, sensory feedback, or changes in dopamine transportation) may account for some of the improvement seen after AT and may influence whether changes in muscle modulation are employed as a compensatory strategy. Understanding the changes in muscle control and whether they are beneficial or harmful to balance performance is a key insight that will allow rehabilitation interventions to address balance impairments in PD more effectively.

4. Changes in muscle modulation during reactive balance and in clinical measures of balance after Adapted Tango depend on baseline balance ability: A case series

4.1. Abstract

BACKGROUND: Abnormal antagonist activity during reactive balance is associated with PD and balance impairments and is a potential balance rehabilitation target. A study of antagonist activity in people with PD who completed an AT intervention did not show changes in antagonist activity (Chapter 3), but this result may be due to participants' high baseline balance ability limiting their capacity to improve with AT. A case series may provide preliminary indications of how antagonist activation changes with functional balance ability after AT, by examining individual participants with various levels of baseline balance ability and directions of change in balance ability after AT. RESEARCH QUESTION: Does muscle modulation during reactive balance decrease in AT participants who show improvement in clinical balance? METHODS: Antagonist muscle activation during reactive balance responses to multidirectional support-surface translation perturbations in 30 participants with mild-moderate PD was assessed at baseline, 12 week, and 16 week time points. Participants were assigned to an AT intervention or control group. Participants in the dance group attended 20 AT lessons between baseline and the 12 week time point, and then returned at 16 weeks for a final assessment. Modulation of muscle activity (i.e., the ability to activate and inhibit muscles appropriately according to the perturbation direction) was quantified using MI derived from minimum and maximum EMG activation levels observed across perturbation directions. Four cases, individuals with mild-moderate PD, were selected to highlight how MI changed with FAB in people who participated in AT. The case series focused on MI within MGAS muscles. RESULTS: In a case with a low baseline FAB score, balance improvements after AT occurred

with no change in MGAS MI. In cases with higher baseline FAB scores, MI decreases accompanied both balance decline and maintenance; MI increase accompanied balance maintenance. CONCLUSION: Improvement from very low balance ability likely occurs not by changes in muscle modulation during reactive balance, but by a different mechanism. The level of baseline balance ability may help determine the functional significance of changes in muscle modulation.

4.2. Introduction

Although a robust association between muscle modulation during reactive balance and AT was not identified in the group outcomes discussed in Chapter 3, there was heterogeneity in the trajectories of participants' clinical scores (Figure 6), as is seen in many rehabilitation intervention studies. The variance seen here is probably similar to previous reports using AT, but individual responses were not reported (McKay et al., 2016). It seemed possible that an association could be present in those participants with room in their balance scores to improve that may have been obscured by the group analysis. To explore this possibility, cases were selected to provide preliminary evidence for the hypothesis that there is a stronger effect of AT on MI in people with lower balance ability.

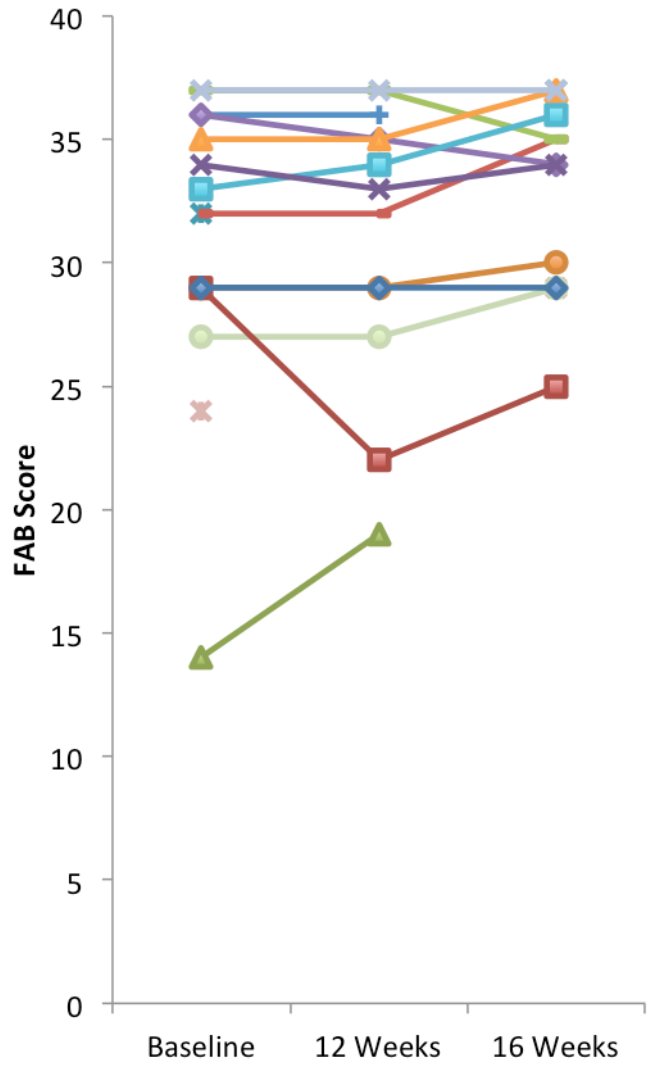

Figure 6. Heterogeneous responses of FAB scores within the AT group

4.3. Methods

To investigate how modulation changed with balance ability after AT, 4 individuals in the AT group were selected based on 1) their baseline FAB score and 2) how their FAB score changed by the 12 week time point. FAB was the balance outcome measure most similar to the laboratory balance task because FAB rates the ability to perform several static and dynamic balance tasks. FAB was also the clinical balance scale least susceptible to ceiling effects. Cases from the nonPD control group were not examined, as the objective was to understand the

relationship between balance ability and AT outcomes in muscle modulation. Case studies were selected to examine 1) low, moderate, and high baseline balance function, relative to the group mean (31) and the established cutoff for fall risk (25) (Hernandez & Rose, 2008) and 2) improvement, no change, or decline in balance ability (FAB) from baseline to the 12 week time point. Participants of similar ages were selected to minimize the role age might play in the interpretation. Cases were all over 70 years of age.

Case 1 was a participant who began the study with the lowest balance ability of the group and improved after AT (Low + Improve). Case 2 was a participant who began the study with a moderate balance ability but declined after AT (Moderate + Decline). Case 3 started at the same moderate balance ability and maintained that performance after AT (Moderate + Maintain). Finally, Case 4 began with a high balance ability, which declined by only 1 point by the 12 week time point and returned to baseline levels by the 16 week time point (High + Maintain). Examining these four participants of similar ages provides examples of different balance ability trajectories seen in this study from low, moderate, and high baseline balance ability levels.

The examination focused on MGAS MI during APRX, as MGAS has clearly defined contributions to maintaining standing balance and much of the previous muscle co-contraction and modulation work focused on these contributions. In addition, previous group analysis (Chapter 3) suggested that MGAS in APRX might be the muscle and time bin where AT had the greatest effect.

4.4. Results

4.4.1 Baseline Characteristics and Clinical Presentation

The four cases are comprised of 3 females and 1 male, all of whom were 71 years of age or older at baseline (Table 6). The cases had moderate PD, ranging from Hoehn and Yahr Stage 2 to 3 and from OFF-medication UPDRS-III 33 to 46. Time since diagnosis ranged from 3-17 years. Both PIGD and TD phenotypes were represented, as well as fallers and nonfallers. Of the cases, one (Case 1) began with a very low FAB score, two (Case 2, Case 3) began with a moderate FAB score (29), which is above the cutoff for fall risk and just below the AT group average (31, Table 3), and one (Case 4) began with a high FAB score (34, one of several AT participants who began with high FAB scores ranging from 32-37).

Table 6. Demographic and clinical characteristics of the cases at baseline.

Case	Age	Sex	Years since PD Diagnosis	UPDRS-III, (OFF medication)	Hoehn & Yahr Stage	PD Phenotype	Falls in Previous 12 Months	FAB (/40)
1	75	F	10	46	3	PIGD	≥2	14
2	82	F	3	37	3	PIGD	0	29
3	84	F	17	44	2.5	TD	≥2	29
4	71	M	5	33	2	TD	0	34

Abbreviations: UPDRS, Unified Parkinson's Disease Rating Scale

4.4.2 Change in balance ability and muscle modulation after Adapted Tango

Case 1 (Low + Improve FAB trajectory) improved from a low balance score after AT, but did not have notable accompanying change in MI (Figure 7). She entered the study with the lowest FAB score (14) and improved to 19 after AT. There was little change (<3) in either MGAS MI (one increased by 0.62 and the other decreased by 2.7). Given that her baseline MI

values were approximately 66 and 78, ceiling effects do not account for this lack of change. Case 1's stable MI measures also suggest that changes in MI seen in other participants are not due to a practice effect from multiple sessions on the perturbation platform. The absolute (as opposed to relative) values of MI allow this direct comparison of muscle coordination across time points, even when muscle activity levels cannot be directly compared (normalizing to a maximum voluntary contraction is not ideal in a population with motor impairments). In short, MI does not appear responsible for this improvement; other mechanisms are the likely cause.

Case 2 (Moderate + Decline FAB trajectory) showed notable decline in FAB and in MGAS MI (Figure 7). At the 12 week assessment, she had decreased from 29 to 22 on FAB. Her MGAS MI decreased 17 points from 92 and 11 points from 85 (left and right sides, respectively). The concurrent decline in MI and FAB seen here fits the initial hypothesis that decreased modulation is related to decreased balance ability.

Case 3 (Moderate + Maintain FAB trajectory) began and maintained moderate balance ability, but this maintenance was accompanied by declines in MGAS MI similar to those seen in Case 2, who declined in balance ability (Figure 7). Case 3 began the study with a 29 FAB score and maintained that at the 12 week assessment. In that time, her MGAS MI scores decreased by 17 and 18 from 58 and 68. The decline in MI scores seen here is consistent with the idea that motor skill learning (such as balance skills learned during AT) is accompanied by increased co-contraction and decreased modulation (Damiano, 1993). Although this case's FAB score did not increase, it is possible that she had improvements not captured by FAB or improvements that counteracted progressive declines seen in PD, thus appearing as no net change.

Case 4 (High + Maintain FAB trajectory) was included to represent participants with high baseline ability who generally maintained that performance and showed both MI increase and

decrease (Figure 7). His baseline score for FAB was 34, which dipped to 33 at 12 weeks but returned to 34 by 16 weeks. From baseline to 12 weeks, he decreased in MI by 12 from 64 on his left MGAS, but increased by 2 points from 79 on his right MGAS. This case shows that MI changes may be side-specific, which is consistent with the fact that PD symptoms are often asymmetric across sides.

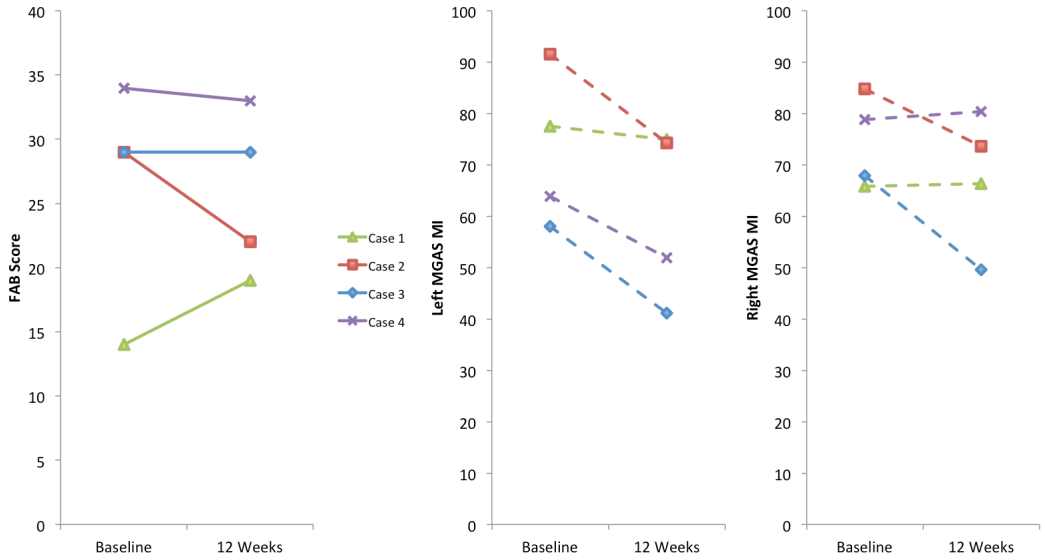

Figure 7. Change in cases' balance ability (Fullerton Advanced Balance Scale, FAB) and left and right MGAS MI after AT.

There were instances of MI increasing by approximately 10 points after AT, in both older (71 years) and younger (54 years) participants with some of the highest baseline levels (36, 37). However, in an effort to represent the general patterns seen, the cases above were selected instead. This modulation increase at high baseline levels does suggest that MI can be increased after AT, a change that is possible at many ages and supports modulation as a potential mechanism of improvement.

4.5. Conclusion

Improvements in balance after AT can occur with no change in MI, suggesting an alternative mechanism enabled the improvements seen from a very low FAB score. MI decreases can accompany balance decline or maintenance; MI increase can accompany balance maintenance. These findings suggest that the level of balance impairment helps determine the functional significance of modulation.

4.6. Discussion

Given the newness of this outcome measure, the amount of change necessary to yield changes in motor performance is not yet known. Changes of 10-20 in MI may not be sufficiently large to impact balance performance as measured by FAB. Alternatively, changes of 10-20 in MI may be large enough to impact balance. The mean MGAS MI value for the AT group at baseline was 74, so a change of 10-20 would be approximately 14-27% of the average initial value. However, the effect of MI change may also be context dependent. As an individual progresses from a healthy older adult to someone with increased PD symptom severity, a decrease in MI may be associated with impaired balance (either as a cause or an effect), but once the symptoms become severe enough, decreasing MI may be a compensatory strategy to increase agonist activation or co-contraction and control. Although an inefficient strategy, co-contraction does have functional benefits and has been reported in people undergoing rehabilitation after stroke (J. L. Allen, Ting, & Kesar, 2018). At lower initial levels of balance ability (e.g., Case 1), balance improvement appears to be linked to a different potential mechanism (e.g., improved dual tasking, ability to initiate movement, improved strength, etc.). Including a broader range of baseline ability levels in future work will help clarify how changes in MI and balance ability are related at moderate balance levels (low enough to avoid limited potential balance improvements,

but high enough that MI is still a potential mechanism). The effects of modulation levels may differ based on balance ability (i.e., a decrease in modulation may indicate a loss of function or an adaption that preserves function). Similarly, the efficacy of altering modulation as a mechanism to improve balance may depend upon the existing balance ability levels.

5. Discussion

5.1. Overview

This dissertation examines muscle co-contraction during reactive balance in people with PD and whether this co-contraction could be a mechanism of balance improvement seen after AT interventions. The work presented here used translational support-surface perturbations to standing balance in people with and without PD and introduced a modified modulation index as a new method to quantify co-contraction across muscles and perturbation directions.

This work contributes to the literature by expanding upon previous reports of increased co-contraction in people with PD. This dissertation 1) presents a method to quantify co-contraction that does not require pre-specifying agonist-antagonist pairs or normalizing EMG data to have a measure that can be compared across muscles, experiments, and participants (Chapter 2), 2) shows that reduced modulation is associated with PD severity and across PD phenotypes, and with clinical quantifications of balance when controlling for effects of muscle and participant (Table 2), and 3) provides evidence suggesting that baseline functional balance ability may be more important to rehabilitation outcomes than age or PD phenotype, with those who stand to benefit most from rehabilitation having lower balance ability (Chapters 3 and 4).

5.2. New methodology for assessing co-contraction

A key contribution of this work is the adapted modulation index, a useful measure for capturing abnormal antagonist muscle modulation without requiring pre-specified directions of agonist and antagonist activity. While used here to examine reactive balance responses in standing balance, the modulation index could also be used to examine modulation in muscles during other balance tasks such as anticipatory postural adjustments or walking. This study used the modulation index to circumvent challenges presented by the study population and range of

muscles and perturbation directions. Other co-contraction measures often directly compare the normalized activity of an agonist and antagonist pair, with clearly delineated directions of agonist and antagonist activity. Normalization is often made with respect to a maximum voluntary contraction, which is challenging to capture in a group of people with a voluntary movement disorder such as PD. Additionally, the larger number of muscles and perturbation directions makes defining appropriate antagonist muscle pairs and directions of agonist activity problematic. I adapted a modulation index previously reported for voluntary reaching movements with predetermined agonist and antagonist activity (Kelly & Bastian, 2005). The index provides a measure of the greatest possible amount of modulation (MI) and a measure of the amount of modulation that occurs when effective agonist activity is important for reactive balance (MI180). MI180 captures instances of antagonist activity that is greater than agonist activity; such instances were infrequent here (≈5% of muscles). MI180 may be more useful in people with more severe PD symptoms, who may be more likely to have instances of antagonist activity greater than agonist activity.

5.3. Muscle modulation is decreased in people with PD and associated with PD severity and balance ability

This dissertation expanded foundational work reporting increased co-contraction in people with PD during reactive balance by demonstrating that the results generalize to a broader selection of PD phenotypes, muscles, and perturbation directions (Carpenter et al., 2004; Dimitrova et al., 2004; Horak et al., 1996; St George et al., 2012). The cross-sectional study comparing people with and without PD (Chapter 2) used the modulation index to find reduced muscle modulation in reactive balance across PD phenotypes, as well as associations between muscle modulation and PD severity and balance ability. These findings suggest that impaired

modulation is a problem across a wide range of people with PD and is a potential target of AT. The inclusion of a larger PD sample and use of a quantification method designed to address technical limitations suggests that the elevated co-contraction is a robust result, and not an artifact of different labs, experimental paradigms, or muscle selection.

This study found that modulation is impaired with PD and did not find evidence that this relationship direction varied across PD phenotypes (PIGD, TD, ID) (Table 2). This is a new development in the literature and suggests that co-contraction is a concern for the overall population of people with PD. Seeing evidence of co-contraction across PD phenotypes suggests that recruiting all PD phenotypes into studies of co-contraction is appropriate and that previous studies which selected participants for minimal tremor generalize to the wider PD population.

This study also suggests that matching PD groups by severity in studies of co-contraction may prevent confounded results. This work found that modulation is decreased with increasing PD severity (Table 2). Therefore, as PD progresses, co-contraction becomes more prominent and may impair function to a greater extent (although the case series suggests the relationship between co-contraction and function may be more nuanced).

This work demonstrated a relationship between impaired modulation and lower performance on the FAB (Table 2), providing additional insight into the mechanisms by which balance performance is affected in older adults with and without PD. This work focused on FAB compared to BBS or DGI due to FAB's lack of ceiling effects and examination of balance instead of gait. The inclusion of clinical balance scales with EMG-based co-contraction quantification to assess the relationship between the two outcome measures is novel. These scales are used frequently in clinics and their inclusion allows the modulation results to be generalized to the functional abilities frequently observed and quantified by clinicians.

This work supports the idea that the impact of age on co-contraction may be overshadowed by factors such as physical training and disease. Here, modulation was not associated with age, which differs from literature demonstrating increased co-contraction with age. This result is likely attributable to the sample of participants, a small portion of which were older adults without PD, and in which the oldest participant (nonPD) was particularly fit and active while the youngest (PD) had impaired mobility. Given the previous evidence of a relationship between age and co-contraction and the fact that age can be related to other potential characteristics that could confound the results (muscular, vascular, synaptic, neurotransmitter levels, structural and functional levels of neuroplasticity), matching on age while examining co-contraction would be an appropriately careful approach.

Taken together, these findings support further investigation of altered co-contraction as a potential outcome of balance rehabilitations. Because all three PD phenotypes were associated with reduced modulation, there is no evidence that balance rehabilitation that alters modulation should be directed at a specific PD phenotype.

5.4. Neither muscle modulation nor balance ability changed significantly after Adapted Tango in a group of participants with high baseline balance ability

In the longitudinal study comparing people with PD who did or did not participate in AT (Chapter 3), there was no change in muscle modulation after AT and very limited improvement in clinical scales. The higher baseline balance ability of this AT group compared to previous studies may explain the lack of significant improvements in clinical balance scales after AT participation. This limited potential improvement with AT suggests that baseline balance ability may be a critical factor determining the amount of improvement predicted after exercise-based interventions, including AT and other interventions challenging balance. If modulation changes

are associated with balance changes, baseline balance ability will also be a critical factor determining the amount of change in modulation. Alternatively, AT-induced balance improvements may not be mediated by modulation, but instead by other mechanisms. Distinguishing between these two possibilities will require studies of participants with a lower baseline balance ability level.

5.5. Effects of modulation levels may differ based on balance ability

The case series (Chapter 4) suggests that the baseline level of balance impairment may determine the functional significance of modulation. Across the cases, modulation decreases accompanied balance decline or maintenance and modulation increase accompanied balance maintenance. No change in modulation accompanied the largest improvement in balance. The direction of functional change seen with a given direction of modulation change appeared to depend on the baseline balance ability. At low baseline balance ability, functional balance improvements occurred with no modulation change; at moderate baseline balance ability, functional balance was maintained in one case and declined in another with modulation decreases; and at high baseline balance ability, functional balance was maintained with modulation decrease and slight increase. Clarifying the relationship between baseline balance ability, modulation change, and balance ability change will require recruiting participants with a wide range of ability levels, to prevent limitations in the amount of possible balance improvement after rehabilitation and to gain a sufficiently detailed understanding of the continuum along which the functional impact of modulation shifts.

5.6. Parkinson's disease, symptom severity, and balance ability are related to abnormal antagonist activation and how changes in that activation relate to functional balance control

In summary, this dissertation suggests abnormal antagonist muscle activity, and presumably co-contraction of agonists and antagonists, is present during automatic postural responses across PD phenotypes. In addition, this abnormal antagonist activity increases with symptom severity (Table 2). Data presented here demonstrates abnormal patterns of leg muscle activity during reactive balance in participants with mild to moderate PD and a range of symptom phenotypes. PD and PD severity predicted lower muscle modulation across perturbation directions (Table 2). These predictions occurred for the TD, PIGD, and ID phenotypes, expanding previous work featuring either phenotypes likely limited to TD (Dimitrova et al., 2004; Horak et al., 1996) or limited muscle and perturbations (Carpenter et al., 2004; St George et al., 2012). That the association between PD and modulation generalizes across phenotypes suggests that co-contraction is not a concern limited to people with minimal tremor. The association between modulation and PD severity (Table 2) suggests that co-contraction becomes more prominent as the disease progresses.

There was not a significant change in the abnormal muscle activity after an AT intervention, though this result may be explained by limitations in the potential amount of improvement the intervention could provide to participants who began the study at a relatively high level of balance ability (McKay et al., 2016). A case series exploring this possibility suggests that changes in antagonist activity may be related to different functional outcomes, depending upon the baseline balance ability level. If so, the effectiveness of targeting antagonist activity with rehabilitation interventions will shift depending on participants' balance ability.

5.7. Limitations

The conclusions presented here should be considered in light of the following methodological limitations.

First, like most postural studies in PD, this study recruited volunteers and the extent to which its results generalize to the population of people with PD is unknown. Similarly, the generalizability to severe cases of PD is unknown. However, even if the results do not generalize to all PD cases, they should generalize to rehabilitation studies, as those investigations have a similar potential recruitment bias and include similar levels of PD severity.

Second, imbalances in the PD and nonPD demographic and clinical variables cannot be completely known. While the PD and nonPD group were matched on age and tested OFF antiparkinsonian medications, they were not matched on other variables such as activity level, and, with fewer inclusion/exclusion criteria, the nonPD control group may not be as well controlled as the PD group. Additionally, PD and nonPD groups, and to a limited extent, the AT and PD control groups, had different barriers to entry with different AT involvement and number of requested laboratory visits. There is a risk of selection bias, as people who are willing and able to participate in a rehabilitation intervention may be more involved and active than others. If present, this selection bias may have led to recruitment of a less active nonPD group. Recruiting the nonPD group from the metro Atlanta area also raises the possibility that the nonPD group was less healthy and active than nonPD groups in other geographic locations (e.g., Washington and Oregon (Dimitrova et al., 2004; Horak et al., 1996; St George et al., 2012), Western Europe (Carpenter et al., 2004)). However, if this were the case, it would bias results toward the null. Finding differences between the PD and nonPD groups when potential bias may have reduced the between group differences speaks to the robustness of the results.

Third, measures of modulation in APR1 may be less precise than in APRX, because time bins were calculated from perturbation onset instead of muscle onset. Latency of muscle onset can vary slightly from trial to trial and also occur later with lower acceleration perturbations, similar to those used here (K.C. Lang, Ting, & McKay, 2014). However, even with the possibility of including limited background-level muscle activity prior to onset, this measure is more robust than measures that quantify co-contraction based solely on muscle onset latency.

Fourth, modulation measures are proxy measures of antagonist activity and co-contraction. While modulation measures capture the general pattern of agonist-antagonist activity, with low modulation values reflecting increased antagonist activation, that pattern can be due to a decrease in agonist activity, an increase in antagonist activity, or both. Increased antagonist activity (duration and/or amplitude) is presumed to yield increased co-contraction, but this result assumes that agonist activity remains the same.

Fifth, the relatively high baseline levels of balance ability in the AT group may have limited potential balance improvements. Limited changes in functional balance ability make it difficult to assess the relationship between those changes and changes in muscle activity during reactive balance.

5.8. Implications for future studies

The MCID in MI scores, which would indicate what amount of change has functional significance, has yet to be established. In addition, understanding whether the MCID changes across the spectrum of balance ability would clarify rehabilitation goals. Further, understanding if and how co-contraction or change in co-contraction is associated with other components of balance control in PD, including cognitive impairment, dual tasking ability, and adaptation over repeated predictable trials would be useful. Such results would provide insight into how other

factors interact with co-contraction (e.g., cognitive impairment and automaticity of balance control, examined via dual tasking) and how plastic co-contraction is within an individual with PD (e.g., adaptation). Furthermore, additional exploration of other potential mechanisms underlying AT-induced balance improvements is warranted. These mechanisms could be compensatory (similar to co-contraction possibly improving balance by stiffening or stabilizing a joint) or could restore function lost in PD. These mechanisms could occur throughout the system of balance control, from perception and supra-spinal sensory processing and motor commands (e.g., dopamine transport, increase in automaticity of control), to motor output (e.g., increased muscle strength or recruitment leading to improved force generation), to decreased fear of falling (e.g., potentially shifting to a less co-contracted motor control strategy).

Examining modulation during instrumented clinical balance tasks in addition to the perturbations would reduce the heterogeneity between the clinical balance tasks and the laboratory task during which EMG is recorded. Making the tasks as comparable as possible would help clarify the relationship between co-contraction, functional balance, and an intervention. Calculating MI during an instrumented and scored UPDRS retropulsion test (Pull Test) or reactive postural control (FAB Item 10, in which support is suddenly removed during a backward lean) would offer a similar task to the translation perturbations but also one that is established with clinicians.

Examining MI along with a more established measure of co-contraction would help establish the usefulness of MI in examining effects of rehabilitation. Despite previously established measures being limited by the need to normalize EMG values and pre-specify muscle pairs and perturbation directions, comparing MI to these older metrics within the same dataset

(perhaps using MGAS and TA) would provide an opportunity to examine how similar MI is to older metrics.

Given the limited post-AT balance improvements in this work, it remains to be seen whether MI changes with balance-targeting rehabilitation interventions. Inclusion criteria restricting participants to those with a FAB score of 27 or lower (the mean score of participants in pilot work) would increase the number of participants that could significantly improve their balance with AT and encourage recruitment of a wider range of balance abilities (McKay et al., 2016). Focusing rehabilitation research on more severely affected individuals in this way can facilitate exploration of underlying mechanisms, but the generalizability of those results to less affected individuals will need to be examined. In addition, a crossover design in which both groups undergo a control period and an AT period would allow for more similar groups (while there were not significant differences at baseline between the AT and Control groups here, the AT group consistently performed better on balance and gait measures).

5.9. Co-contraction: Helpful or harmful in Parkinson's disease?

The appropriate level of co-contraction for a person with PD likely changes with balance ability and disease severity. When considering co-contraction and its relationship to balance in PD, it is important to consider that co-contraction is a motor control strategy that is not necessarily "good" or "bad." Instead, co-contraction may be optimized for a given situation and balance domain.

Increased co-contraction may be an appropriate strategy to increase stability and compensate for balance impairments in people with PD. In this instance, increased co-contraction is a more conservative approach to motor control, prioritizing control and balance loss prevention over energy cost (Damiano, 1993). When considering maintenance of standing

balance, increased co-contraction and the accompanying stiffness could decrease sway, which decreases proprioceptive inputs, but also decreases the greater CoM movements associated with falls in PD (Schoneburg et al., 2013). Increased co-contraction could reduce the displacement caused by a sudden perturbation, thereby reducing the amount of balance correction needed (although some work suggests the opposite may be true, with stiffness amplifying the effects of a perturbation (Gruneberg, Bloem, Honegger, & Allum, 2004)). Increased co-contraction could also allow faster generation of force, with more rapid muscle recruitment (De Luca & Mambrito, 1987).

Increased co-contraction may also be appropriate for people with PD undergoing a balance rehabilitation intervention. In general, co-contraction is high early in the process of learning a motor skill and decreases with mastery (although this is not true in all motor tasks) (Damiano, 1993; Engelhorn, 1983). Given that rehabilitation participants are learning and improving their motor skills, increased co-contraction could be appropriate.

However, increased co-contraction becomes problematic at an excessively high level. At that point, the stiffness and competing action of the antagonist activation reduce the efficacy of the agonist's balance-restoring action, both in automatic postural responses and in balance more broadly. Given that agonist activation is more fragmented in PD, this antagonist opposition is especially problematic (Horak et al., 1996).

5.10. Co-contraction: Cause and effect of balance impairment? What effect should rehabilitation have on co-contraction?

While co-contraction has been extensively associated with balance, the precise cause and effect pathway of that relationship remains unknown. Co-contraction may be both a cause of and compensation for balance impairment.

Co-contraction may result when impaired balance leads to more antagonist muscle activity. Balance may be impaired by neurophysiological changes that accompany aging (muscle strength reduction) and PD pathophysiology (sensory weighting, muscle tone/rigidity, ability to dual-task) (Rinalduzzi et al., 2015; Schoneburg et al., 2013). These impairments, perhaps coupled with experiencing a fall, may increase the fear of falling, leading a person with PD to adopt a more cautious balance control strategy. This strategy likely features increased co-contraction and stiffness, similar to that seen when people without PD adjust their control strategy to face environmental balance challenges (e.g., balancing on ice or other unsteady surface) (Pasman, Murnaghan, Bloem, & Carpenter, 2011).

While co-contraction may have some immediate benefits to balance, using co-contraction excessively, either to a very high level or consistently over time, may impair balance. First, elevated co-contraction leaves little room for additional increases in motor control – if everyday life is lived as if it is a strenuous balance challenge, there is no additional room to scale up the response when a more taxing challenge arises. Second, a conservative, co-contraction-heavy strategy is energy intensive and increases stiffness, potentially leading to decreased physical activity and conditioning, which could impair future balance control. Finally, and perhaps most importantly in the context of this work, having increased co-contraction prior to a perturbation may cause inappropriate co-contraction during the APR. Previous work (Lewis et al., 2010) shows that increasing levels of antagonist activation prior to a perturbation (even at a low percentage of the muscle's maximum voluntary contraction) led to elevated activation of that antagonist after the perturbation. In real world expected perturbations (e.g., a bus starting to move underfoot), this destabilizing effect would likely increase fear of falling and increase the use or level of co-contraction, creating a detrimental feedback loop. While co-contraction may be

an appropriate strategy at optimized levels, employing co-contraction broadly is detrimental to balance control, especially if an external perturbation occurs during that period.

Given both the helpful and harmful implications of co-contraction on balance, rehabilitation should aim to optimize the level of co-contraction for an individual. As suggested by the case series (Chapter 4), the optimal level of co-contraction likely varies with balance ability, as the cost-benefit ratio of co-contraction shifts with the severity and type of balance control impairments. Co-contraction does not respond to L-DOPA or deep brain stimulation (St George et al., 2012) but does change after training (Freyler et al., 2014; Hakkinen et al., 1998; Nagai, Yamada, Tanaka, et al., 2012), making co-contraction a logical focus of rehabilitation. Future work will need to explore further how an optimal level of co-contraction changes with increasing disease severity, balance impairment, and time since rehabilitation.

5.11. Summary

This work found that decreased muscle modulation, suggestive of increased co-contraction, is related to PD severity and balance ability and is present in people with different PD phenotypes. While muscle modulation is a potential mechanism of balance improvement after AT, this work did not see an association between AT participation and modulation at the group level. However, given the study's limitations, co-contraction remains a viable potential mechanism of balance improvement after exercise-based rehabilitation interventions. Additionally, understanding how balance ability shapes the functional impact of modulation changes will help determine when co-contraction may be an appropriate or inappropriate strategy and if and how rehabilitation interventions should target co-contraction in a given individual or sub-group.

6. References

Allen, J. L., Ting, L. H., & Kesar, T. M. (2018). Gait Rehabilitation Using Functional Electrical Stimulation Induces Changes in Ankle Muscle Coordination in Stroke Survivors: A Preliminary Study. *Frontiers in Neurology, 9*, 1127. doi: 10.3389/fneur.2018.01127

Allen, N. E., Sherrington, C., Paul, S. S., & Canning, C. G. (2011). Balance and falls in Parkinson's disease: a meta-analysis of the effect of exercise and motor training. *Movement Disorders, 26*(9), 1605-1615. doi: 10.1002/mds.23790

Basmajian, J.V., & Blumenstein, R. . (1980). *Electrode Placement in EMG Biofeedback*. Baltimore/London: Williams & Wilkins.

Benjuya, N., Melzer, I., & Kaplanski, J. (2004). Aging-induced shifts from a reliance on sensory input to muscle cocontraction during balanced standing. *Journals of Gerontology. Series A: Biological Sciences and Medical Sciences, 59*(2), 166-171.

Berg, K., Wood-Dauphinee, S., & Williams, J. I. (1995). The Balance Scale: reliability assessment with elderly residents and patients with an acute stroke. *Scandinavian Journal of Rehabilitation Medicine, 27*(1), 27-36.

Bingham, J. T., Choi, J. T., & Ting, L. H. (2011). Stability in a frontal plane model of balance requires coupled changes to postural configuration and neural feedback control. *Journal of Neurophysiology, 106*(1), 437-448. doi: 10.1152/jn.00010.2011

Bloem, B. R., Beckley, D. J., van Dijk, J. G., Zwinderman, A. H., Remler, M. P., & Roos, R. A. (1996). Influence of dopaminergic medication on automatic postural responses and balance impairment in Parkinson's disease. *Movement Disorders, 11*(5), 509-521. doi: 10.1002/mds.870110506

Bloem, B. R., Grimbergen, Y. A., Cramer, M., Willemsen, M., & Zwinderman, A. H. (2001). Prospective assessment of falls in Parkinson's disease. *Journal of Neurology, 248*(11), 950-958.

Carpenter, M. G., Allum, J. H., Honegger, F., Adkin, A. L., & Bloem, B. R. (2004). Postural abnormalities to multidirectional stance perturbations in Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry, 75*(9), 1245-1254. doi: 10.1136/jnnp.2003.021147

Cenciarini, M., Loughlin, P. J., Sparto, P. J., & Redfern, M. S. (2010). Stiffness and damping in postural control increase with age. *IEEE Transactions on Biomedical Engineering, 57*(2), 267-275. doi: 10.1109/TBME.2009.2031874

Cleworth, T. W., Chua, R., Inglis, J. T., & Carpenter, M. G. (2016). Influence of virtual height exposure on postural reactions to support surface translations. *Gait and Posture, 47*, 96-102. doi: 10.1016/j.gaitpost.2016.04.006

Damiano, D. L. (1993). Reviewing Muscle Cocontraction. *Physical & Occupational Therapy in Pediatrics, 12*(4), 3-20. doi: 10.1080/J006v12n04_02

David, F. J., Robichaud, J. A., Vaillancourt, D. E., Poon, C., Kohrt, W. M., Comella, C. L., & Corcos, D. M. (2016). Progressive resistance exercise restores some properties of the triphasic EMG pattern and improves bradykinesia: the PRET-PD randomized clinical trial. *Journal of Neurophysiology, 116*(5), 2298-2311. doi: 10.1152/jn.01067.2015

De Luca, C. J., & Mambrito, B. (1987). Voluntary control of motor units in human antagonist muscles: coactivation and reciprocal activation. *Journal of Neurophysiology, 58*(3), 525-542. doi: 10.1152/jn.1987.58.3.525

Deliagina, T. G., Beloozerova, I. N., Orlovsky, G. N., & Zelenin, P. V. (2014). Contribution of supraspinal systems to generation of automatic postural responses. *Frontiers in Integrative Neuroscience, 8*, 76. doi: 10.3389/fnint.2014.00076

Diener, H. C., Horak, F. B., & Nashner, L. M. (1988). Influence of stimulus parameters on human postural responses. *Journal of Neurophysiology, 59*(6), 1888-1905. doi: 10.1152/jn.1988.59.6.1888

Dimitrova, D., Horak, F. B., & Nutt, J. G. (2004). Postural muscle responses to multidirectional translations in patients with Parkinson's disease. *Journal of Neurophysiology, 91*(1), 489-501. doi: 10.1152/jn.00094.2003

Duncan, R. P., & Earhart, G. M. (2012). Randomized controlled trial of community-based dancing to modify disease progression in Parkinson disease. *Neurorehabilitation and Neural Repair, 26*(2), 132-143. doi: 10.1177/1545968311421614

Duncan, R. P., & Earhart, G. M. (2014). Are the effects of community-based dance on Parkinson disease severity, balance, and functional mobility reduced with time? A 2-year prospective pilot study. *Journal of Alternative and Complementary Medicine, 20*(10), 757-763. doi: 10.1089/acm.2012.0774

Engelhart, D., Pasma, J. H., Schouten, A. C., Aarts, R. G., Meskers, C. G., Maier, A. B., & van der Kooij, H. (2016). Adaptation of multijoint coordination during standing balance in healthy young and healthy old individuals. *Journal of Neurophysiology, 115*(3), 1422-1435. doi: 10.1152/jn.00030.2015

Engelhorn, R. (1983). Agonist and antagonist muscle EMG activity pattern changes with skill acquisition. *Research Quarterly for Exercise and Sport, 54*(4), 315-323.

Espay, A. J., LeWitt, P. A., & Kaufmann, H. (2014). Norepinephrine deficiency in Parkinson's disease: the case for noradrenergic enhancement. *Movement Disorders, 29*(14), 1710-1719. doi: 10.1002/mds.26048

Fahn, S., & Elton, R.L. (1987). The unified Parkinson's disease rating scale. In S. Fahn, C. D. Marsden, D. B. Calne & M. Goldstein (Eds.), *Recent Developments in Parkinson's Disease* (Vol. 2, pp. 153-163). Florham Park, NJ: Macmillan Healthcare Information.

Falconer, K., & Winter, D. A. (1985). Quantitative assessment of co-contraction at the ankle joint in walking. *Electromyography and Clinical Neurophysiology, 25*(2-3), 135-149.

Franchignoni, F., Horak, F., Godi, M., Nardone, A., & Giordano, A. (2010). Using psychometric techniques to improve the Balance Evaluation Systems Test: the mini-BESTest. *Journal of Rehabilitation Medicine, 42*(4), 323-331. doi: 10.2340/16501977-0537

Freyler, K., Weltin, E., Gollhofer, A., & Ritzmann, R. (2014). Improved postural control in response to a 4-week balance training with partially unloaded bodyweight. *Gait and Posture, 40*(2), 291-296. doi: 10.1016/j.gaitpost.2014.04.186

Giladi, N., Shabtai, H., Simon, E. S., Biran, S., Tal, J., & Korczyn, A. D. (2000). Construction of freezing of gait questionnaire for patients with Parkinsonism. *Parkinsonism & Related Disorders, 6*(3), 165-170.

Grimbergen, Y. A., Schrag, A., Mazibrada, G., Borm, G. F., & Bloem, B. R. (2013). Impact of falls and fear of falling on health-related quality of life in patients with Parkinson's disease. *Journal of Parkinson's Disease, 3*(3), 409-413. doi: 10.3233/JPD-120113

Gruneberg, C., Bloem, B. R., Honegger, F., & Allum, J. H. (2004). The influence of artificially increased hip and trunk stiffness on balance control in man. *Experimental Brain Research, 157*(4), 472-485. doi: 10.1007/s00221-004-1861-x

Hackney, M. E. (2015). *Teacher Training in Adapted Tango Group Classes for Older Individuals and those with Movement Disorders: Fundamentals*.

Hackney, M. E., & Earhart, G. M. (2009a). Effects of dance on movement control in Parkinson's disease: a comparison of Argentine tango and American ballroom. *Journal of Rehabilitation Medicine, 41*(6), 475-481. doi: 10.2340/16501977-0362

Hackney, M. E., & Earhart, G. M. (2009b). Short duration, intensive tango dancing for Parkinson disease: an uncontrolled pilot study. *Complementary Therapies in Medicine, 17*(4), 203-207. doi: 10.1016/j.ctim.2008.10.005

Hackney, M. E., & Earhart, G. M. (2010). Effects of dance on gait and balance in Parkinson's disease: a comparison of partnered and nonpartnered dance movement. *Neurorehabilitation and Neural Repair, 24*(4), 384-392. doi: 10.1177/1545968309353329

Hackney, M. E., Kantorovich, S., Levin, R., & Earhart, G. M. (2007). Effects of tango on functional mobility in Parkinson's disease: a preliminary study. *Journal of Neurologic Physical Therapy, 31*(4), 173-179. doi: 10.1097/NPT.0b013e31815ce78b

Hackney, M. E., Lee, H. L., Battisto, J., Crosson, B., & McGregor, K. M. (2015). Context-Dependent Neural Activation: Internally and Externally Guided Rhythmic Lower Limb Movement in Individuals With and Without Neurodegenerative Disease. *Frontiers in Neurology, 6*, 251. doi: 10.3389/fneur.2015.00251

Hackney, M. E., & McKee, K. (2014). Community-based adapted tango dancing for individuals with Parkinson's disease and older adults. *J Vis Exp*(94). doi: 10.3791/52066

Hakkinen, K., Kallinen, M., Izquierdo, M., Jokelainen, K., Lassila, H., Malkia, E., . . . Alen, M. (1998). Changes in agonist-antagonist EMG, muscle CSA, and force during strength

training in middle-aged and older people. *J Appl Physiol (1985), 84*(4), 1341-1349. doi: 10.1152/jappl.1998.84.4.1341

Hallett, M., & Khoshbin, S. (1980). A physiological mechanism of bradykinesia. *Brain, 103*(2), 301-314.

Herman, T., Weiss, A., Brozgol, M., Giladi, N., & Hausdorff, J. M. (2014). Gait and balance in Parkinson's disease subtypes: objective measures and classification considerations. *Journal of Neurology, 261*(12), 2401-2410. doi: 10.1007/s00415-014-7513-6

Hernandez, D., & Rose, D. J. (2008). Predicting which older adults will or will not fall using the Fullerton Advanced Balance scale. *Archives of Physical Medicine and Rehabilitation, 89*(12), 2309-2315. doi: 10.1016/j.apmr.2008.05.020

Hirsch, M. A., Toole, T., Maitland, C. G., & Rider, R. A. (2003). The effects of balance training and high-intensity resistance training on persons with idiopathic Parkinson's disease. *Archives of Physical Medicine and Rehabilitation, 84*(8), 1109-1117.

Ho, C. Y., & Bendrups, A. P. (2002). Ankle reflex stiffness during unperceived perturbation of standing in elderly subjects. *Journals of Gerontology. Series A: Biological Sciences and Medical Sciences, 57*(9), B344-350.

Horak, F. B., Frank, J., & Nutt, J. (1996). Effects of dopamine on postural control in parkinsonian subjects: scaling, set, and tone. *Journal of Neurophysiology, 75*(6), 2380-2396.

Horak, F. B., & Nashner, L. M. (1986). Central programming of postural movements: adaptation to altered support-surface configurations. *Journal of Neurophysiology, 55*(6), 1369-1381. doi: 10.1152/jn.1986.55.6.1369

Horak, F. B., Nutt, J. G., & Nashner, L. M. (1992). Postural inflexibility in parkinsonian subjects. *Journal of the Neurological Sciences, 111*(1), 46-58.

Hortobagyi, T., & DeVita, P. (2000). Muscle pre- and coactivity during downward stepping are associated with leg stiffness in aging. *Journal of Electromyography and Kinesiology, 10*(2), 117-126.

Hortobagyi, T., & Devita, P. (2006). Mechanisms responsible for the age-associated increase in coactivation of antagonist muscles. *Exercise and Sport Sciences Reviews, 34*(1), 29-35.

Huot, P., & Fox, S. H. (2013). The serotonergic system in motor and non-motor manifestations of Parkinson's disease. *Experimental Brain Research, 230*(4), 463-476. doi: 10.1007/s00221-013-3621-2

Jacobs, J. V., & Horak, F. B. (2007). Cortical control of postural responses. *J Neural Transm (Vienna), 114*(10), 1339-1348. doi: 10.1007/s00702-007-0657-0

Jacobs, J. V., Horak, F. B., Van Tran, K., & Nutt, J. G. (2006). An alternative clinical postural stability test for patients with Parkinson's disease. *Journal of Neurology, 253*(11), 1404-1413. doi: 10.1007/s00415-006-0224-x

Jones, G.M. (2000). Principles of Neural Science. In E. R. Kandel, J. H. Schwartz & T. M. Jessell (Eds.), (4 ed.). New York: McGraw-Hill Health Professions Division.

Kelly, V. E., & Bastian, A. J. (2005). Antiparkinson medications improve agonist activation but not antagonist inhibition during sequential reaching movements. *Movement Disorders, 20*(6), 694-704. doi: 10.1002/mds.20386

Keus, S. H., Munneke, M., Nijkrake, M. J., Kwakkel, G., & Bloem, B. R. (2009). Physical therapy in Parkinson's disease: evolution and future challenges. *Movement Disorders, 24*(1), 1-14. doi: 10.1002/mds.22141

Khallaf, M. E., & Fayed, E. E. (2015). Early postural changes in individuals with idiopathic Parkinson's disease. *Parkinson's Disease, 2015*, 369454. doi: 10.1155/2015/369454

Kim, S. D., Allen, N. E., Canning, C. G., & Fung, V. S. (2013). Postural instability in patients with Parkinson's disease. Epidemiology, pathophysiology and management. *CNS Drugs, 27*(2), 97-112. doi: 10.1007/s40263-012-0012-3

Klein, P. J., Fiedler, R. C., & Rose, D. J. (2011). Rasch Analysis of the Fullerton Advanced Balance (FAB) Scale. *Physiotherapy Canada, 63*(1), 115-125. doi: 10.3138/ptc.2009-51

Lang, K. C., Hackney, M. E., Ting, L. H., & McKay, J. L. (2019). Antagonist muscle activity during reactive balance responses is elevated in Parkinson's disease and in balance impairment. *PloS One, 14*(1), e0211137. doi: 10.1371/journal.pone.0211137

Lang, K.C., Ting, L. H., & McKay, J. L. (2014). *Support surface acceleration affects tibialis anterior onset latency during support surface translation perturbations*. Paper presented at the International Society for Posture and Gait Research World Congress, Vancouver, B.C., Canada. Poster retrieved from

Laughton, C. A., Slavin, M., Katdare, K., Nolan, L., Bean, J. F., Kerrigan, D. C., . . . Collins, J. J. (2003). Aging, muscle activity, and balance control: physiologic changes associated with balance impairment. *Gait and Posture, 18*(2), 101-108.

Lee, A., & Gilbert, R. M. (2016). Epidemiology of Parkinson Disease. *Neurologic Clinics, 34*(4), 955-965. doi: 10.1016/j.ncl.2016.06.012

Lees, A. J., Hardy, J., & Revesz, T. (2009). Parkinson's disease. *Lancet, 373*(9680), 2055-2066. doi: 10.1016/S0140-6736(09)60492-X

Lewek, M. D., Rudolph, K. S., & Snyder-Mackler, L. (2004). Control of frontal plane knee laxity during gait in patients with medial compartment knee osteoarthritis. *Osteoarthritis and Cartilage, 12*(9), 745-751. doi: 10.1016/j.joca.2004.05.005

Lewis, G. N., MacKinnon, C. D., Trumbower, R., & Perreault, E. J. (2010). Co-contraction modifies the stretch reflex elicited in muscles shortened by a joint perturbation. *Experimental Brain Research, 207*(1-2), 39-48. doi: 10.1007/s00221-010-2426-9

Lotzke, D., Ostermann, T., & Bussing, A. (2015). Argentine tango in Parkinson disease--a systematic review and meta-analysis. *BMC Neurology, 15*, 226. doi: 10.1186/s12883-015-0484-0

Macpherson, J.M., & Horak, F.B. (2013). Principles of Neural Science. In E. R. Kandel, J. H. Schwartz, T. M. Jessell, S. A. Siegelbaum & A. J. Hudspeth (Eds.), (5 ed.). New York: McGraw-Hill Medical.

Mancini, M., Horak, F. B., Zampieri, C., Carlson-Kuhta, P., Nutt, J. G., & Chiari, L. (2011). Trunk accelerometry reveals postural instability in untreated Parkinson's disease. *Parkinsonism & Related Disorders, 17*(7), 557-562. doi: 10.1016/j.parkreldis.2011.05.010

Mancini, M., Rocchi, L., Horak, F. B., & Chiari, L. (2008). Effects of Parkinson's disease and levodopa on functional limits of stability. *Clinical Biomechanics (Bristol, Avon), 23*(4), 450-458. doi: 10.1016/j.clinbiomech.2007.11.007

Marras, C., Beck, J. C., Bower, J. H., Roberts, E., Ritz, B., Ross, G. W., . . . Parkinson's Foundation, P. Group. (2018). Prevalence of Parkinson's disease across North America. *NPJ Parkinsons Dis, 4*, 21. doi: 10.1038/s41531-018-0058-0

Marsden, C.D. . (1996). Movement disorders. In L. J. Weatherall DJ, Warrell DA, (Ed.), *Oxford textbook of medicine* (Vol. 3, pp. 3998–4022). New York.: Oxford University Press Inc.

McKay, J. L., & Ting, L. H. (2012). Optimization of muscle activity for task-level goals predicts complex changes in limb forces across biomechanical contexts. *PLoS Computational Biology, 8*(4), e1002465. doi: 10.1371/journal.pcbi.1002465

McKay, J. L., Ting, L. H., & Hackney, M. E. (2016). Balance, Body Motion, and Muscle Activity After High-Volume Short-Term Dance-Based Rehabilitation in Persons With Parkinson Disease: A Pilot Study. *Journal of Neurologic Physical Therapy, 40*(4), 257-268. doi: 10.1097/NPT.0000000000000150

McKee, K. E., & Hackney, M. E. (2013). The effects of adapted tango on spatial cognition and disease severity in Parkinson's disease. *J Mot Behav, 45*(6), 519-529. doi: 10.1080/00222895.2013.834288

McNeely, M. E., Mai, M. M., Duncan, R. P., & Earhart, G. M. (2015). Differential Effects of Tango Versus Dance for PD in Parkinson Disease. *Frontiers in Aging Neuroscience, 7*, 239. doi: 10.3389/fnagi.2015.00239

Melton, L. J., 3rd, Leibson, C. L., Achenbach, S. J., Bower, J. H., Maraganore, D. M., Oberg, A. L., & Rocca, W. A. (2006). Fracture risk after the diagnosis of Parkinson's disease: Influence of concomitant dementia. *Movement Disorders, 21*(9), 1361-1367. doi: 10.1002/mds.20946

Melzer, I., Benjuya, N., & Kaplanski, J. (2001). Age-related changes of postural control: effect of cognitive tasks. *Gerontology, 47*(4), 189-194. doi: 10.1159/000052797

Muller, M. L., & Bohnen, N. I. (2013). Cholinergic dysfunction in Parkinson's disease. *Current Neurology and Neuroscience Reports, 13*(9), 377. doi: 10.1007/s11910-013-0377-9

Nagai, K., Yamada, M., Mori, S., Tanaka, B., Uemura, K., Aoyama, T., . . . Tsuboyama, T. (2013). Effect of the muscle coactivation during quiet standing on dynamic postural control in older adults. *Archives of Gerontology and Geriatrics, 56*(1), 129-133. doi: 10.1016/j.archger.2012.08.009

Nagai, K., Yamada, M., Tanaka, B., Uemura, K., Mori, S., Aoyama, T., . . . Tsuboyama, T. (2012). Effects of balance training on muscle coactivation during postural control in older adults: a randomized controlled trial. *Journals of Gerontology. Series A: Biological Sciences and Medical Sciences, 67*(8), 882-889. doi: 10.1093/gerona/glr252

Nagai, K., Yamada, M., Uemura, K., Tanaka, B., Mori, S., Yamada, Y., . . . Tsuboyama, T. (2012). Effects of fear of falling on muscular coactivation during walking. *Aging Clinical and Experimental Research, 24*(2), 157-161. doi: 10.3275/7716

Nagai, K., Yamada, M., Uemura, K., Yamada, Y., Ichihashi, N., & Tsuboyama, T. (2011). Differences in muscle coactivation during postural control between healthy older and young adults. *Archives of Gerontology and Geriatrics, 53*(3), 338-343. doi: 10.1016/j.archger.2011.01.003

Nelson-Wong, E., Appell, R., McKay, M., Nawaz, H., Roth, J., Sigler, R., . . . Walker, M. (2012). Increased fall risk is associated with elevated co-contraction about the ankle during static balance challenges in older adults. *European Journal of Applied Physiology, 112*(4), 1379-1389. doi: 10.1007/s00421-011-2094-x

Nussbaum, R. L., & Ellis, C. E. (2003). Alzheimer's disease and Parkinson's disease. *New England Journal of Medicine, 348*(14), 1356-1364. doi: 10.1056/NEJM2003ra020003

Parkinson, J. (1817). An essay on the Shaking Palsy.

Pasman, E. P., Murnaghan, C. D., Bloem, B. R., & Carpenter, M. G. (2011). Balance problems with Parkinson's disease: are they anxiety-dependent? *Neuroscience, 177*, 283-291. doi: 10.1016/j.neuroscience.2010.12.050

Pfann, K. D., Buchman, A. S., Comella, C. L., & Corcos, D. M. (2001). Control of movement distance in Parkinson's disease. *Movement Disorders, 16*(6), 1048-1065.

Rinalduzzi, S., Trompetto, C., Marinelli, L., Alibardi, A., Missori, P., Fattapposta, F., . . . Curra, A. (2015). Balance dysfunction in Parkinson's disease. *Biomed Res Int, 2015*, 434683. doi: 10.1155/2015/434683

Rosa, M. C., Marques, A., Demain, S., Metcalf, C. D., & Rodrigues, J. (2014). Methodologies to assess muscle co-contraction during gait in people with neurological impairment - a systematic literature review. *Journal of Electromyography and Kinesiology, 24*(2), 179-191. doi: 10.1016/j.jelekin.2013.11.003

Schlenstedt, C., Muthuraman, M., Witt, K., Weisser, B., Fasano, A., & Deuschl, G. (2016). Postural control and freezing of gait in Parkinson's disease. *Parkinsonism & Related Disorders, 24*, 107-112. doi: 10.1016/j.parkreldis.2015.12.011

Schoneburg, B., Mancini, M., Horak, F., & Nutt, J. G. (2013). Framework for understanding balance dysfunction in Parkinson's disease. *Movement Disorders, 28*(11), 1474-1482. doi: 10.1002/mds.25613

Shen, X., Wong-Yu, I. S., & Mak, M. K. (2016). Effects of Exercise on Falls, Balance, and Gait Ability in Parkinson's Disease: A Meta-analysis. *Neurorehabilitation and Neural Repair, 30*(6), 512-527. doi: 10.1177/1545968315613447

Shumway-Cook, A., & Woollacott, M.H. (1995). *Motor Control: Theory and Practical Applications.* Baltimore, MD: Williams & Wilkins.

Speelman, A. D., van de Warrenburg, B. P., van Nimwegen, M., Petzinger, G. M., Munneke, M., & Bloem, B. R. (2011). How might physical activity benefit patients with Parkinson disease? *Nature Reviews: Neurology, 7*(9), 528-534. doi: 10.1038/nrneurol.2011.107

St George, R. J., Carlson-Kuhta, P., Burchiel, K. J., Hogarth, P., Frank, N., & Horak, F. B. (2012). The effects of subthalamic and pallidal deep brain stimulation on postural responses in patients with Parkinson disease. *Journal of Neurosurgery, 116*(6), 1347-1356. doi: 10.3171/2012.2.jns11847

Stebbins, G. T., Goetz, C. G., Burn, D. J., Jankovic, J., Khoo, T. K., & Tilley, B. C. (2013). How to identify tremor dominant and postural instability/gait difficulty groups with the movement disorder society unified Parkinson's disease rating scale: comparison with the unified Parkinson's disease rating scale. *Movement Disorders, 28*(5), 668-670. doi: 10.1002/mds.25383

Strouwen, C., Molenaar, E. A., Munks, L., Keus, S. H., Bloem, B. R., Rochester, L., & Nieuwboer, A. (2015). Dual tasking in Parkinson's disease: should we train hazardous behavior? *Expert Review of Neurotherapeutics, 15*(9), 1031-1039. doi: 10.1586/14737175.2015.1077116

Teasdale, H., Preston, E., & Waddington, G. (2017). Proprioception of the Ankle is Impaired in People with Parkinson's Disease. *Mov Disord Clin Pract, 4*(4), 524-528. doi: 10.1002/mdc3.12464

Torres-Oviedo, G., & Ting, L. H. (2007). Muscle synergies characterizing human postural responses. *Journal of Neurophysiology, 98*(4), 2144-2156. doi: 10.1152/jn.01360.2006

Tucker, M. G., Kavanagh, J. J., Barrett, R. S., & Morrison, S. (2008). Age-related differences in postural reaction time and coordination during voluntary sway movements. *Hum Mov Sci, 27*(5), 728-737. doi: 10.1016/j.humov.2008.03.002

Vaillancourt, D. E., Prodoehl, J., Sturman, M. M., Bakay, R. A., Metman, L. V., & Corcos, D. M. (2006). Effects of deep brain stimulation and medication on strength, bradykinesia, and electromyographic patterns of the ankle joint in Parkinson's disease. *Movement Disorders, 21*(1), 50-58. doi: 10.1002/mds.20672

Warnica, M. J., Weaver, T. B., Prentice, S. D., & Laing, A. C. (2014). The influence of ankle muscle activation on postural sway during quiet stance. *Gait and Posture, 39*(4), 1115-1121. doi: 10.1016/j.gaitpost.2014.01.019

Welch, T. D., & Ting, L. H. (2009). A feedback model explains the differential scaling of human postural responses to perturbation acceleration and velocity. *Journal of Neurophysiology, 101*(6), 3294-3309. doi: 10.1152/jn.90775.2008

Wirdefeldt, K., Adami, H. O., Cole, P., Trichopoulos, D., & Mandel, J. (2011). Epidemiology and etiology of Parkinson's disease: a review of the evidence. *European Journal of Epidemiology, 26 Suppl 1*, S1-58. doi: 10.1007/s10654-011-9581-6