University of Rhode Island

DigitalCommons@URI

Open Access Dissertations

2020

LSVT[®] BIG EXERCISE-INDUCED NEUROPLASTICITY IN PEOPLE WITH PARKINSON'S DISEASE: AN ASSESSMENT OF PHYSIOLOGICAL AND BEHAVIORAL OUTCOMES

Christine Marie Clarkin

University of Rhode Island, chrisclarkin@uri.edu

Follow this and additional works at: https://digitalcommons.uri.edu/oa_diss

Recommended Citation

Clarkin, Christine Marie, "LSVT[®] BIG EXERCISE-INDUCED NEUROPLASTICITY IN PEOPLE WITH PARKINSON'S DISEASE: AN ASSESSMENT OF PHYSIOLOGICAL AND BEHAVIORAL OUTCOMES" (2020). *Open Access Dissertations*. Paper 1151.
https://digitalcommons.uri.edu/oa_diss/1151

This Dissertation is brought to you for free and open access by DigitalCommons@URI. It has been accepted for inclusion in Open Access Dissertations by an authorized administrator of DigitalCommons@URI. For more information, please contact digitalcommons@etal.uri.edu.

LSVT®BIG
EXERCISE-INDUCED NEUROPLASTICITY
IN
PEOPLE WITH PARKINSON’S DISEASE:
AN ASSESSMENT OF PHYSIOLOGICAL AND BEHAVIORAL OUTCOMES
BY
CHRISTINE MARIE CLARKIN

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE
REQUIREMENTS FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
IN
NEUROSCIENCE

UNIVERSITY OF RHODE ISLAND

2020

DOCTOR OF PHILOSOPHY

CHRISTINE MARIE CLARKIN

APPROVED:

Dissertation Committee:

Major Professor

Leslie Mahler

Frank Menniti

Jennifer Audette

Kunal Mankodiya

Nasser H. Zawia

DEAN OF THE GRADUATE SCHOOL

UNIVERSITY OF RHODE ISLAND

2020

ABSTRACT

Background and Purpose

The primary aim of this study was to investigate the impact of LSVT®BIG, an intensive, whole-body, amplitude-based exercise protocol for people with Parkinson's disease (PwPD), on functional mobility, quality of life, and markers of neuroplasticity. A secondary aim was to evaluate correlations between neurobiological measures (serum brain derived neurotrophic factor - sBDNF) and functional changes associated with the intervention.

Methods

Nine people with Parkinson's disease (PwPD), age = 69.9 years $\pm$ 4.9, were recruited from the local community and enrolled in LSVT BIG, which includes 16, one-hour individual treatment sessions delivered over one month (4 sessions per week for 4 weeks). Dependent variables were measured at baseline (BASE), end of treatment (EOT), and 4 weeks after EOT (EOT+4). Mobility measures included stride length, gait speed, step length, functional gait assessment (FGA), MiniBEST Test, Timed Up and Go (TUG), and the MDS-UPDRS Part III Motor. Psychometric self-report measures of fatigue, depression, confidence with activities, and Parkinson's disease quality of life were also included. Cellular neuroplasticity was evaluated using changes in sBDNF.

Results

Statistically significant ($\alpha = .05$) changes were identified in four of the six primary mobility variables at EOT+4 including the MDS-UPDRS Part III:

Motor Examination, Functional Gait Assessment (FGA), MiniBEST balance, and step length but not in gait speed or the TUG. Participants made statistically significant changes at EOT and EOT+4 on the Activities-specific Balance Confidence (ABC) measure. No statistically significant changes were identified in measures of fatigue, depression, or health related quality of life measures. The sBDNF levels showed a 10.11% decline at EOT and an overall 30.94% decline from BASE to EOT+4, which was statistically significant but was weakly correlated with all mobility and psychometric variables.

Discussion and Conclusions

LSVT BIG is an effective behavioral treatment intervention for PwPD that can be implemented in a clinical setting for people experiencing mild to moderate disease severity. Improved function on several mobility variables, confidence with activities, and a positive impact on quality of life which was consistent with our first and second hypothesis. The strength of LSVT BIG may lie in its utilization of principles of neuroplasticity especially mode of delivery, saliency, intensity, frequency, and duration. Future research into the role each of these components may play will help guide future exercise prescription and open options for application of LSVT BIG to people with other neurologic diagnoses and beyond the population of PwPD.

A decline in sBDNF levels was significant but in contrast to the expected hypothesized increase in levels. There was an unexpected weak negative relationship with sBDNF across several variables. This decrease versus increase may be interpreted as a reflection of decreased disease load but requires further investigation

and integration of additional neurotrophic factors to further expand our understanding of the role of sBDNF and its response to exercise.

This study provides insight into the potential benefits of a behavioral intervention that incorporates principles of motor learning that drive activity dependent changes in neural plasticity. Improvement in mobility measures were not statistically significant immediately following treatment but were significant four weeks following the completion of treatment. This finding may reflect that measurable changes in behavior occurred prior to changes in neural plasticity that is consistent with previous research (Adkins, Boychuk, Remple, & Kleim, 2006) and emphasizes the need for long term follow up for PwPD to fully understand the impact of exercise based treatment.

This study is unique in its integration of comprehensive functional, psychometric, and neurobiological measures in PwPD to broaden our understanding of the complex nature of exercise-induced neuroplasticity. These results further expand the limited body of research in the area of PD behavioral interventions and markers of neuroplasticity. In particular, this research has taken steps towards addressing the gap in treatment research by identifying specific measures regarding the efficacy of LSVT BIG, a well-defined treatment, as well as introduce the use of sBDNF as a potential link between functional neuroplasticity and cellular neuroplasticity.

Keywords: Neuroplasticity; Parkinson's disease: LSVT BIG; BDNF; Physical Therapy

ACKNOWLEDGMENTS

I want to start by acknowledging ALL of the individuals over the many years who were my patients and I their therapist. From my very beginnings as a then twenty-one year old new graduate from the University of Vermont starting a career in the San Francisco, California bay area, my patients have been my inspiration. One day as I worked with an elderly woman on the acute med-surg unit trying to guide her return to walking I must have been a bit impatient with her. Despite her significant cognitive impairment due to Alzheimer's disease, she did not hesitate to put me in my place saying, "Patience is a virtue, possess it if you can. It's seldom found in woman, and never found in man!". It was then, very early in my career, that I realized and embraced the idea that my patients had just as much (if not more) to teach me as I had to teach them as long as I kept myself open to it. I believe it is that perspective that my patients have gifted to me and in doing so provided a lifetime vocation that remains engaging and joyful. I am forever grateful to them all.

I want to specifically thank the nine individuals who volunteered and participated in my dissertation research. Although my "selling" point was they would receive four weeks of free therapy, anyone who has participated in LSVT BIG or LOUD knows that "free" therapy takes hard work, dedication, and perseverance. Parkinson's disease is something you are diagnosed with - it is not who you are. These individuals and their dedicated partners and caregivers face each day anew and accept the challenge before them. I want to thank them for their support of my journey and for the privilege to be a part of theirs.

I want to acknowledge the support of the URI Physical Therapy Department faculty, staff, and students. They opened their doors, gyms, and hallways to my endeavors as well as cheered me and my patients each step of the way. I am honored to become an official member of their team as a faculty member.

I want to acknowledge the RI-INBRE lab and staff, specifically Kim Andrews, who with her generosity of time and patience taught me the basics of bench science techniques which allowed me to complete a unique aspect of my research.

I want to say thank you to the student members on my research team, specifically, Morgan McKenney (2020), Briana O’Grady (2020), Nicole Mahan (2021), and Natalie Peterson (2021). Their assistance was invaluable. Briana and Morgan became LSVT BIG certified and assisted in the direct treatment of the participants, while Nicole and Natalie assisted with assessments, data collection, and filming. They have also become BIG certified and continue to assist in my lab. I hope that their experience with research and working with people with Parkinson’s disease will inspire them to go forward in their clinical careers with compassion and enthusiasm that will serve as a foundation for the advancement of new ideas and treatments.

I want to say a special thank you to Dr. Christie Ward-Ritacco, Assistant Professor in Kinesiology. Our “chance” introduction by Dr. Leslie Mahler led to her willingness and openness to assist me in a very important part of my research, looking at neurotrophic factors in the blood. She completed all the necessary blood draws for each participant and taught and assisted me in the processing and storage of the samples. This component of my research would not have been possible without her. I

am looking forward to returning the favor as well as working with her on future research collaborations.

I want to acknowledge the time, energy, and input of my dissertation committee – Dr. Leslie Mahler, Dr. Frank Menniti, Dr. Susan Roush (through my written and oral comprehensive exams before her retirement), Dr. Jennifer Audette, and Dr. Kunal Mankodiya. Your ongoing feedback, mentorship, and support has made all the difference.

It is safe to say I would not have been able to accomplish all that I have without the support of my major professor, Dr. Leslie Mahler, Associate Professor Department of Communicative Disorders and Director, Interdisciplinary Neuroscience Program. She has been my mentor and guide on this journey and in the process has become a colleague and a friend. The first time I met Dr. Mahler was when she was lecturing on speech and communication impairments related to neurologic disease processes in the Introduction to Neuroscience class. We shared a similar interest and passion in neuroscience and in the treatment of people with Parkinson's disease. She was honest and open to the challenges that would be before me especially as a “non-traditional” student returning to school as her path had been a similar one. Thankfully she agreed to take me on as a PhD student. MODEL - SHAPE - DRIVE – STABILIZE – CALIBRATE. This is the credo of the LSVT treatment. It is based on principles of neuroplasticity. Yet, when you really give it thought, it is not unique to LSVT or to the treatment of PD. Dr. Mahler has applied this credo to her mentorship style. She has served as an excellent MODEL in her role as professor, researcher, clinician, and colleague. She has SHAPED my performance in each of those roles. She

has DRIVEN me to be a better clinician, to develop a solid foundation of research both in practice and ethics, to transition my clinical mind into a teaching mind, and to develop solid collaborative relationships with those around me. As I reached each milestone she has STABILIZED me by providing concrete and constructive feedback and identifying my accomplishments. Finally, she acknowledged my CALIBRATION by advancing my teaching and research opportunities which revealed her confidence in my abilities. I hope Dr. Mahler can see my success as a reflection of her success and that she can accept my deepest gratitude and ongoing friendship.

It is with joy in my heart that I share this accomplishment with my friends and family as without their unwavering support of my efforts and belief in my abilities, I could not have reached my goal. I cannot name all of my friends and family members whose kind words and inquiry into my studies and research bolstered me but do want to mention just a few.

My dearest friend and running partner, Nancy O'Brien. She endured many a discussion of neuroscience, graduate school drama, and frustrations and excitement over each small step of the way as we ran the dirt trails of the Carolina Management Area. She also tolerated many a missed run due to time constraints with family, work, school, and research schedules. I told her it was short term with a goal in sight but three and half years tends to feel longer than "short term", so thank you Nancy for your patience. Let the running continue!

My sister, Monica Carmichael and her family. Our families have shared great times in parallel with this journey as our children have reached their own milestones, we have travelled together, and joined in many family celebrations. We have also

endured some difficult times and significant loss in the passing of both our parents in the same time frame. I am grateful to have you in my life and your presence and support in ALL that I undertake means everything to me.

Finally, I want to acknowledge my three children – Christopher, Cheyenne, and Cody. I feel in many ways we all three have had the shared experience of going to college together. It seems fitting after many years of home schooling and serving as your teacher, I should return to school and become your peer. You all helped me navigate the many aspects of the new learning environment, dealing with online systems, figuring out literature reviews, formatting papers, studying for exams, and perhaps most importantly, knowing the best place on and off campus to get coffee. You have all shown me nothing but support in my endeavor as I would often find written notes of encouragement at random locations in the house. I am so proud of each of your accomplishments – Christopher (West Point 2018), Cheyenne (URI 2018), and Cody (URI 2020). I hope I have shown you by example that we never stop learning and to always remain curious about the world around you. Most importantly, please know that as proud as I am of earning my degree, my greatest accomplishment is the three of you!

DEDICATION

In loving memory of my mother and father,

Anne Marie (DeRoche) and Raymond Peter Leamy

Their unfaltering love and belief in me remain my guiding force!

TABLE OF CONTENTS

ABSTRACT.....	ii
ACKNOWLEDGMENTS.....	v
DEDICATION.....	x
TABLE OF CONTENTS.....	xi
LIST OF TABLES.....	xiv
LIST OF FIGURES.....	xv
CHAPTER 1.....	1
INTRODUCTION.....	1
CHAPTER 2.....	5
REVIEW OF THE LITERATURE.....	5
Parkinson’s Disease Overview.....	5
Pathophysiology of Parkinson’s Disease.....	7
Role of Genetics and Epigenetic Triggers.....	14
Diagnosis and Treatment of Parkinson’s Disease.....	16
LSVT BIG Treatment Intervention.....	28
Neuroplasticity and Exercise Prescription.....	33
Conclusion.....	38
CHAPTER 3.....	39
METHODOLOGY.....	39
Study Design.....	39
Recruitment/Participants.....	40
LSVT BIG Intervention.....	41

Initial Assessment Measures.....	42
Clinical Outcome Measures.....	43
Functional Mobility Measures.....	44
Psychometric Measures.....	46
Neurobiological Measures.....	48
Participation and Adherence.....	49
Statistical Analysis.....	50
CHAPTER 4.....	53
RESULTS.....	53
Demographics and Initial Assessment Measures.....	53
Intervention.....	54
Compliance.....	54
Functional Mobility Measures.....	55
Psychometric Measures.....	62
Neurobiological Measures.....	67
CHAPTER 5	70
DISCUSSION.....	70
Hypothesis 1: Exercise intervention using LSVT BIG will produce positive statistically significant changes in functional mobility outcome measures in PwPD.....	71
Hypothesis 2: Exercise intervention using LSVT BIG will produce positive statistically significant changes in psychometric measures including quality of life in PwPD.....	79

Hypothesis 3: There will be measurable changes in sBDNF levels following LSVT BIG treatment as a result of intensive exercise.....	86
Hypothesis 4: There will be positively correlated changes between sBDNF level and functional mobility outcomes measures.....	87
Neuroplasticity, Exercise Prescription and Clinical Implications.....	88
Limitations.....	91
CHAPTER 6.....	94
CONCLUSION.....	94
Recommendations for Future Research.....	94
Conclusion.....	96
APPENDICES.....	98
BIBLIOGRAPHY.....	117

LIST OF TABLES

TABLE	PAGE
Table 1. Demographic Characteristics.	41
Table 2. Clinical Characteristics	43
Table 3. Outcome Measures Summary and MCID and MDC	52
Table 4. Unified Parkinson’s Disease Rating Scale III (UPDRS-III) Results.....	56
Table 5. Functional Gait Assessment (FGA) Results.....	57
Table 6. Mini Balance Evaluation System Test (MiniBEST) Results.....	58
Table 7. Timed Up and Go (TUG) Results	59
Table 8. Gait Speed Results	60
Table 9. Step Length Results.....	61
Table 10. Activity-specific Balance Confidence Scale Results	63
Table 11. Parkinson’s Disease Quality of Life 39 Summary Index (PDQ39-SI) Results	64
Table 12. Geriatric Depression Scale (GDS) Results.....	65
Table 13. Parkinson’s Fatigue Scale Results.....	66
Table 14. Serum Brain Derived Neurotrophic Factor (sBDNF) Results	68

LIST OF FIGURES

FIGURE	PAGE
Figure 1. Basal Ganglia Anatomy	8
Figure 2. Basal Ganglia Circuitry.....	9
Figure 3. Modulation Circuit - Dopamine	10
Figure 4. Treatment Protocol Timeline	39
Figure 5. Serum Brain Derived Neurotrophic Factor (sBDNF) Correlates	69
Figure 6. Functional Mobility Outcomes.....	71
Figure 7. Gait Outcome Measures	72
Figure 8. Falls Risk at BASE and EOT+4	79
Figure 9. Balance Confidence and Quality of Life	80
Figure 10. Depression and Fatigue	81
Figure 11. Serum Brain Derived Neurotrophic Factor	87

CHAPTER 1

INTRODUCTION

This sickness has no boundaries

No oceans it won't cross

An illness that's invisible

Submerged in utter chaos

- Anonymous PwPD

Parkinson's disease (PD) is a progressive neurodegenerative disorder affecting the dopaminergic neurons of the substantia nigra pars compacta (SNpc) and affects over one million people in the United States and up to three million people in all of North America (Marras et al., 2018). People with PD (PwPD) experience a decline in functional mobility and quality of life as well as an increased need for support due to factors directly associated with the progression of motor and nonmotor symptoms. Individuals diagnosed with PD continue to have limited options for treatment of symptoms beyond pharmacological interventions such as dopamine replacement therapy or surgery such as deep brain stimulation. People are often not referred for physical therapy (PT), occupational therapy OT), or speech therapy (SLP) until there has been significant disease progression and they demonstrate a marked decline in quality of life, activities of daily living, impaired

mobility, and/or speech or swallowing issues. Physical therapists address balance, mobility, and gait issues for PwPD with a wide variety of behavioral (exercise-based) treatment interventions. Research has revealed significant improvements with physical functioning, health related quality of life (HRQoL), strength, balance, and gait speed (Goodwin et al., 2008; Tomlinson et al., 2012) as a result of treatment but with limited evidence to support which interventions are most effective for patients. A 2001 Cochrane review of Physiotherapy for Parkinson's disease: a comparison of techniques (Tomlinson et al., 2001) identified only seven potential randomized exercise trials compared to 43 trials identified in 2012. This review identified research supporting a variety of PT exercise interventions to be effective in PD but concluded that there is no robust evidence to support any one physical therapy approach over another in the treatment of PD related impairments (Tomlinson et. al., 2012). The studies were subdivided into six categories because there was which included general physical therapy, exercise, treadmill training, cueing, dance, and martial arts. The Lee Silverman Voice Treatment (LSVT), specifically LSVT[®]BIG study (the focus of this research), was one of those studies included (Tomlinson et al., 2012). This reflects the growing interest in behavioral interventions for this population but more importantly, the need to establish evidence-based treatment interventions and exercise prescription recommendations within the PT discipline along with valid, sensitive outcome measures.

In this study, we investigated the impact of LSVT BIG on functional mobility, quality of life, and markers of neuroplasticity. Neuroplasticity is a general term used to indicate the brain's ability to reorganize itself in an adaptive manner in response to the

environment or injury. For the purposes of this paper there will be two operational definitions that will be utilized. The first is functional neuroplasticity which relates to changes in the brain that are observed or measured as final neural activity or behavioral response and represent the system-wide output. The second is cellular neuroplasticity which represents the vast collection of brain changes that include molecular, structural, and biological components. These include, but are not limited to, increased dendritic spine density, changes in receptor density, angiogenesis, neurotrophic factor release, and synaptogenesis.

LSVT BIG is an intensive, whole-body, amplitude-based training protocol for individuals with PD. LSVT BIG incorporates principles of motor learning that drive activity dependent changes in functional neuroplasticity outlined by Kleim and Jones (2008), including intensity, repetition, task specificity, “use it or lose it,” and salience of treatment exercises. LSVT BIG, like other exercise interventions, has limited evidence-based research to support treatment efficacy at this time. The purpose of this study was to assess the impact of treatment on mobility, HRQoL, and serum brain derived neurotrophic factor (sBDNF) of patients following administration of the LSVT BIG program.

Individuals with PD were recruited from the local community and, after undergoing an initial screening to ensure they met inclusion criteria, were seen for a full assessment that included specific functional, balance and gait measures, non-motor symptom self-report measures such as fatigue and depression, and a blood draw. They then completed the LSVT BIG treatment protocol, which was one hour per day, four days per week for four weeks. They were seen for a full follow-up

assessment immediately after completion of the program and one month later. Blood samples were drawn at each assessment time point and sBDNF levels were measured. This provided an opportunity to assess the potential link between functional neuroplasticity (changes in functional outcome in response to a treatment intervention) and cellular neuroplasticity (sBDNF).

Principle aims of this study:

Aim 1: Determine the effects of LSVT BIG on functional mobility measures as well as quality of life measures in people with Parkinson's disease (PwPD).

Hypothesis 1: Exercise intervention using LSVT BIG will produce positive statistically significant changes in functional mobility outcome measures in PwPD.

Hypothesis 2: Exercise intervention using LSVT BIG will produce positive statistically significant changes in psychometric measures including quality of life in PwPD.

Aim 2: Determine the correlation between neurobiological measures (serum BDNF) and functional changes associated with a behavior treatment intervention (LSVT BIG).

Hypothesis 3: There will be measurable increases in sBDNF levels following LSVT BIG treatment as a result of intensive exercise.

Hypothesis 4: There will be positive correlation between increased sBDNF level and improvement in functional mobility outcomes measures.

CHAPTER 2

REVIEW OF LITERATURE

Parkinson's Disease Overview

Parkinson's disease (PD) was first described as the “the shaking palsy” in James Parkinson's original essay published in 1817. His description of the symptoms of PD as “involuntary tremulous motion, with lessened power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace; the senses and intellects being uninjured” remains true today (Parkinson 1817, p. 1). However, the etiology of PD and treatment of the symptoms of PD remain incompletely understood. Parkinson's disease is a complex progressive neurodegenerative disorder affecting the dopamine (DA) producing neurons in the substantia nigra, part of the basal ganglia network. It is characterized by changes in motor function, specifically primary motor signs such as tremor, bradykinesia, rigidity, and postural instability (Kandel, Swartz, and Jessell, 2013, p. 991-992). Additional motor signs can include micrographia, hypophonia, difficulty swallowing, drooling, freezing, mask-like expression, and unwanted accelerated movements. There are also nonmotor symptoms such as constipation, nocturia, impacted sleep pattern, orthostatic hypotension, depression, and dementia. These symptoms vary in severity as the disease progresses and can have a significant negative impact on functional mobility as well as quality of life.

Parkinson's disease is the second most common neurodegenerative disease after Alzheimer's disease. The Parkinson's Disease Foundation estimates PD affects almost one million Americans, sixty-thousand people are newly diagnosed each year, and a financial impact including direct and indirect costs are estimated to be \$52 billion annually in the United States alone (Parkinson's Foundation, 2019). The number of people affected world-wide is estimated to be 6.2 million (GBD, 2018) but could be as high as 10 million due to under reporting. A systematic review of 47 studies from 1985 to 2010 reported the overall prevalence of PD across the globe ranges from 113 to 873 per 100,000 with males having a significantly increased prevalence 134 per 100,000 compared with females at 41 per 100,000 (Pringsheim, Jette, Frolkis, & Steeves 2014).

Age is the greatest risk factor for developing PD (Collier, Kanaan, and Kordower, 2011; Collier et al., 2017; Reeve, Simcox, and Turnbull, 2014). The current U.S. population of adults 65 years and older is expected to increase from 56.1 million in 2020 to 73.1 million in 2030, a 30 percent increase with continued growth to 95.4 million, a 53 percent increase, by 2050 (United States Census Bureau, 2016). According to An Aging World: 2105 International Population Report (He, Goodkind, and Kowal, 2016), 617.1 million people of the 7.3 billion people worldwide are aged 65 years and older with a projected increase of more than 60 percent in just 15 years, by 2030, the equivalent of 12 percent of the total population. This is expected to increase to 16.7 percent of total world population of 9.4 billion by 2050. These numbers will be mirrored by significant increases in the number of people world-wide that will struggle with the consequences of disease, especially neurodegenerative

disease such as PD. The significant impact of PD on individuals and society, especially an aging society, supports the ongoing investigation of not only the underlying causes but also evidence-based treatment approaches and a move towards finding a cure.

Pathophysiology of Parkinson's Disease

Anatomy and Circuitry

Parkinson's disease is a progressive neurodegenerative disease associated with dysfunction of dopaminergic neurons located in the substantia nigra (SN), which is part of a group of nuclei called the basal ganglia (Little and Brown, 2014; Rizzi and Tan, 2017). The basal ganglia are responsible for processing sensorimotor information for proper movement generation, selection, planning, and execution of locomotion and all voluntary movement (Rizzi and Tan, 2017). Four principal loops (motor, oculomotor, executive/associative, and emotion/motivation) have been identified that integrate this complex information to allow specific behavioral outputs (Martin, 2012; Kandel et al., 2013). The motor loop includes the striatum (caudate and putamen) which is the major input structure for the basal ganglia receiving inputs from cortex, thalamus, and brainstem. Information is further modified within the basal ganglia via intrinsic circuitry that includes the Globus pallidus externus (GPe), SN pars compacta (SNpc) and subthalamic nucleus (STN). The STN receives inputs from GPe, cortex, thalamus, and brainstem and sends output to Globus pallidus internus (GPi), GPe, and SN pars reticulata (SNpr). The GPi is one of the major output structures along with the

(SNpr) that sends signals upstream to the thalamus and downstream to the pedunculo-pontine nucleus in the brainstem. (Figure 1: Basal Ganglia Anatomy)

This complex network of communication and circuitry can be summarized by the rate model which includes three intrinsic pathways – Direct pathway, Indirect pathway, and a Hyper-direct pathway - each traversing different nuclei, releasing different neurotransmitters, and modifying the output signal in different ways (Rizzi and Tan, 2017). The direct pathway (motor-permissive or GO pathway), as its name implies, is the shortest path for excitation and facilitation of movement (striatum – GPi – thalamus). When the cortex releases glutamate to stimulate the striatum, this directly

inhibits the GPi. The GPi is also inhibitory in nature, so when the striatum directly inhibits the GPi, the result is increased firing in the thalamus which increases activity in the motor cortex thus increasing movement. The indirect pathway (motor-suppressive or NO GO pathway) takes a more circuitous route (striatum – GPe – STN – GPi – thalamus). When the striatum releases GABA at the GPi, it also releases it at the GPe. The GPe normally inhibits the STN but if the striatum has inhibited or decreased the amount of inhibition of the GPe this allows the STN to be facilitated. The STN is excitatory and stimulates the GPi. When the GPi is stimulated it releases more GABA onto the thalamus thereby inhibiting thalamic activity which results in decreased motor cortex activation. The hyper-direct pathway is direct facilitation of the STN via direct cortical input and causes less movement. (Figure 2: Basal Ganglia Circuitry)

Internal to this network is a neuromodulation circuit, specifically the SNpc, the mediodorsal portion of the SN which projects heavily to the striatum. These projection neurons are dopaminergic and the DA they release bind to two different receptors in the striatum, D1 and D2 receptors. Dopamine released by SNpc bind to D1 receptors that excite the direct pathway and increase thalamic activity resulting in more movement. The dopamine also binds to D2 receptors that inhibit the indirect pathway which results in increased thalamic activity and results in more movement. This modulation allows for finer tuned control of movement. However, under pathological conditions such as decreased dopaminergic input in the case of PD, there is less available dopamine to bind to D1 and D2 receptors resulting in less excitation of the direct pathway and less inhibition of the indirect pathway with an end result of decreased thalamic activity and less movement. (Figure 3: Modulation Circuit – Dopamine)

Figure 3: Modulation Circuit - Dopamine

The basal ganglia and its related networks are known to play a key role in procedural learning and movement regulation, therefore, damage to this region can result in different types of movement disorders depending on the nuclei and pathways affected. Movement disorders arising from involvement of this network can range from hyperkinetic (too much DA) such as Huntington's Disease to hypokinetic (too little DA) such as Parkinson's disease with characteristics well summarized by Kandel et al. (2013, p.991), as "impaired initiation (akinesia), reduction in amplitude and velocity of voluntary movement (bradykinesia), muscular rigidity (increased resistance to passive displacement), and a 4-6 Hz tremor at rest and flexed posture". These clinical manifestations of altered movement represent the cardinal motor impairments associated with PD and are a direct result of decreased availability of DA as described in the previous section. Although much of the literature is focused on motor impairment it is important to keep in mind that individuals with PD also experience sensory deficits, specifically, an alteration in sensory input and its integration into modulation of motor behavior which contribute significantly to decreased internal monitoring of amplitude of movements effecting motor production across speech and mobility domains (Mahler, Ramig, and Fox, 2015; Farley and Koshland, 2005).

Cellular Pathogenesis

Dysregulation of DA is a central player in the clinical presentation of PD but the cause of neurodegeneration of the DA system is not well understood. Advances in technologies for improved staining and tissue analysis along with mapping of the

human genome and the explosion of genetic research has provided further insight into this question.

In 1912 Friedrich Lewy described intraneuronal inclusions in the nucleus basalis of Meynert and the dorsal motor nucleus of vagus in the brains of people with PD at autopsy which were later confirmed to be present in the substantia nigra and other areas of the brain effected by PD as well (Shults, 2006). These inclusions were subsequently named Lewy Bodies (LB)(spherical) and Lewy neurites (LN)(thread-like appearance). Maria Spillantini (1997) utilized a staining technique to identify α -synuclein (α -syn) as one of the proteins in the Lewy Bodies. This, along with advances in genetics which identified two missense autosomal-dominant mutations in the α -synuclein gene in kindreds with early-onset familial PD one year earlier, opened an entirely new area of study into the pathogenesis of PD (Goedert, Spillantini, and Davies, 1998) and the identification and definition of PD as a synucleinopathy (Postuma et al., 2015).

The protein α -syn is a small, hydrophilic, natively unfolded, 140-amino acid that normally exists in many nerve cells of the human nervous system (Braak et al., 2004); it is located in presynaptic terminals (Goedert, Spillantini, and Davies, 1998; Shults, 2006). The function of normally occurring α -syn is not fully understood however, it has been suggested to play a role in the activity-dependent modulation of nigrostriatal DA transmission, be involved in long-term regulation and maintenance of presynaptic terminals and be required for the genesis and localization of presynaptic vesicles and modulation of neurotransmitter release (Shults, 2006). Misfolding of α -syn and subsequent aggregations and its' relationship to PD has been well elucidated

over recent years and appears to have a central role in the underlying pathology of PD (Desplats et al., 2009). When the cell cannot keep up with the demand to clear the misfolded α -syn it starts to aggregate forming fibrils (LN) or cytoplasmic inclusion bodies (LB). The inability of the cell to clear the misfolded α -syn, and additional alterations in gene expression involving proteins involved in the breakdown and clearance of intracellular proteins, has implicated the proteasomal system in the pathogenesis of PD (Shults, 2006). It has been suggested that this excessive amount of misfolded α -syn contributes to high amounts of oxidative stress and mitochondrial dysfunction contributing to cell death of the dopaminergic neurons (Rietdijk et al., 2017). Current literature supports three potential pathways involving LB and LN that lead to cell death – protein aggregation, impaired protein degradation, and mitochondrial and oxidative stress possibly also involving inflammation (Shults, 2006).

Accumulation of aggregated α -syn has been shown to follow a highly predictable pattern of progression, from the olfactory bulb and lower brain stem to higher centers of the neocortex (Desplats et al., 2009; Rietdijk et al., 2017; Braak et al., 2004). Braak et al. (2003) published their hypothesis that PD is caused by a pathogen that enters the body via the nasal cavity and is eventually swallowed entering the nervous system by the digestive tract and enteric nervous system. They went on to identify six neuropathological stages of the disease that can be divided into pre-symptomatic (stages 1 and 2) and symptomatic phases (stages 3-6). Each stage in the Braak et al. model is marked by distinctive inclusion bodies that present as either

Lewy neurites (LN) or Lewy bodies (LB) which are unique to PD and not signs of “healthy” aging.

One thing that all the models agree about is that there are substantial changes in the nervous system by the time there are enough symptoms to clinically diagnose PD. This is important because even people who seek treatment soon after diagnosis (and most don't) already have significant disease (Braak et al., 2004).

The Role of Genetics and Epigenetic Triggers

Two forms of PD have been identified, familial and sporadic. Familial, or hereditary forms of PD are rare, accounting for only 10-15% of cases while sporadic PD, also known as idiopathic, accounts for 80-85% of diagnosed cases (Little and Brown, 2014). Sporadic PD occurs in the general population, has no germ line mutations but may have genetic contributions, and typically occurs in older individuals (>60 years). Familial PD occurs in only specific kindreds, is an inherited germ line dominant or recessive mutation and typically has an early onset (<60 years).

Several epigenetic triggers have been associated with PD. Direct and indirect exposure to industrial chemicals such as manganese and carbon monoxide and pesticides such as agent orange and permethrin can lead to an accumulation within the human body and lead to severe injury to a multitude of systems including the nervous system and associated motor impairments that are parkinsonism but not necessarily confirmed PD (Weiner, Shulman, and Lang, 2013; Kim, Kim, and Kumar, 2019). It has also been well established that parkinsonism can be drug induced by medications such as neuroleptics like Thorazine and Haldol, antidepressants such as amitriptyline

and trazodone, and antihypertensives such as methyldopa and reserpine all of which produce extrapyramidal dysfunction and are reversible states with removal of the offending agent. These are just a few of the identified potential environment triggers that have come to light in the past few decades with many yet to be identified. Understanding these potential environmental contributors to PD-like symptoms are important to be aware of and screened for when assessing individuals with PD.

Research into familial PD, although much rarer, has led to discoveries into the genetic causes of inherited forms of PD and has provided significant insight into the underlying pathophysiology of sporadic PD. Each protein coded for by mutated genes (i.e. PARK-2, PINK1, and LRRK2) appears to play a role in the proteasomal pathway, mitochondrial function, or oxidative stress management. It suggests that when a dysfunction in that protein occurs through altered genetic expression it acts in a toxic manner in the cell leading to cell dysfunction and ultimately death. Genome-wide association studies (GWAs) have provided support for PD to be considered a “complex genetic disorder” meaning that not just one abnormal gene but an array of genes (perhaps as many as 10-40) each exert a very small effect align and triggers PD (Williams-Gray and Worth 2016; Weiner, Shulman, and Lang, 2013, p. 28). This, along with further identification of environmental triggers and the process that leads to cell death in vulnerable neuronal populations can assist in guiding the direction of future research, developing biomarkers and diagnostic techniques for early detection, treatment interventions, and perhaps ultimately a cure for PD.

Diagnosis and Treatment of Parkinson's Disease

Diagnosis, Clinical Presentation, and Diagnostics

There is no definitive test or biomarker for the diagnosis of PD and therefore it is often a diagnosis of elimination based on symptomology, behavioral observations, history of the evolution of symptoms, the systematic ruling-out of other potential causes of parkinsonism, and response to levodopa medication (Postuma et al., 2015). A pathological diagnosis of PD is definitive only through postmortem histological analysis of brain tissue which confirms the presence of Lewy body pathology (LP) in the basal ganglia (Jankovic et al., 2008; Trail, Protas, and Lai, 2008, p. 15). The progression of the disease is as nonlinear and unpredictable across the population as the presenting symptoms. It is critical for the individual to undergo a thorough neurological evaluation when a Parkinson diagnosis is suspected as there are several differential diagnoses based on underlying pathology requiring different treatment approaches. Parkinsonism can be classified as four types: Primary PD (idiopathic), Secondary PD (acquired), Heredodegenerative (inherited), and multisystem degeneration (Parkinson-Plus syndromes) (Jankovic et al., 2008). Primary and Heredodegenerative PD are typically very similar and can only be differentiated by age of onset and genetic testing. Secondary parkinsonism can be caused by stroke, brain tumor, post-encephalitic virus, toxins, drug induced (prescriptive and illicit), and certain metabolic conditions while progressive supranuclear palsy (PSP), multisystem atrophy (MSA), and cortico-basal degeneration (CBD) fall under the Parkinson-Plus syndromes. In addition, other conditions such as normal pressure hydrocephalus, essential tremor, and Creutzfeldt-Jacob Disease also need to be ruled out.

The four cardinal features of PD are often identified with the acronym TRAP: Tremor, Rigidity, Akinesia (also known as bradykinesia), and Postural instability with a possible positive diagnosis considered when an individual has any two of these four symptoms. The United Kingdom Parkinson's Disease Society Brain Bank and the National Institute of Neurologic Disorders and Stroke (NINDS) both have clear diagnostic criteria outlined but neither reliability nor validity of these criteria have been established. One study that looked at 100 people clinically diagnosed with PD revealed only a 76% pathological diagnosis on postmortem analysis (Jankovic et al., 2008). Once the cardinal signs have been confirmed the next step is to exclude any other cause of the parkinsonism. Even though it has been identified that there is no confirmatory diagnostic test for PD, medical evaluation such as blood work, MRI, and PET scans may be performed. Positron emission tomography (PET) using 18F-fluorodopa can show reduced uptake in the striatum, especially the putamen in PD patients. Single photon emission computerized tomography (SPECT) with dopamine transporter ligands, beta-CIT and TORDAT, also called a DaT-Scan quantitatively measures the level of dopamine in the basal ganglia with a deficiency indicative of Parkinsonism. This test, however, cannot differentiate between the four types (Jankovic et al. 2008; Weiner, Shulman, and Lang, 2013, p. 114).

Even once a clinical diagnosis of primary PD has been made, there are three further subtypes that have been identified: 1) postural instability and gait disorder predominant (PIGD); 2) tremor-dominant (TD), and 3) a mixed form (Jankovic 2008). Postural instability and gait disorder predominant PD has been shown to present with a poor prognosis and more rapid progression of the disease, a limited response to

levodopa, and higher rates of depression and cognitive impairment when compared to the Tremor-dominant type (Jankovic 2008).

PD severity scales are used to track the progression of the disease and to draw a clearer clinical picture of the individual diagnosed with PD . The most universal is the Unified Parkinson's Disease Rating Scale (UPDRS) which was originally developed in the 1980s. It was revised under sponsorship of the International Parkinson and Movement Disorder Society (MDS) and renamed the MDS-UPDRS. It is used as the primary international rating scale for PD clinical care and research (Goetz et al., 2008). The MDS-UPDRS has four parts: I Non-motor Experiences of Daily Living (13 items); II Motor Experiences of Daily Living (13 items); III Motor Examination (18 items); IV Motor Complications (6 items). There is a 5-point range for each item - normal (0), slight (1), mild (2), moderate (3), and severe (4) with a higher score indicating higher disability. Factor structure of the new scale has been determined to be both clinimetrically sound and clinically relevant when each of the four parts (I-IV) are reported separately and not collapsed into a single "total MDS-UPDRS" summary score (Goetz et al., 2008).

There has been a long history of interest in staging PD progression. In 1967 Hoehn and Yahr (H&Y) offered a staging schema with five categories which is still used extensively today (Hoehn & Yahr 1967). These categories are: 0 – Asymptomatic, 1 – Unilateral involvement only, 2 – Bilateral involvement without impairment of balance, 3 – Mild to moderate involvement; some posture instability but physically independent; Needs assistance to recover from the pull test, 4 – Severe disability; still able to walk or stand unassisted, and 5 – Wheelchair bound or bed

ridden unless aided. The Hoehn & Yahr scale mixes impairment and disability and is considered nonlinear thus the MDS recommends it be used as a more global clinical descriptor of disease severity such as demographic descriptor and for inclusion and exclusion in research (Goetz et al., 2004).

The Braak staging, discussed earlier, is based on immunohistochemistry and postmortem analysis and is not used as a clinical staging tool. Some studies support the caudo-rostral development but identify a lack of correlation between medullary and cortical disease severity (Kingsbury et al., 2010). Other studies indicate no relationship between Braak staging and clinical severity of PD (Burke, Dauer, and Vonsattel, 2008). This type of staging may play a different role in clinical management in the future once a biomarker of early disease is discovered.

A clear understanding of disease severity and subtype can serve to clarify the symptoms and their impact on mobility and quality of life as well as aid in decisions regarding treatment options for PwPD.

Treatment Overview

Currently there is neither a cure for PD nor a disease modifying intervention that will stop or reverse the progression of the disease (Kriebel-Gasparro, 2018) although some progress has been made in disease deceleration in animal models (Pedrosa and Timmerman 2013). Treatments available for people diagnosed with PD are exclusively targeted at symptom management and fall into one of three categories: pharmacological intervention; surgical intervention such as deep brain stimulation (DBS); and behavioral intervention such as PT, OT, and ST (Pedrosa and Timmerman

2013). These interventions are based on clinical indicators as symptomatic monotherapy, symptomatic adjunct therapy to levodopa, treatment of motor complications such as dyskinesia, and prevention or delay of disease progression or motor complications each with their own strengths and weaknesses (Fox et al., 2011).

Pharmacological Intervention

The current understanding of PD pathology points to the decreased DA production as the primary perpetrator of the motor symptoms such as tremor and rigidity. Therefore, pharmacological interventions to increase DA is considered to be “best medical treatment” to address associated motor symptoms. Medications utilized in the treatment of PD can replace DA or enhance existing DA levels and are usually classified as 1) Carbidopa/Levodopa, 2) Dopamine agonists, 3) Anticholinergics, 4) Monoamine oxidase inhibitor B (MAO-B), 5) Catechol-O-methyltransferase (COMT) inhibitors, or 6) Other medications (Fox et al., 2018; Kriebel-Gasparro 2016).

One benefit of DA replacement therapy is clinically significant remediation, and often elimination, of the specific motor impairments associated with PD such as tremor, akinesia, and rigidity (Pedrosa and Timmerman 2013). These motor symptoms are often the greatest complaint of people with the idiopathic PD and have the most significant impact on their quality of life. They also report the most relief and easing of symptoms once started on medication. There are drawbacks, however, to consider. Most of the DA replacement medications have a very short half-life thus benefits are short lived while high levels of DA in dorsal striatum (over time) allows increased permissive signaling which can lead to dyskinesia and associated mental health issues

such as obsessive-compulsive disorder and psychosis (Yahr et al., 1969).

Desensitization to medications requires higher doses and DA medications can become ineffective later in disease process when they need it most, so the decision as to when medications should start has been highly debated.

Surgical Intervention

In the early 1900's surgical interventions for PD were primarily ablative procedures targeting different regions of the basal ganglia. These were replaced by medication due to the discovery of levodopa in the 1960's. Surgery saw a resurgence in the form of deep brain stimulation (DBS) in the 1980's when in 1987 Dr. Alim Benabid, a neurosurgeon from Grenoble, France, placed the stimulator in the ventral intermediate nucleus of the thalamus as an effective treatment for tremor then later for motor symptoms in PD. This led to FDA approval of DBS in 1997 for essential tremor and 2002 for PD (Mirza et al., 2017; Hariz, 2017). Deep brain stimulation involves the delivery of electrical impulses via an implant of electrodes deep in the brain with a battery controller in the chest wall similar to a pacemaker (DeMaagd and Philip 2015). The control unit allows for setting adjustments that can modulate the activity of deep brain structures whose dysfunction is associated with common neurologic and psychiatric conditions. The main target sites for DBS are the GPi and STN. The Ventral Lateral posterior nucleus (VLp), an earlier target for ablative surgery, has been found to be less comprehensive in addressing the cardinal symptoms using DBS when compared with the STN or GPi and is therefore used only when other options are not practical. The pedunculopontine nucleus (PPNa) has been considered an additional

target that can provide management of freezing of gait (FOG) and gait disorders at low frequencies (10-25 Hz) or potentially symptoms of postural instability at higher frequencies (60-80 Hz) (Nosko 2015). These results, however, remain controversial when compared to other studies. This suggests the need for further study, mapping of circuitry, and development of more sophisticated stimulators and placement techniques (Pedrosa and Timmerman 2013).

The GPi is a large anatomic structure and allows for more precise placement and control of stimulation but because of this, it requires a much higher charge density and more frequent battery replacement. In comparison, the much smaller STN is one third the size and requires a lower amplitude pulse but can have more side effects related to the spreading of signal to proximal limbic and associative loop pathways. Thus consensus in the field supports an individualized and team decision based on patient specific needs and symptoms as each site offers strengths and drawbacks based on therapeutic benefit, mechanism of action, and adverse effects and the overall risk-benefit ratio (Mirza et al., 2017).

Treatment of PD symptoms using DBS has demonstrated significantly better management of tremor and motor function and improved quality of life compared to the best pharmacological intervention in PwPD. The recommendation from the International PD and Movement Disorders Society regarding the use of DBS remains, “efficacious for motor fluctuations and dyskinesias with the implication for clinical practice as ‘clinically useful’ with ‘acceptable risk with specialized monitoring’ regarding safety concerns” (Fox et al., 2018, p. 1256). The main drawback is that DBS has been associated with significant potential surgical complications including

intracranial hemorrhage (4.4%), infection (4%), seizures (3.2%), and migration of leads (2.4%) (Mirza et al., 2017) resulting in speech difficulties, balance issues, and poor quality of life (Kahn et al., 2012; DeMaagd and Philip, 2015). According to Mirza et al. (2017, p. 11) these “failures” can often be attributed to “inadequate presurgical screening, improper patient selection, incorrectly placed leads, suboptimal programming, battery failure, and hardware related issues” emphasizing the importance of an interdisciplinary team approach to DBS treatment recommendations.

The use of DBS has allowed for the decreased use of medication by treating the debilitating symptoms of Parkinson’s disease in more than 150,000 people worldwide over the past 30 years. How DBS works, however, still has not been well elucidated (Hariz, 2017; Mirza et al., 2017; Pedrosa and Timmerman 2013). It may involve the modulation of thalamic signals and/or the local release of glutamate and adenosine in the targeted areas (DeMaagd and Philip, 2015) or may have multiple actions including a depolarizing blockade, synaptic inhibition, synaptic depression, and stimulation-disruption of the pathological network (Pedrosa and Timmerman 2013). Ongoing research and future advances in technology will hopefully lead to greater understanding of basal ganglia anatomy and circuitry allowing for greater refinement of DBS targets and disease management in PD.

Behavioral Intervention

Pharmacological intervention focuses on amelioration of the cardinal motor symptoms associated with PD but there is a broad range of additional motor and nonmotor symptoms for which medications are not effective. Behavioral interventions

such as exercise exert global and system wide changes throughout the nervous system including release of neurotrophic factors, cardiovascular improvements, increased mitochondrial energy production, and reductions in inflammation that can produce further cascades of cellular neuroplasticity and neuroprotection not offered by medication alone (Zigmond and Smeyne, 2014). Exercise should therefore be seen as a primary or adjunct treatment for individuals with PD (Cotman, Berchtold, and Christie, 2007).

Behavioral interventions provided by PT, OT, and SLP have been shown to be highly effective in improving balance, gait, function, and quality of life especially as an adjunct to pharmacological intervention (Tomlinson et al., 2012; Pedrosa and Timmerman 2013) and have been recommended as “clinically useful” strategies (Fox et al., 2018). The benefits are fairly extensive in that exercise and behavior interventions have been shown to facilitate functional neuroplasticity (Voss, Erickson et al., 2013; Montiero-Junior et al., 2015; Petzinger et al., 2013).

Clinical diagnosis based on manifestation of symptoms of PD often does not occur until the SNpc has sustained at least 70 percent degeneration of the dopaminergic neurons (Rizzi and Tan 2017). This aligns with the later stages outlined by Braak’s model (2004) which indicates there are already significant and irreversible changes in the nervous system by the time a PD diagnosis is determined. Early diagnosis and referral for treatment is critical to potentially stave off functional decline. Unfortunately, many patients are not referred to therapy until they are many years into the disease process and significant functional impairments are beginning to surface. Research still supports the benefits of exercise intervention even in later

stages of the disease (Rafferty et al., 2017). The challenge can be that initiation and motivation can be compromised (as part of the disease process) impacting an individual's ability and drive to participate in treatment and research.

The focus of PT intervention was initially based on a model that relied on the relationship between the impairments in PD (the cardinal signs) and the subsequent disabilities that resulted (Schenkman and Butler 1989). The earliest evolution of physical therapy involvement in the individual with PD cited exercise as an important regular part of their daily activities and that PT involvement should begin as early as possible in the disease process (Schenkman and Butler 1989). Over the next few decades scientific advances have been improving our understanding of PD pathology and with it, evidence-based practice recommendations for PT and exercise prescription have started to take a clearer form. Six core areas for PT to address in PD were identified: transfers, posture, reaching and grasping, balance and falls, gait, and physical capacity and activity (Kues et al., 2007). Comprehensive clinical summaries (Ellis and Schenkman 2011, revised 2017) and an evidence based database (PD EDGE 2014) were developed by the American Physical Therapy Association (APTA) to guide effectiveness. These resources also recommend clinical and research outcome measures. Physical therapists are uniquely positioned as movement specialists to address the needs of individuals with PD and work closely within an interdisciplinary team to facilitate an optimal program with exercise and physical activity as a central component.

Role of Physical Activity and Exercise in the Treatment of Parkinson's Disease

Along with diet/nutrition, sleep, and social interaction/mental stimulation, exercise and physical activity are one of the cornerstones supporting a healthy lifestyle for the general population. Exercise has the ability to stimulate tissue change and adaptation such as increased muscle mass, strength, and cardiovascular endurance (Johnston, 2018). This contributes to improved functional status related to sports, activities of daily living (ADLs), and can protect against injury. The Centers for Disease Control and Prevention (CDC) outline the many benefits of physical activity including weight control, decreased risk of falls, cardiovascular disease, diabetes, some cancers, pain management, strengthening of bones and muscles, improved mental health and mood, improved ability to do ADLs, and increased longevity (Center for Disease Control, 2018).

There is evidence in human and animal studies that suggest exercise-induced brain plasticity occurs across the life span which may be interpreted to be neuroprotective to age related health risks, such as the development of neurodegenerative disease (Voss, Erickson, et al., 2013; Voss, Vivar, et al., 2013; Zigmond and Smeyne 2014). Neurobiological hypotheses of physical exercise as a treatment for PD include the hypothesis that physical exercise reduces chronic oxidative stress, stimulates mitochondria biogenesis, and antioxidant enzymes become more active and effective. A second hypothesis asserts that physical exercise stimulates neurotransmitter (e.g. dopamine) and trophic factor (e.g. GDNF, BDNF) synthesis thus providing maintenance of neuronal health and stimulation of neuroplasticity (Montiero-Junior et al., 2015; Voss, Vivar, et al., 2013). Research into

neurodegenerative diseases such as PD need to focus on interventions that will facilitate neuroplasticity changes, provide neuroprotection, and/or prevent neurodegeneration.

The 2008 Physical Activity Guideline (CDC, 2018) recommends that adults, including adults with disabilities, get 150 minutes (2.5 hours) of moderate aerobic activity or 75 minutes (1.5 hours) of vigorous activity per week. According to the CDC, only 21 percent of adults and 27.8 percent of US adults 50 years or older with disabilities met these guidelines (Oguh, Eisenstein, Kwasny, & Simuni, 2014). This reflects a significant gap between research and actual practice yet also points to an area of health behavior change that has significant promise and potential to improve the lives of all adults in general, and PwPD specifically.

Studies have shown that physical activity improves movement initiation and that higher patterns of lifetime physical activity were correlated with a lower incidence of PD (Goodwin et al., 2008; Zigmond and Smeyne 2014). They also found improved cortico-motor excitability in PD and increased cortical and hippocampal volumes in the general population suggesting potential neuroplasticity and a potential role in decreasing the risk of cognitive impairments. This suggests that midlife regular exercise may reduce subsequent risk for PD as well as have a disease attenuating effect (Ahlskog, 2011; Zigmond and Smeyne, 2014).

The research continues to support exercise interventions for persons newly diagnosed with PD as well as those with more advanced disease. These recommendations are slowly starting to be reflected in current clinical practice (Speelman, van Mimwegen, Bloem, and Munneke, 2014; Oguh et al., 2014; Rafferty

et al., 2017; Uhrbrand, Stenager, Pedersen, & Dalgas 2015). Organizations such as the American Academy of Neurology (AAN) are acknowledging that while the past treatment of PD focused on medications and surgeries with only a nod to exercise and physical therapy, recent evidence suggests that exercise has multiple important health benefits including improved physical and mental functioning and quality of life and should be “recommended to ALL patients with PD” (Factor et al., 2016, p. 2281). The National Parkinson Foundation recently published a longitudinal analysis of regular exercise (>150 minutes per week), quality of life, and mobility in PwPD concluding that exercising regularly was associated with small but significant protective effects on quality of life and mobility over two years (Rafferty et al., 2017). There were greater benefits of exercise in advanced PD suggesting that clinicians should encourage, facilitate, and monitor long term exercise participation across all stages of PD (Rafferty et. al., 2017). PwPD who exercise regularly (>150 minutes per week) were associated with better quality of life, improved mobility and physical function, less progression of disease, less caregiver burden, and less cognitive decline one year later (Oguh et. al., 2014). Now that most agree that exercise is important as a treatment intervention for PwPD, which exercise are the most effective?

LSVT BIG Treatment Intervention

The Lee Silverman Voice Treatment - LSVT®LOUD is an evidence-based treatment intervention for speech disorders in PwPD supported with more than 25 years of treatment efficacy research. It is an intensive voice treatment for individuals with PD that “requires intensive high effort exercise combined with a simple,

redundant and salient treatment target to transfer loudness into functional daily life” and “adheres to many of the fundamental principles of exercise and motor training that have been shown to promote neural plasticity and brain reorganization in animal models of PD” (Frazzitta et al., 2008, p. 257). The principles of LSVT LOUD were applied to limb movement in PwPD and called LSVT®BIG. Initial results indicated training large, axial body movements (large amplitude) resulted in improvements in balance, posture, and distal functioning (Farley and Koshland, 2005). An LSVT BIG study, often referred to as the Berlin study in the literature, compared this intervention to a group Nordic walking program and a non-supervised home exercise program (Ebersbach et al., 2010). The results indicated LSVT BIG participants made significant improvement in their UPDRS scores as well as timed-up-and-go (TUG) and timed-10 m test scores, supporting LSVT BIG as an effective technique to improve motor performance in patients with PD.

LSVT BIG has been highly marketed making it a well-known treatment available to PwPD but it has very limited research to support its efficacy and no research supporting it as a significantly more effective treatment compared to other PT interventions. A Cochrane Review of 43 studies revealed extensive research supporting a variety of PT exercise interventions to be effective in PwPD but concluded that there is no robust evidence to support any one physical therapy approach over another in the treatment of PD (Tomlinson et. al., 2012). Ebersbach et al. (2010) was the only BIG study included in that review.

Two separate review articles on evidence-based treatment interventions for voice and speech in PwPD cite well over 20 studies supporting the efficacy of LSVT

LOUD (Fox, Ebersbach, Ramig, and Sapir, 2012; Mahler, Ramig, and Fox, 2015) in contrast, only two studies were cited in support of LSVT BIG (Ebersbach et al., 2010; Farley and Koshland, 2005). A systematic review of LSVT BIG on the PubMed database using the search parameters “LSVT BIG” and “Parkinson’s disease” by this author performed 6/30/2018 and updated 7/12/19, identified only 13 articles after duplicates, nonapplicable articles, posters, and reviews and commentaries were removed. Six studies were excluded for the following reasons: Two were LSVT BIG specific reviews (Fox et al. 2012; McDonnell et al., 2017); three were case studies (Chatto, York, Slade, and Hansson 2018; Fishel, Hitchkiss, and Brown, 2018; Janssens, Malfroid, Nyffeler, Bohlhalter, and Vanbellinghen, 2014); and one was a single subject design n=2 completed with individuals with stroke (Metcalf, Egan, Sauve-Schenk, 2019). The remaining seven articles included three prospective studies (Farley & Koshland, 2005; Millage, Visey, Finkelstein, and Anheluk, 2017; Ueno et al., 2017) and four randomized controlled studies (Dashtipour et al., 2015; Ebersbach et al., 2010; Ebersbach, 2014; Ebersbach et al., 2015) of which three were by the same author and two used data from the same study.

The Berlin study, is cited in support of LSVT BIG (Ebersbach et al., 2010) as improving UPDRS motor, Timed Up and Go (TUG), and 10- meter walk test scores compared to Nordic walking and home exercise programs. However, this study had several significant limitations that impact the interpretation of the data. It had no control group, either to neurotypical individuals completing the same intervention or PwPD not completing any intervention. It looked at only motor outcome measures and no quality of life or nonmotor symptoms. It compared three different treatment

delivery systems - intensive one to one interaction (BIG), a group intervention (WALK), and unsupervised exercise (HOME). It delivered those treatment interventions at different intensities (BIG 4x a week x 4 weeks; WALK was 2x a week x 8 weeks; HOME received a one hour instruction). They also did not look at immediate outcomes but long term/residual effect at week 16 (BIG ends at 4 weeks while the WALK group ended at 8 weeks).

The 2014 Ebersbach article re-utilized data from the original 2010 LSVT BIG Berlin study and discussed the impact of BIG vs WALK vs HOME on cued and non-cued upper extremity reaction. The results indicated that physical exercise in the BIG and WALK groups was associated with improvement in cognitive aspects of movement preparation expressed as improvements in cued reaction time in both groups but not in the HOME group. There were no differences in non-cued reaction time. A subsequent short protocol of BIG (5x a week 2 weeks) by the same researcher found no difference in motor scores between the standard 4-week vs 2-week short protocol but instead only revealed a difference in patient perceived benefit from the treatment (Ebersbach et al. 2015).

Dashtipour et al. (2015) endeavored to address some of the limitations in the Ebersbach et al. (2010) study. Their study which examined both motor and nonmotor symptoms, compared LSVT BIG to a standardized exercise program delivered at an equal intensity (1 hour), duration (4x a week x 4 weeks), and system of delivery (1:1 therapist). The study also assessed participants at baseline and immediately following the intervention as well as at a 3 month and 6 month follow-up time point. They concluded there was no difference between standard versus LSVT BIG intervention

and that both were equally effective in improving motor symptoms as measured by UPDRS, and that both interventions were associated with long term benefits at the six month assessment. Their limitations included a small sample size (11 participants (exercise n=5; LSVT BIG n=6) and all participants were in the early stage of the disease. There continues to be a need for larger studies, with participants across the spectrum of disease progression, and more comparative therapeutic treatment arms.

There is significant data in animal models of PD about the positive impact of exercise on disease progression, however future studies are needed to assess the impact of physical exercise on human PD progression (Hirsch et al., 2016; Voss, Vivar et al., 2013). The authors of the chapter, Voice and Speech Disorders in Parkinson's Disease and Their Treatment (Fox et al., 2008) recommend future research in LSVT LOUD needs to include documentation of long-term maintenance effects, large multi-site effectiveness studies (clinical trials), alternative modes of administration (e.g. different dosage intensity), and further study of treated PwPD to better define predictors of success or failure with the treatment. These recommendations can be applied to the study of LSVT®BIG as well. Further studies are needed to understand the effectiveness of specific exercise interventions, ideal exercise dosing, the impact on functional mobility and quality of life, and to support consistent use of specific outcome measures and their validity. The current research will contribute and further expand the growing body of research in the area of PD behavioral interventions. This study includes the use of participants as their own "control", include an additional immediate completion time point to collect data as well as an 8 week assessment, include more nonmotor symptom assessments, and

integrate neurobiological measures in the form of BDNF serum levels. Additionally, this study positions the next subsequent systematic study to start to examine changes in dosage on outcome. In particular, this research takes steps towards addressing the gap in effectiveness research by providing specific motor, non-motor, and neurobiological measures regarding the efficacy of LSVT BIG, a popular and mainstream intervention, despite limited research.

Neuroplasticity and Exercise Prescription

Prescription for PwPD

Physical activity is any bodily movement produced by skeletal muscle that increases energy consumption and includes non-exercise activity and exercise thermogenesis (Caspersen, Powell, & Christenson 1985; Voss, Vivar et al., 2013). Caspersen et al. (1985) defines exercise as a subset of physical activity that is planned, structured and repetitive and performed for the maintenance and improvement of physical fitness. The neuroscience of exercise has been robustly explored at a behavioral and cellular level in animal models but, due to obvious limitations of obtaining human brain tissue samples, has favored more behavioral and assessment of system-level changes for human models. Despite these limitations the findings in the human research has been consistent with the rodent literature suggesting there are broad and long-lasting benefits of exercise on brain function and structure (Voss, Vivar et al., 2013). The search for human neurobiological measures has led researchers to study the role of neurotrophic factors (NTFs) such as brain-derived neurotrophic factor (BDNF), glial-derived neurotrophic factor (GDNF), insulin-like

growth factor (IGF-1), and vascular endothelial growth factor (VEGF). Due to a robust response to exercise-induced changes these NTFs may represent potential biomarkers. Since BDNF and GDNF have been recognized as key proteins modulating brain plasticity and are widely distributed throughout the brain (Ahlskog, 2011) they may serve as a viable measure of brain health and neuroplasticity.

BDNF is a neurotrophin and a member of a family of proteins that is responsible for the survival, development, and function of neurons and synaptic plasticity and may be a viable biomarker for age and clinically relevant brain dysfunction (Voss, Erickson et al., 2013). Although the underlying mechanisms of the effect of exercise on cellular neuroplasticity is unclear, it is the neurotrophin that has been proposed to mediate the effect (Voss, Vivar et al., 2013; Voss, Erickson et al., 2013). A study by Voss, Erickson et al., (2013) evaluated the impact of a one-year moderate aerobic exercise program on circulating BDNF, IGF-1, and VEGF levels in healthy adults who had low baseline activity. Functional MRI studies to measure changes in functional coupling (synaptic connectivity) were also conducted. They concluded their results revealed the first evidence for an association between circulating BDNF, IGF-1, and VEGF and exercise related functional plasticity in humans. Exercise associated upregulation of NTFs may help offset age related reductions in cellular neuroplasticity (such as synaptogenesis, angiogenesis, and synaptic plasticity). This could lead to a more resilient brain in the face of age-related structural and functional degeneration. Further research is warranted to further understand how exercise type, duration, intensity can influence both functional and cellular neuroplasticity.

Understanding the mechanisms of neuroplasticity allows PT, OT, and SLP to choose effective therapeutic interventions when treating individuals with neurologic impairments. Kleim and Jones (2008) outlined ten principles of experience-dependent neural plasticity and implications for rehabilitation following brain damage including loss of function related to neurodegenerative disease. The first two are “use it or lose it” and “use it and improve it”. These are fairly familiar concepts in that neural circuits not activated over a period of time will start to degrade through the loss of neural connections. Conversely, neural circuits that are stimulated will strengthen. These are the underlying foundational principles employed in deprivation vs enrichment research. Enriched environments have been linked to dendritic arborization, synapse formation, neurogenesis, increased NTFs such as BDNF as well as an array of molecules that promote N-Methyl-D-Aspartate (NMDA) function and facilitate long term potentiation (LTP) (Griesbach and Hovda, 2015). In the case of PD, decreased initiation (a component of the disease process itself) of an activity such as walking or speech results in performing the task less frequently which contributes to a further decline in function and loss of connectivity serving as a negative feedback loop. Maintaining existing function and utilizing these existing circuits to expand further functionality is a core tenant guiding rehabilitation interventions based on principles of functional neuroplasticity facilitating return of function and/or prevention of loss in function.

There is nothing more powerful in the toolbox of therapists trying to enhance neuroplasticity than exercise! Exercise increases mitochondrial energy production, stimulates antioxidant defenses, reduces inflammation contributing to improved

immune function (Petersen and Pedersen ,2005), facilitates angiogenesis (Voss, Vivar et al., 2013), produces synaptogenesis (Zigmond and Smeyne, 2014; Voss, Erickson et al. 2013), and increases endogenous neurotrophic factors especially BDNF and GDNF (Kleim and Jones, 2008; Hirsch, Iyer, and Sanjak 2016; Petzinger et al. 2013; Monteiro-Junior et al. 2015; Cotman, Berchtold, & Christie 2007). All examples of neuroprotection. Exercise can be seen as neurorestorative as it down regulates striatal dopamine transporter (DAT) and vesicular monoamine transporter (VMAT2) thus increasing dopamine in the extracellular space (Hirsch et al., 2016) which may help restore neurophysiological properties of synapses within the injured striatum (Petzinger et al., 2013). This is particularly important in the case of PD. Exercise may also facilitate neuroplasticity and general brain health through its neuroprotective mechanisms of increased cerebral blood flow which influences improved vasculature through angiogenesis and altered blood brain barrier (BBB) permeability (Petzinger et al., 2013; Voss, Vivar et al., 2013; Cotman et al., 2007). Further hypotheses are being explored regarding the role of exercise in modifying genes and molecular pathways and reversing dendritic spine loss further enhancing neuroplasticity at both a neuroprotective and neurorestorative level. Integrating our understanding of neuroplasticity can guide the timing, intensity, and frequency of exercise for optimal outcomes.

The principles of functional neuroplasticity that most guide exercise prescription are “specificity” (the nature of the training experience dictates the nature of the plasticity), “repetition matters” (induction of plasticity requires sufficient repetition), “intensity matters” (induction of plasticity requires sufficient training

intensity), and “saliency matters” (the training experience must be sufficiently salient to induce plasticity) (Kleim and Jones, 2008). Therapists must establish exercise programs that are specific, integrate high repetition, high intensity, and have meaning to the individual being treated whether the activity is movement or speech related. Research is ongoing to find the “ideal” exercise prescription. Protocols such as LSVT BIG and LSVT LOUD integrate these neuroplasticity principles effectively in the treatment of individuals with Parkinson’s disease yet continue to try to balance standardized protocol with patient-specific and individually designed (Farley, Ramig, and McFarland, 2008; Ebersbach et al., 2010).

Exercise includes a wide variety of categories (stretching and flexibility, aerobic capacity/endurance, strengthening, balance, and whole body such as martial arts/dance), intensities (high versus low), and delivery modes (individual 1:1, group, and independent). All of these variables that can impact treatment outcomes and make it challenging to compare treatment interventions. While many studies support exercise as a beneficial nonpharmacological intervention for people with PD (Uhrbrand et al., 2015; King et al., 2015; Ridgel, Vitek, & Alberts, 2009; Schenkman et al., 2012), a Cochrane Review from 2012 found formal comparisons and meta-analyses between exercise interventions specifically with PwPD was not possible due to the extensive variability in implementation and clinical assessment, as well as inconsistent descriptions of treatment regimens (Tomlinson et al., 2012).

Recommendations regarding exercise prescription including type, frequency, duration, and outcome measures remain limited as a result of the diversity and inconsistency within the literature.

Conclusion

Parkinson's disease is a progressive, neurodegenerative disease that has significant detrimental impact on functional mobility and HRQoL as well as far reaching emotional and financial consequences on individuals and caregivers living with PD and society at large. Behavioral interventions, such as those delivered by PT, OT, SLP can provide symptomatic relief and improve mobility and quality of life. Despite a large body of evidence supporting exercise interventions as beneficial, this study represents the research needed to specifically assess the efficacy of LSVT BIG in PwPD and further elucidate the role these interventions may have on the functional outcome and cellular substrates of neuroplasticity.

CHAPTER 3

METHODOLOGY

Study Design

This study is a clinical effectiveness trial using a within-subject multiple baseline design (MBD)(Montero and Le, 2007). Participants who met the inclusion criteria received baseline assessments (BASE) including the MDS-Unified Parkinson Disease Rating Scale, gait analysis, balance testing, quality of life surveys, depression survey, fatigue survey, and physical activity assessment, as well as basic vitals and blood draw to measure potential biomarkers of plasticity, such as brain-derived neurotrophic factors (BDNF). Participants completed the LSVT BIG protocol, four one-hour sessions per week for four weeks immediately following the BASE assessment. Participants were instructed to continue performing their BIG exercises once daily for the remainder of the study. Post-treatment assessments were performed the week following end of treatment (EOT) and then a final follow-up assessment was completed one month after the end of treatment (EOT+4). (Figure 4: Treatment Protocol Timeline and Appendix A)

Figure 4: Treatment Protocol Timeline

Note: BASE = baseline; EOT = end of treatment; EOT+4 = 4 weeks after end of treatment

Recruitment/Participants

Nine individuals with PD from the local community and ongoing programs at the University of Rhode Island were recruited to participate in this study. A sample size of eight was needed for determining statistically significant differences in the dependent variables based on an a priori G-power analysis using a large effect of .8 and power of .80 (Faul, Erdfelder, Lang, and Buchner, 2007). Inclusion criteria include diagnosis of idiopathic PD and no contraindications to exercise including uncontrolled cardiovascular disease as well as sufficient cognition to complete the exercises independently as part of homework. Comorbidities were documented as well as disease severity. Exclusion criteria included history of stroke or other neurologic diagnosis, or surgical procedure for treatment of PD including deep brain stimulator (DBS), pallidotomy, or thalamotomy. Exclusion factors for the study were minimal so as to include a broad cross section of people with PD (PwPD) in the study and more closely resemble the variability seen in the clinical setting. Signed consent was obtained from all participants for treatment and blood draws (Appendix B and Appendix C).

The average age of participants was 69.9 years (± 4.9) with fairly even distribution between gender 5/4 (male/female). The mean disease duration was 7.22 years (± 6) however there was a wide range from 1 to 17 years. A high number of participants ($n=7$; 78%) reported experiencing On/Off periods related to their medication. Participants were identified as tremor dominant (TD; 33%), postural instability gait dominant (PIGD; 56%), or indeterminate (11%) based on their UPDRS-III (Stebbins et al., 2013). There were no significant baseline differences

noted between participants when checked for normal distribution except for H&Y staging ($p < .05$) with 78% ($n=7$) stage 2 while 22% ($n=2$) were stage 3. (Table 1: Demographic Characteristics)

Table 1: Demographic Characteristics

Participant	Age	Sex	Education	H&Y	Disease Duration	SubType	Medication LEDD (in mg.)	On/Off
1	65.16	M	1	2.0	5	TD	300	Yes
2	64.75	M	2	2.0	3	PIGD	600	Yes
3	73.16	F	3	3.0	16	PIGD	1050	No
4	65.16	F	3	2.0	1	TD	120	No
5	74.25	F	3	2.0	2	TD	450	Yes
6	76.25	M	4	2.0	7	Indeterminate	800	Yes
7	65.83	M	4	2.0	18	PIGD	1100	Yes
8	75.75	F	4	3.0	4	PIGD	263	Yes
9	68.83	M	1	2.0	9	PIGD	700	Yes
Average	69.90	5M/4F		2.22	7.22		598.11	

Note: Education 1 = High School; 2 = Some College/Technical School; 3 = College; 4 = Graduate Degree; H&Y = Hoehn and Yahr; LEDD = Levodopa equivalent daily; PI GD = Postural Instability Gait Dominant; dose; TD = Tremor Dominant

LSVT BIG Intervention

The treatment protocol for LSVT BIG includes a total of 16, one-hour individual treatment sessions delivered over one month (4 sessions per week x 4 weeks). Each session includes daily exercises, daily functional tasks, hierarchical tasks, and carry over/homework (see Appendix D or Fox et al., 2012 for full protocol description). The intervention was delivered by the lead PI and two students in the physical therapy clinical doctorate program; all were certified in LSVT BIG. The students were under the direct supervision of the lead PI and completed sufficient treatment practice with non-research patients to the satisfaction of the principal investigator, prior to assisting in research level treatment.

Initial Assessment Measures

Comprehensive demographic and pertinent patient history/information was collected during the initial interview including sex, age, race, education level, living situation, current medications to allow for determination of levodopa equivalent daily dosage (LEDD), disease severity (Hoehn & Yahr stage), PD subtype designation based on MDS-UPDRS, and length of disease based on medical diagnosis. Additional measures at baseline included the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) an interview-based instrument to measure medical comorbidity in relationship to disability and has been validated for use with PwPD (Visser et al., 2004); Next, the Montreal Cognitive Assessment (MoCA), a 30-point test, served as a descriptive measure for cognitive status (Nasreddine et al., 2005). This test has been used in a variety of patient populations and assesses eight cognitive domains: 1) visuospatial/executive functioning; 2) memory and delayed recall; 3) attention; 4) concentration; 5) working memory; 6) language and naming; 7) abstraction, and 8) orientation. The MOCA provides a recommended cutoff score (<26) to detect mild cognitive impairment (MCI) for people with PD. Specificity of the MoCA to exclude elderly normal controls is good (87%) and sensitivity in detecting mild cognitive impairment is excellent (90%) (Brown et al., 2016; Zadikoff et al., 2008); and, finally, the Physical Activity and Disability Survey (PADS-R), a measure of physical activity in people with neurologic conditions (Kayes et al., 2009). These measures are all interview based questionnaires or tests that allowed for a clearer clinical picture of each participant in accounting for medical comorbidities, cognitive status, and physical activity levels, respectively. (Table 2: Clinical Characteristics)

Table 2: Clinical Characteristics

Participant	SubType	UPDRS III Baseline	CIRS-G	MOCA	PADS-R
1	TD	15	0.80	28	77.40
2	PIGD	28	0.60	27	3.80
3	PIGD	15	1.33	26	253.70
4	TD	25	2.00	27	123.70
5	TD	26	1.86	23	137.00
6	Indeterminate	28	1.67	20	34.40
7	PIGD	50	1.86	20	20.60
8	PIGD	29	3.80	30	3.80
9	PIGD	26	3.50	28	12.60
Average		26.89	1.94	25.44	74.11

Note: CIRS-G = Cumulative Illness Rating Scale; MOCA = Montreal Cognitive Assessment; PADS-R = Physical Activity Disability Scale; PI GD = Postural Instability Gait Dominant; TD = Tremor dominant

Objective measures of mobility in the off-medication state are more indicative of patient perception of mobility disability and balance confidence compared with on-medication state measures (Curtze, Carlson-Kuhta, Mancini, and Horak, 2016) however, review of the literature reveals the on-medication state is the state in which most assessments are conducted and was the standard for this study.

Clinical Outcome Measures

Attempts to compare research on exercise and PD have been difficult due to the inconsistency of outcome measures across studies (Tomlinson et al., 2012) and lack of sensitivity of measures (King et al., 2013). The APTA Parkinson's Disease EDGE (Evidence Database to Guide Effectiveness) task force reviewed 60 outcome measures, evaluated them for psychometrics and clinical utility, and formulated

recommendations for which outcome measures that were highly recommended for use in PwPD in the clinic as well as use for research (Kegelmeyer et al., 2014)., The task force also took the three International Classification of Function, Disability, and Health (ICF) identified levels (participation, activity, and body structure and function) in their final recommendations.

The World Health Organization outlined the ICF in 2000 to integrate a more comprehensive perspective of disability, complement research outcome measures, and provide consistent, comparable, and universal guidance between researchers as well as on an international level (Organization, 2000). The ICF interactive model identifies three levels of human functioning: functioning at the level of body or body part, the whole person, and the whole person in his or her complete environment. These levels in turn define three functional dimensions: body functions and structures, activities, and participation that can be addressed with specific measures. The outcome measures utilized for this study were based on the ICF structure and APTA - PD EDGE recommendations but for the purposes of this paper, are divided into mobility and psychometric measures. (see Appendix D and E)

Functional Mobility Measures

The primary dependent variables, related to mobility, for the study were the MDS-UPDRS Part III: Motor Examination, Functional Gait Assessment (FGA), MiniBEST, gait speed, step length and TUG.

The Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS; a revision of the UPDRS) is used as the primary international rating

scale for PD clinical care and research (Goetz et al., 2008). The MDS-UPDRS has four parts: I Non-motor Experiences of Daily Living (13 items); II Motor Experiences of Daily Living (13 items); III Motor Examination (18 items); IV Motor Complications (6 items). There is a 5-point range for each item - normal (0), slight (1), mild (2), moderate (3), and severe (4) with a higher score indicating higher disability. It is typically administered by a physician or allied health care professional that has completed a training course. Confirmatory factor analysis of the new scale has been determined to be clinimetrically sound ($>.90$) and clinically pertinent when reporting results from each of the four sections. It has been recommended that each of the four parts (I-IV) be reported separately and not collapsed into a single “total MDS-UPDRS” summary score (Goetz et al., 2008).

The MDS-UPDRS Part III is comprised of 18 items but due to several subsections has a total of 33 scores. Each item is scored with a 0-4 rating for a total range from 0 to 136 with a higher score indicating higher level of severity and disability. It also includes a question regarding medication, ON/OFF state at time of exam, and a final Hoehn & Yahr stage rating (Goetz et al., 2008).

Functional mobility tests were performed to capture baseline and changes in balance and gait measures and reflect tests that are accessible and feasible in a clinic setting. The FGA is a 10-item test focused on a variety of gait tasks with each item scored on a 4 point ordinal scale, 0-3 with a total score of 30. The higher the score the higher the functional performance (Weber et al., 2016). The Mini-Balance Evaluation System Test (Mini BESTest) is a clinical balance scale to assess falls risk and postural control in people with PD with high test – retest reliability ($ICC = .92$) and inter-rater

reliability (ICC = .91) (Duncan & Leddy 2013; Leddy, Crowner, and Earhart, 2011). It is a 14 point unidimensional test modified from the original 36 item BESTest and focuses specifically on dynamic balance (Bravini et al., 2016). Each of the 14 items are scored on a 3-point ordinal scale (0-2 rating) with a maximum score of 28 and a higher score indicating better performance (Franchignoni and Velozo, 2010; Schlenstedt et al., 2015). It includes the TUG, an assessment of mobility, balance, walking ability, and falls risk in older adults which has good inter-rater reliability (ICC = .99) and intra-rater reliability (ICC = .98) and is useful for following clinical change over time as well as predict safety with gait (Morris et al., 2001; Bennie et al., 2003; Podsiadlo and Richardson, 1991). Finally, gait speed and step length were determined using the 10-Meter walk, which, along with turning speed, have been found to be highly negatively correlated to severity of disease and patient perception of mobility disability (Curtze et al., 2016). (Refer to Appendix E)

Psychometric Measures

The ability of an individual to participate in day to day activities may be restricted by functional mobility, however, they may also be limited by a variety of psychological states such as an individual's confidence in their mobility, fatigue level, and mood which can ultimately have a considerable impact on their quality of life. These states might influence an individual's ability to benefit from or might change in response to the treatment intervention therefore psychometrics were obtained at each of the three assessment timepoints using a variety of self-reported measures.

Confidence with mobility was measured using the Activities Specific Balance Confidence Scale (ABC), a subjective self-reported measure of confidence in performing various ambulatory activities without falling or experiencing a sense of unsteadiness (Powell and Meyers, 1995). It is a 16-item questionnaire reported as a percentage with 100% presenting the highest confidence. It has a high level of internal consistency (Cronbach's $\alpha = .95$) (Steffen and Seney, 2008). The MDS-UPDRS Part II: Motor Experiences of Daily Living is a self-administered survey of 13 items with a 0-4 rating for a range from 0 to 52 with a higher score indicating a higher level of severity and disability.

The Parkinson's Disease Fatigue Scale (PFS-16) is a self-report scale that measures fatigue, one of the non-motor symptoms associated with Parkinson's, and measures the presence of fatigue and its impact on daily function (Brown, Dittner, Findley, and Wessely, 2005). PwPD answer 16 questions on a 5 point Likert scale ranging from 1 - "strongly disagree" to 5 - "strongly agree" with an average score of greater than 3.3 identifying those individuals perceiving fatigue to be a problem. This scale has been determined to have excellent internal consistency (Cronbach's $\alpha = .98$) and reliability (ICC = .83) (Brown et al., 2005).

Depression, also a common complaint among PwPD, was measured using the Geriatric Depression Scale (GDS – 30), a thirty item self-report, yes/no screening instrument for depression in the elderly (Yesavage et al., 1982). The GDS is short and easily understood, making it appropriate for use in both clinical research and routine clinical care as a screening instrument for depression in elderly PD patients (Schrag et al., 2007). It focuses on the psychological aspects and social consequences of

depression, avoiding symptom overlap with medical disorders, such as PD, or aging in general. Each question on the GDS-30 can only be scored “0” or “1,” for a total score of 30. The higher score indicating higher severity of depression (normal 0-9; mild depressive 10-19; severe depressive 20-30). It reports high internal consistency (Cronbach’s $\alpha = .92$) (Ertan et al., 2005).

Finally, to capture the participant’s perception of quality of life, the Parkinson’s Disease Questionnaire-39 (PDQ-39), a self-report quality of life questionnaire used to assess HRQoL in individuals with PD. (Peto et al., 1995; Hagell, Whalley, McKenna, and Lindall, 2003; Hagell and Nygen, 2007). This questionnaire is composed of 39 items which are rated on a 5 point Likert scale as 0 – “Never” to 4 – “Always”. The set of 39 questions creates eight domains or scales including mobility (ten items), activities of daily living (eight items), emotional well-being (six items), stigma (four items), social support (three items), cognition (four items), communication (three items), and bodily discomfort (three items) with each scale totaled and transformed to a range of 0 (best; no problem) to 100 (worst; maximal problem). These eight domains can be reported as a health profile which offers more detailed information or as a summary (PDQ-39*SI*) in which the eight domain scores are transformed into a summary index score which can be used to reflect an overall impact of PD (Jenkinson and Peto, 1997; Peto, Jenkinson, and Fitzpatrick 1998). PDQ39 Summary index scores were used for analysis in this study.

Neurobiological Measures

Blood sampling for serum brain-derived neurotrophic factor (sBDNF) was performed at each assessment time point during the study (BASE, EOT, EOT+4). Subjects reported to the phlebotomy lab at URI, blood was collected (non-fasting) from the antecubital vein in sterile serum separator tubes. Samples were kept at room temperature for 20 minutes to allow for clotting and then centrifuged for 10 minutes at 4 degrees Celsius. Serum samples were separated into aliquots and then stored at -80 degrees Celsius until analysis. Once all samples were collected analysis was completed according to manufacturer's guideline for ELISA (ABCAM, 2019) at the RI Idea Network of Biomedical Research Excellence (INBRE) lab located on the URI campus. Assays were performed in triplicate, blinded to the clinical status of the participant. Concentrations are expressed as pg/mL and lower detection limits for all analyzed molecules were 10 pg/mL.

Participation and Adherence Measures

Log of exercise program/treatment protocol as well as an activity log was maintained by the participant throughout the study. A Post Intervention Participant Survey was also administered to capture participant's perception of the treatment intervention, its potential self-perceived benefits, and feedback to the researchers regarding the study as a whole. (See Appendix F)

Statistical Analysis

Statistical analyses were completed using SPSS V26. First, univariate distributions were examined to provide insight into participant characteristics and ensure that variables were appropriately distributed for the analysis (i.e. skewness, kurtosis < |1.0|). Multilevel modeling was used to examine the effects of treatment while controlling for expected covariates. The structure to the analysis included two levels so that observations were nested in participants. There was a total of three timepoints (i.e. BASE, EOT, EOT+4) on each of nine participants for a total of 27 observations. Outcome variables included the mobility measures (UPDRS III score, FGA, MiniBEST, gait speed, step length, and TUG), psychometric measures (ABC, PDQ-39, GDS-30, and PFS-16), and a neurobiological measure (sBDNF). Covariates included the following: Age; Gender; Education level; Years with PD; H&Y Rating; PD subtype; UPDRS Initial Score; LEDD. The missing observations were addressed by multiple imputation. Ten imputations for sBDNF were sampled from a multivariate normal distribution and adjusted by Bartlett's method. The results were averaged for the final multilevel model estimates (Little & Rubin, 2002).

The focus of the analysis was on the treatment effect parameters. It was hypothesized that there would be a meaningful improvement in functional mobility and HRQoL measures in PwPD from BASE to EOT. It was further hypothesized that there would be a meaningful improvement from BASE to EOT+4 even though it may be reduced compared to immediately following treatment. The model, as described above, predicted means at BASE, EOT, and EOT+4 were estimated to assess the

efficacy of treatment. The percentage change in symptoms was reported as an additional metric of treatment effects.

Challenges in conducting research with PwPD lie in the high variability of disease manifestation and progression and inconsistency in how data are reported across studies. This can sometimes lead to clinically relevant effects being missed during aggregation of data or for statistically significant results to be reported that have no substantial clinical implications. It is for this reason that minimal clinically important difference (MCID), which determines whether a medical intervention improves perceived outcomes in patients, and minimal detectable change (MDC), an estimate of the smallest amount of change that can be detected by a measure that corresponds to a noticeable change in ability (Ramprasad 2010) for outcome measures were evaluated at the individual and group level in addition to statistical analysis.

Statistical significance below an alpha level of 0.05 as well as MCID or MCD in measurements were taken as evidence of treatment efficacy. (Table 3: Outcome Measures Summary with MCID and MDC).

Table 3 : Outcome Measures Summary with MCID and MDC

Measure	Range	Direction / Interpretation	MCID or MDC	Reference
MDS-UPDRS III Motor	0-136	Lower number = less impairment High number = more impairment	-3.25 improvement +4.63 worsening	Horvath et al. 2015
FGA	0-30	Higher number = less impairment Lower number = more impairment	+4 improvement -4 worsening	Peterson, Steffan, Paly, Dorvak, and Nelson 2016
MiniBEST	0-28	Higher number = less impairment/falls risk Lower number = more impairment/falls risk	+5.52 improvement -5.52 worsening	Leddy et al., 2011
TUG	NA	Lower = less impairment/reduced falls risk >14 sec increased falls risk (Podsiadlo 1991)	-4.85 improvement +4.85 worsening	Dal Bello-Haas et al., 2011
Step length	NA	Longer = less impairment		
Gait speed m/s	NA	Faster = less impairment < 1.1 m/s = predictive of falls (Lindholm 2013)	+0.06 m/s improvement -0.06 m/s worsening	Hass et al., 2014
ABC	0-100%	Higher = more confidence Lower = less confidence	+11.12 more confidence -11.12 less confidence	Dal Bello-Haas et al., 2011
GDS	0-30	0-9 Normal 10-19 Mild depressives 20-30 Severe depressives	None available	Schrag et al., 2007
PFS	0-5	Higher = more fatigue/impairment >2.95 experiencing fatigue vs no fatigue >3.30 fatigue is a problem	None available	Brown et al., 2005
PDQ39-SI		Higher = poorer quality of life	-1.6 = improvement +1.6 = worsening	Peto et al. 2001

Note: ABC= activities balance confidence; FGA= functional gait assessment; GDS= geriatric depression scale; MCID= minimal clinical improvement detected;
MDC= minimal detectable change; MDS-UPDRS= Unified Parkinson's Disease Rating Scale; m/s = meters per second; PDQ39-SI= Parkinson's disease quality of life-Summary Index; PFS= Parkinson's fatigue scale; TUG= Times up and go

CHAPTER 4

RESULTS

This study examined the effects of LSVT BIG on functional and health related quality of life (HRQoL) measures in people with Parkinson's disease (PwPD) and investigated the potential relationship with changes in serum brain derived neurotrophic factor (sBDNF).

Results of mobility and psychometric dependent variables are presented individually and by group using multilevel modeling. Statistical significance was set at $\alpha = .05$ throughout the paper unless otherwise noted. Minimal clinically important difference (MCID) and minimal detectable change (MDC) were identified, for those measures where they existed, at the individual participant and group level. Percent changes between each timepoint are also listed.

Demographic and Initial Assessment Measures

A total of twelve participants were screened for the study. Two people did not meet inclusion criteria due to surgery for deep brain stimulation and one person could not obtain transportation to the clinic for assessment or treatment. A total of nine participants (n=9) completed BASE measurements, the full 4-week LSVT BIG treatment protocol, EOT assessments, and follow up EOT+4 assessments.

Intervention

The LSVT BIG treatment protocol was completed by all nine participants. There was a 0% attrition rate although one participant completed a baseline assessment, started the LSVT BIG protocol for one week, and then reported a back injury and subsequent pneumonia unrelated to the research activity. Their participation was placed on hold for 2 months and then a full restart/reassessment completed with no data from first assessment included in the data analysis. The average number of days from BASE to starting treatment was six although one individual had an unexpected delay to start of treatment (19 days).

Compliance

All participants completed the full LSVT BIG treatment protocol of four visits a week for four weeks for a total of 16 individual one-hour treatment sessions delivered in one month. Adherence to homework during the treatment period was difficult to fully assess as participants verbally reported completing their homework and additional sets of exercises on the day they received their treatment and two times a day on the days they did not come into the clinic. However, their written homework logs were inconsistent with this verbal report. Participants were instructed to continue their LSVT BIG exercises daily during the period between completion of treatment and follow up assessments that took place four weeks later. All but one participant returned complete homework logs at assessment EOT+4. Participants adhered to their homework 72.77% of the time averaging 20.28 sessions out of a possible 28 sessions during this time period.

Functional Mobility Measures

Statistically significant changes were identified between BASE and EOT+4 in four of the six primary outcome measures including the MDS-UPDRS Part III: Motor Examination ($p=.046$), FGA ($p=.010$), MiniBEST ($p=.045$), and step length ($p=.051$). No significant changes in gait speed ($p=.369$) or TUG ($p=.831$) at EOT+4 were identified. None of the mobility measures were significant at the EOT time point [UPDRS III: Motor ($p=.684$), FGA ($p=.10$), MiniBEST ($p=.40$), TUG ($p=.165$), gait speed ($p=.096$), and step length ($p=.786$)].

Minimal clinically important difference and MDC were identified in a variety of participants across the UPDRS-III Motor, gait speed, and FGA scores at both the EOT and EOT+4 timepoints but was only identified in the UPDRS-III Motor score (-4.406) at the group level at EOT+4. (Table 4: UPDRS-III Results; Table 5: FGA Results; Table 6: MiniBEST Results; Table 7: TUG Results; Table 8: Step Length Results; Table 9: Gait Speed Results)

Table 4: Unified Parkinson's Disease Rating Scale (UPDRS) -III Results

	ID	Subtype	UPDRS - III				
					Change		Change
			BASE	EOT	at EOT	EOT+4	Overall
I N D I V I D U A L							
	1	TD	15	11	-4	9	-6
	2	TD	28	29	1	22	-6
	3	PIGD	15	15	0	7	-8
	4	PIGD	25	17	-8	19	-6
	5	TD	26	16	-10	18	-8
	6	Indeter	28	38	10	35	7
	7	PIGD	50	36	-14	52	2
	8	PIGD	29	16	-13	15	-14
	9	PIGD	26	40	14	17	-9
G R O U P	Average		26.964	26.065	-0.899	22.558	-4.406
	P value				0.684		0.046
	CI - LL		22.937	21.235		18.148	
	CI - UL		30.910	30.895		26.968	
	% Change				-3.33%		-16.34%

MCID Improvement (- 3.25)

MCID Decline (+4.63)

P < .05

Note: Base=baseline; CI-LL=confidence interval lower limit; CIUL=confidence interval upper limit; EOT=end of treatment; EOT+4=4 weeks after end of treatment; Indeter=indeterminant; MDC = minimal detectable change; PI GD=posture instability gait dominant; TD=tremor dominant

Table 5: Functional Gait Assessment (FGA) Results

	ID	Subtype	FGA				
					Change		Change
			BASE	EOT	at EOT	EOT+4	Overall
I N D I V I D U A L							
	1	TD	30	30	0	30	0
	2	TD	28	30	2	27	-1
	3	PIGD	28	27	-1	29	1
	4	PIGD	22	19	-3	18	-4
	5	TD	13	22	9	25	12
	6	Indeter	22	23	1	23	1
	7	PIGD	3	6	3	6	3
	8	PIGD	11	18	7	18	7
	9	PIGD	22	25	3	29	7
G R O U P	Average		22.599	24.201	1.602	25.104	2.505
	P value				0.100		0.010
	CI - LL		20.87	22.126		23.21	
	CI - UL		24.329	26.275		26.998	
	% Change				7.09%		11.08%

MDC Improvement (+ 4)
 MDC Decline (- 4)
 P < .05

Note: Base=baseline; CI-LL=confidence interval lower limit; CIUL=confidence interval upper limit; EOT=end of treatment; EOT+4=4 weeks after end of treatment; Indeter=indeterminant; MDC = minimal detectable change; PI GD=posture instability gait dominant; TD=tremor dominant

Table 6: Mini Balance Evaluation System Test (MiniBEST) Results

	ID	Subtype	MiniBEST				Change Overall
					Change		
			BASE	EOT	at EOT	EOT+4	
I N D I V I D U A L							
	1	TD	26	27	1	27	1
	2	TD	24	24	0	26	2
	3	PIGD	26	26	0	26	0
	4	PIGD	19	18	-1	19	0
	5	TD	15	23	8	22	7
	6	Indeter	22	22	0	23	1
	7	PIGD	12	8	-4	8	-4
	8	PIGD	13	18	5	18	5
	9	PIGD	22	23	1	25	3
G R O U P	Average		21.916	22.504	0.588	23.308	1.392
	P value				0.400		0.045
	CI - LL		20.651	20.987		21.923	
	CI - UL		23.18	24.021		24.693	
	% Change				2.68%		6.35%

MDC Improvement (+ 5.52)

MDC Decline (- 5.52)

P < .05

Note: Base=baseline; CI-LL=confidence interval lower limit; CIUL=confidence interval upper limit; EOT=end of treatment; EOT+4=4 weeks after end of treatment; Indeter=indeterminant; MDC = minimal detectable change; PIGD=posture instability gait dominant; TD=tremor dominant

Table 7: Timed Up and Go (TUG) Results

		ID	Subtype	TUG (sec)			
				BASE	EOT	Change at EOT	Change EOT+4
							Overall
INDIVIDUAL		1	TD	7.94	9.14	1.2	8.59
		2	TD	12	11.44	-0.56	11.14
		3	PIGD	9.25	9.4	0.15	8.37
		4	PIGD	9.98	12.6	2.62	10.61
		5	TD	15.55	13.18	-2.37	11.68
		6	Indeter	11.32	14.33	3.01	11.45
		7	PIGD	20.06	18.72	-1.34	23.56
		8	PIGD	17.6	14.49	-3.11	13.3
		9	PIGD	8.79	8.04	-0.75	9.91
GROUP	Average			11.971	12.802	0.831	12.043
	P value					0.165	0.899
	CI - LL			10.9	11.518		10.87
	CI - UL			13.042	14.087		13.21
	% Change					6.94%	0.60%

MDC Improvement (-4.85)

MDC Decline (+4.85)

P < .05

Note: Base=baseline; CI-LL=confidence interval lower limit; CIUL=confidence interval upper limit; EOT=end of treatment; EOT+4=4 weeks after end of treatment; Indeter=indeterminant; MDC = minimal detectable change; PIGD=posture instability gait dominant; TD=tremor dominant

Table 8: Gait Speed Results

		Speed m/s				
	ID	Subtype	Change			
			BASE	EOT	at EOT	Overall
I N D I V I D U A L	1	TD	1.372	1.490	0.118	-0.055
	2	TD	0.911	1.109	0.198	0.141
	3	PIGD	1.524	1.277	-0.247	-0.195
	4	PIGD	0.914	0.997	0.082	0.113
	5	TD	0.768	0.899	0.131	0.223
	6	Indeter	0.951	1.003	0.052	0.046
	7	PIGD	0.418	0.567	0.149	-0.158
	8	PIGD	0.646	0.899	0.253	0.183
	9	PIGD	1.301	1.274	-0.027	0.076
G R O U P	Average		1.118	1.197	0.079	0.041
	P value				0.096	0.369
	CI - LL		1.037	1.116		1.079
	CI - UL		1.198	1.277		1.24
	% Change				7.04%	3.67%

MDC Improvement (+ .06 m/s)
 MDC Decline (- .06 m/s)
 P < .05

Note: Base=baseline; CI-LL=confidence interval lower limit; CIUL=confidence interval upper limit;
 EOT=end of treatment; EOT+4=4 weeks after end of treatment; Indeter=indeterminant; MDC =
 minimal detectable change; PI GD=posture instability gait dominant; TD=tremor dominant

Table 9: Step Length Results

	ID	Subtype	Step (cm)				
			BASE	EOT	Change	EOT+4	Change
					at EOT		Overall
I N D I V I D U A L	1	TD	60.96	76.20	15.24	71.73	10.77
	2	TD	53.14	60.96	7.82	55.37	2.24
	3	PIGD	67.74	67.72	-0.03	67.72	-0.03
	4	PIGD	50.80	46.74	-4.06	53.01	2.21
	5	TD	50.80	53.01	2.21	55.42	4.62
	6	Indeter	71.63	67.74	-3.89	76.20	4.57
	7	PIGD	30.48	30.48	0.00	26.42	-4.06
	8	PIGD	34.82	40.64	5.82	46.89	12.07
	9	PIGD	71.70	72.49	0.79	76.20	4.50
G R O U P	Average		60.27	60.68	0.41	63.19	2.92
	P value				0.786		0.051
	CI - LL		57.54	57.40		60.20	
	CI - UL		63.00	63.96		66.18	
	% Change				0.67%		4.84%

MDC Improvement (N/A)

MDC Decline (N/A)

P < .05

Note: Base=baseline; CI-LL=confidence interval lower limit; CIUL=confidence interval upper limit; EOT=end of treatment; EOT+4=4 weeks after end of treatment; Indeter=indeterminant; MDC = minimal detectable change; N/A = Not available; PI GD=posture instability gait dominant; TD=tremor dominant

Psychometric measures

Participants made statistically significant changes at EOT ($p=.021$) and EOT+4 ($p=.001$) on the Activities-specific Balance Confidence (ABC) measure despite not meeting MDC for the group mean change. No statistically significant change was identified in the PD Quality of Life-Summary Index (PDQ-SI; $p=.573$; $p=.293$), Geriatric Depression Scale (GDS; $p=.063$; $p=.224$), or the Parkinson's Fatigue Scale (PFS; $p=.678$; $p=.885$) at EOT or EOT+4 respectively.

A MDC was found for several individuals for the ABC and PDQ-SI at both EOT and EOT+4. There was an MDC for the group mean change for PDQ-SI at EOT+4. No MDC has been established for the GDS or PFS but two of the five individuals who scored in the mildly depressed range (10-19) on the GDS at BASE improved enough to move into the range identified as normal (0-9) at EOT and maintained that improvement through to EOT+4. A similar pattern was seen with a PFS score with one of the four individuals who identified fatigue as a problem (>3.30) at BASE improved to the normal range at EOT and maintained their improvement at EOT+4. (Table 10: Activities-specific Balance Confidence (ABC) Results; Table 11: PD Quality of Life-Summary Index (PDQ-SI) Results; Table 12: Geriatric Depression Scale (GDS) Results; Table 13: Parkinson's Fatigue Scale (PFS) Results)

Table 10: Activities-specific Balance Confidence Scale (ABC) Results

	ID Subtype		ABC				
					Change		Change
			BASE	EOT	at EOT	EOT+4	Overall
I N D I V I D U A L							
	1	TD	98.75	96.88	-1.88	99.38	0.62
	2	TD	74.69	88.13	13.44	85.00	10.31
	3	PIGD	87.50	96.88	9.38	96.56	9.06
	4	PIGD	68.75	80.00	11.25	85.63	16.88
	5	TD	70.00	64.38	-5.62	74.38	4.38
	6	Indeterminate	83.75	83.13	-0.62	82.50	-1.25
	7	PIGD	54.38	80.63	26.25	69.06	14.69
	8	PIGD	49.38	65.00	15.63	70.00	20.63
G R O U P	9	PIGD	86.88	80.63	-6.25	91.25	4.38
	Average	(Inferential)	81.10	86.60	5.50	89.30	8.20
	P value				0.021		0.001
	CI - LL		77.10	81.70		84.80	
	CI - UL		85.20	91.50		93.70	
	% Change				6.78%%		10.11%

MDC Improvement (+ 11.12)

MDC Decline (- 11.12)

P < .05

Note: Base=baseline; CI-LL=confidence interval lower limit; CIUL=confidence interval upper limit; EOT=end of treatment; EOT+4=4 weeks after end of treatment; Indeter=indeterminant; MDC = minimal detectable change; PIGD=posture instability gait dominant; TD=tremor dominant

Table 11: Parkinson's Disease Quality of Life – Summary Index (PDQ-SI) Results

	ID	Subtype	PDQ-SI				
					Change		Change
			BASE	EOT	at EOT	EOT+4	Overall
I N D I V I D U A L							
	1	TD	9.6	5.8	-3.8	5.1	-4.5
	2	TD	14.7	17.3	2.6	10.9	-3.8
	3	PIGD	5.1	1.3	-3.8	3.2	-1.9
	4	PIGD	15.4	16.0	0.6	12.2	-3.2
	5	TD	24.4	30.8	6.4	12.8	-11.6
	6	Indeterminate	31.4	32.1	0.7	34.0	2.6
	7	PIGD	35.3	26.9	-8.4	41.0	5.7
	8	PIGD	38.5	34.0	-4.5	32.7	-5.8
	9	PIGD	17.9	16.7	-1.2	15.4	-2.5
G R O U P	Average	(Inferential)	20.88	21.79	0.90	19.24	-1.64
	P value				0.573		0.293
	CI - LL		17.96	18.28		16.04	
	CI - UL		23.81	25.29		18.63	
	% Change				4.33%		-7.85%

MDC Improvement (- 1.6)

MDC Decline (+1.6)

P < .05

Note: Base=baseline; CI-LL=confidence interval lower limit; CIUL=confidence interval upper limit; EOT=end of treatment; EOT+4=4 weeks after end of treatment; Indeter=indeterminant; MDC = minimal detectable change; PIGD=posture instability gait dominant; TD=tremor dominant

Table 12: Geriatric Depression Scale (GDS) Results

	ID	Subtype	GDS-30				
					Change		Change
			BASE	EOT	at EOT	EOT+4	Overall
I N D I V I D U A L	1	TD	1	2	1	2	1
	2	TD	7	7	0	4	-3
	3	PIGD	0	0	0	0	0
	4	PIGD	10	10	0	14	4
	5	TD	10	9	-1	6	-4
	6	Indeterminate	11	10	-1	13	2
	7	PIGD	14	2	-12	5	-9
	8	PIGD	11	12	1	11	0
	9	PIGD	7	5	-2	7	0
G R O U P	Average	(Inferential)	6.85	4.87	-1.98	5.62	-1.22
	P value				0.063		0.224
	CI - LL		4.97	2.62		3.57	
	CI - UL		8.72	7.12		7.68	
	% Change				-28.91%		-17.85%

MDC Improvement (N/A)

MDC Decline (N/A)

P < .05

Note: Base=baseline; CI-LL=confidence interval lower limit; CIUL=confidence interval upper limit; EOT=end of treatment; EOT+4=4 weeks after end of treatment; Indeter=indeterminant; MDC = minimal detectable change; N/A = Not available; PIGD=posture instability gait dominant; TD=tremor dominant

Table 13: Parkinson's Fatigue Scale (PFS) Results

	ID	Subtype	PFS				
			BASE	EOT	Change at EOT	EOT+4	Change Overall
INDIVIDUAL							
	1	TD	1.1	1.0	-0.06	2.3	1.19
	2	TD	2.8	3.0	0.13	2.9	0.05
	3	PIGD	1.1	1.0	-0.06	1.1	0.06
	4	PIGD	2.6	2.5	-0.06	1.8	-0.81
	5	TD	3.1	3.4	0.38	2.9	-0.19
	6	Indeterminate	4.3	3.5	-0.81	3.9	-0.38
	7	PIGD	3.4	2.9	-0.50	3.3	-0.13
	8	PIGD	4.1	3.5	-0.56	3.8	-0.25
	9	PIGD	3.3	3.2	-0.13	2.7	-0.63
GROUP	Average	(Inferential)	2.64	2.59	-0.06	2.62	-0.02
	P value				0.678		0.885
	CI - LL		2.39	2.28		2.35	
	CI - UL		2.90	2.89		2.90	
	% Change				-2.19%		-0.72%

MDC Improvement (N/A)

MDC Decline (N/A)

P < .05

Note: Base=baseline; CI-LL=confidence interval lower limit; CIUL=confidence interval upper limit; EOT=end of treatment; EOT+4=4 weeks after end of treatment; Indeter=indeterminant; MDC = minimal detectable change; N/A= Not available; PIGD=posture instability gait dominant; TD=tremor dominant

Neurobiological Measure

Blood samples were obtained from seven participants at BASE. The blood draws on two participants were unsuccessful at BASE and no further attempts were made to obtain samples. Six samples were drawn at EOT and one was not successful. Five samples were obtained at EOT+4. This resulted in a total of 18 samples from a potential of 27. The assays were performed in triplicate with concentrations of sBDNF expressed as pg/mL. Randomly generated values for the missing data using multiple imputation along with Bartlett's method (Little & Rubin, 2002) allowed for these data to be included in the multi-level modeling analysis.

The mean for BDNF levels at BASE was 995.03 pg/mL (95% CI 812.6 pg/mL to 1087.44 pg/mL) and showed a 2% decline at EOT ($p=.802$) and an overall 23.02% decline from BASE to EOT+4 which was statistically significant ($p=.005$). (Table 14: Serum Brain Derived Neurotrophic Factor (sBDNF) Measures)

Table 14: Serum Brain Derived Neurotrophic Factor (sBDNF) Results

ID	Subtype	BDNF				
				Change		Change
		BASE	EOT	at EOT	EOT+4	Overall
1	TD	1044.252	1017.402	-26.85	1012.474	-31.778
2	TD	1009.0935	1013.8105	4.717	986.2765	-22.817
3	PIGD	598.414	333.729	-264.685	386.298	-212.116
4	PIGD	918.144	1017.342	99.198	311.767	-606.377
5	TD	950.936	871.917	-79.019	-	
6	Indeter	-	-	-	-	-
7	PIGD	1000.608	-	-	-	-
8	PIGD	-	-	-	-	-
9	PIGD	1067.397	1030.307	-37.09	1017.463	-49.934
Average		995.026	931.157	-63.869	731.289	-263.737
P value				0.802		0.005
CI - LL		812.609	766.344		580.823	
CI - UL		1087.443	1095.971		881.755	
% Change				-1.99%		-23.02%

■ MDC Improvement (N/A)
 ■ MDC Decline (N/A)
 ■ P < .05

Note: Base=baseline; CI-LL=confidence interval lower limit; CIUL=confidence interval upper limit; EOT=end of treatment; EOT+4=4 weeks after end of treatment; Indeter=indeterminant; N/A= Not available; PIGD=posture instability gait dominant; TD=tremor dominant

Correlation analysis revealed only weak positive relationships between sBDNF and the UPDRS-III ($r = 0.1988$) and weak negative relationship between FGA ($r = -0.207$), MiniBEST ($r = -0.26$), step ($r = -0.28$), and ABC ($r = -0.24$). (Figure 5: Serum Brain Derived Correlates)

Figure 5: Serum Brain Derived Neurotrophic Factor (sBDNF) Correlates

Note: ABC=Activity Specific Balance Confidence Scale; FGA=functional gait assessment; GDS-30=Geriatric Depression Scale; MiniBEST=miniBEST test; PDQ-SI=Parkinson's Disease Quality of Life Summary Index; PFS=Parkinson's Fatigue Scale; TUG=timed up and go

CHAPTER 5

DISCUSSION

This study investigated the impact of LSVT BIG, an intensive, whole-body, amplitude-based training protocol, on functional mobility, quality of life, and markers of neuroplasticity in PwPD. In light of limited treatment options for PwPD, it is important to establish effective evidence-based treatment interventions within the PT discipline along with valid, sensitive outcome measures. This treatment efficacy study used a within-subject multiple baseline design (A-B-A-A). The findings demonstrated statistically significant improvements in the gait measures of step length and gait speed, confidence with balance, and improved quality of life measures but not in TUG, fatigue, or depression measures by EOT+4. These findings are consistent with our first and second hypothesis that exercise intervention using LSVT BIG would produce positive statistically significant changes in mobility outcomes and quality of life measures in PwPD. The third hypothesis that there would be measurable changes in sBDNF levels following LSVT BIG was not supported. Serum BDNF declined which was opposite the direction expected. The fourth hypothesis that there would be correlations between sBDNF and functional measures was also not supported because no significant correlations were found.

Hypothesis 1: Exercise intervention using LSVT BIG will produce positive statistically significant changes in functional mobility outcome measures in PwPD

This study supports LSVT BIG as an effective behavioral treatment intervention for PwPD implemented in a university clinic with people experiencing mild to moderate disease severity that positively impacts functional mobility.

Statistically significant changes were identified at the group level between BASE and EOT+4 in four of the six primary outcome measures including the MDS-UPDRS Part III: Motor Examination, Functional Gait Assessment, MiniBEST, and step length all contributing to an overall improved mobility presentation. (Figure 6: Functional Mobility Outcome Measures; Figure 7: Gait Outcome Measures)

Figure 6: Function Mobility Outcome Measures – Group Level Averages

* p value < .05

Note: Base=baseline; EOT=end of treatment; EOT+4=4 weeks after end of treatment; FGA=functional gait assessment; MiniBEST=MiniBEST test; UPDRS-III=Unified PD Rating Scale

Figure 7: Gait Outcome Measures -- Group Level Averages

Movement Disorder Society -Unified Parkinson's Disease Rating Scale (MDS-UPDRS) – III Motor Scale

Significant improvements were identified in the MDS-UPDRS III Motor score at EOT+4 (8 weeks from BASE) and were consistent with findings reported in other LSVT BIG studies (Dashtipour et al., 2015; Ebersbach et al., 2010; Ebersbach et al., 2014; Ebersbach et al., 2015). Similar to the current study, Dashtipour et al. (2015) reported no significant improvements at EOT while none of the Ebersbach et al., studies (2010; 2014; 2015) reported data from EOT assessments. Two other LSVT

BIG studies identified MCID at EOT and EOT+8 (Millage et al., 2017; Ueno et al., 2017) but did not complete statistical analysis while one study did not collect MDS-UPDRS scores (Farley et al., 2005).

Changes in the MDS-UPDRS-III Motor score reported in studies of interventions employing similar “intensive” exercise have been positive but not consistently significant. King et al., (2015) utilized the ABC (Agility Boot Camp) protocol to compare delivery setting – Home exercise program, group class, and individual treatment - which resulted in an improvement in the MDS-UPDRS III scores but not to a level of significance or meeting MCID. A study investigating high intensity boot camp compared to usual care found significant improvements in MDS-UPDRS III scores at the EOT (8 weeks from baseline) in both groups but these gains were not maintained at six months following treatment in either group (Landers et al., 2019). A systematic review of PD and intensive exercise by Uhrbrand et al. (2015) subdivided results from 10 studies into resistance training, endurance training, and “other intensive” training and reported results across those categories as utilizing MDS-UPDRS III scores. The analysis of the results were mixed with all three resistance studies and one “other intensive” training study reporting significant improvement and all four endurance studies and two of the “other intensive” training studies reporting no significant change as measured by MDS-UPDRS III scores.

Variability of treatment impact on PwPD’s MDS-UPDRS III score across studies may be a reflection of the wide variability that exists in type of intervention, exercise dosage, and timing of outcome assessments as summarized in the Cochrane review comparing treatment interventions in PwPD (Tomlinson et al., 2012).

Tomlinson et al. (2012) reported 17 of 43 studies reported MDS-UPDRS III data and 14 studies revealed no difference in the motor score between treatments but did not indicate if there was any significant improvement across the treatment arms being compared. Three studies reported significant improvement MDS-UPDRS III scores when compared with an alternative treatment intervention, one of which was the LSVT BIG Berlin study (Ebersbach et al., 2010) and two additional studies (Ridgel et al., 2009; Gupta et al., 2011).

The MDS-UPDRS is the international rating system identified as the gold standard in assessing PwPD. The items on this scale and some of its sections can be utilized to identify subtypes of PD such as tremor dominant (TD) and postural instability gait disturbance (PIGD) (Stebbins et al., 2013), freezing of gait, and impact of dyskinesia. It has been demonstrated to have excellent internal consistency ($\alpha = .93$) and validity ($r = .96$) as a clinical outcome measure and can be administered in a timely manner (Goetz, et al., 2008). The availability of a clinician who is trained to administer and score the scale may be its primary limitation in its broader application in treatment efficacy studies.

Functional Gait Assessment (FGA) and Mini Balance Evaluation System Test (MiniBEST)

The FGA and the MiniBEST tests were used to evaluate mobility. The FGA focuses on postural stability and dynamic gait (Weber et al., 2016) while the MiniBEST focuses on dynamic balance, postural responses, and anticipatory transitions (Franchignoni et al., 2010). In this cohort, the FGA appeared to be more

sensitive to change with two participants meeting MDC for improvement and group mean statistical significance at both EOT and EOT+4 while the MiniBEST identified just one participant as meeting MDC and a group mean statistical significance only at EOT+4. The difference in sensitivity did not appear to be related to a ceiling effect. (Table: 5; Figure 6:Functional Mobility Outcome Measures)

This finding is consistent with the only other LSVT BIG study that used the FGA (Millage et al., 2017) which reported MCID in three of the nine PwPD. Some of the LSVT BIG studies included generalized gait measures (gait speed, TUG, and step length) but none, except Millage et al. (2017) included a specific balance measure. The finding is also consistent with the report of significant improvement in the MiniBEST score in PwPD receiving individual and group Agility Boot Camp training (King et al., 2015), highly challenging balance training (Leavy et al., 2020), and high intensity boot camp (Landers et al., 2019).

It is disappointing that so few studies appear to integrate specific balance assessments in their outcome measures given the significant issue with postural instability, balance confidence, and falls that PwPD experience. Balance and gait have been identified as independent domains when assessing mobility in PwPD. A single measure of static conditions cannot reliably predict dynamic postural instability as seen in gait activities (Horak et al., 2016). It has been suggested that clinicians should consider outcome measures at each of the International Classification of Function (ICF) levels to direct treatment intervention (King et al., 2013) rather than only utilizing body structure (i.e. MDS-UPDRS III) and function level of the ICF in research.

A strength of the current study is the inclusion of two separate balance measures to address dynamic gait and postural instability. These findings, related to improvements in FGA and MiniBEST following LSVT BIG treatment, contribute to the body of knowledge regarding the choice of clinical outcome measures a clinician may opt for when treating PwPD. Findings suggest the FGA may be a more precise measure for PwPD, however, it is possible that the subtype of PD (tremor dominant (TD) versus postural instability gait disturbance (PIGD)) may play a role in supporting one measure over another. These findings may suggest that LSVT BIG is more effective in addressing gait impairments compared with balance disturbance but further investigation is needed.

Gait Speed, Step Length, and Timed Up and Go (TUG)

Gait speed, step length, and turning speed are closely integrated measures of gait performance. They have been identified as predictors of quality of life, morbidity, and mortality in PwPD (Ellis et al., 2011), activities of daily living limitations in PwPD (Tan et al., 2012), and impending disability in older adults (Ellis et al., 2016). Often these parameters are measured only in part and independent of each other in both the research and clinical setting, yet they may offer a more accurate and clinically meaningful interpretation when considered together.

Gait speed, the driver of an individual's performance on the TUG, has been identified as a key predictor of falls in PwPD when it is less than 1.1 m/s (Lindholm et al., 2018). Only three of the nine participants had a gait speed >1.1 m/s at BASE. None of the participants improved above the 1.1 m/s threshold at EOT. Six

participants remained in the increased falls risk category. This finding was consistent with Ueno et al. (2017) study, which showed no change in gait speed as measured by 10 meter walk, a finding that is in contrast to several other LSVT BIG studies reporting significant improvements in gait velocity or improvement in 10 meter walk (Ebersbach et al., 2010; Ebersbach et al., 2015; Farley and Koshland, 2005; Millage et al., 2017). This may have been influenced by the high number of individuals that exhibited somewhat lower gait speed at baseline. (Table: 8)

PwPD often experience an altered gait pattern characterized by short, shuffling steps. This decreased step length along with decreased gait speed can contribute to falls. Only one participant in this cohort was assessed with what would be considered “normal” step length - 79 cm for men (Murray, Drought, and Kory, 1964) and 66 cm for women (Murray, Kory, and Sepic, 1970) - at BASE and EOT+4. This is consistent with improved step length reported in Ebersbach et al. (2015), the only LSVT BIG study reporting step length as a dependent variable.

Impairment of turning during gait and functional tasks is a hallmark characteristic of PwPD and can contribute to freezing of gait (FOG), decreased confidence with activities, and loss of balance (LOB) (Curtze et al., 2011). While not measured individually, turning speed is a measure integrated into the FGA and is scored on a scale from 0 (severe) to 3 (normal). While only two of the participants in this study scored within normal range for turn speed at BASE (mild impairment n=4; moderate impairment n=2; severe impairment n=1) the trend moved towards less impairment at EOT (normal n=5; mild=3; moderate n=0; severe n=1) with seven

participants reaching normal turning speed by EOT+4 leaving one participant at mild and one at moderate impairment.

The TUG did not appear to serve as a sensitive measure of significant change following treatment intervention in the current study. TUG was assessed as showing statistical significance in two of the seven LSVT BIG studies (Ebersbach et al., 2010; Ebersbach et al., 2015) while one study showed no significant changes (Ueno et al., 2017). Neither Ebersbach et al., (2010; 2015) reported MCID for the TUG as the changes were fairly small (-.75 sec and -1.3 sec, respectively). Three case series reports of LSVT BIG excluded from the systematic review discussed earlier all completed TUG and none showed any significant change at EOT or at any other follow up assessment (Chatto et al., 2018; Fishel et al., 2018; Janssens et al., 2014). The results for this study were consistent with these findings - no statistically significant change in the TUG and none of the participants met the threshold for MCID which is reported to be 11 seconds (Steffen and Seney, 2008).

Three of the participants in this study scored >14 seconds identifying them for high falls risk at BASE yet two of them improved to below the cut-off for falls risk (Podsiadlo 1991) by the EOT+4. Our findings support TUG and gait speed as clinical tools to identify people at risk for falls but suggest additional measures, specifically step length and turning speed, to capture changes related to treatment intervention, provide a more comprehensive clinical picture of the PwPD, and inform clinical intervention decision making. This study suggests that LSVT BIG may contribute to a reduction in falls by impacting gait speed, step length, and turning speed potentially

decreasing the impact of disability in PwPD (Table 7; Table 8; Table 9; Figure 8: Falls Risk at BASE and EOT+4)

Hypothesis 2: Exercise intervention using LSVT BIG will produce positive statistically significant changes in psychometric measures including quality of life in PwPD.

This study supports LSVT BIG as an effective behavioral treatment intervention for PwPD implemented in a university clinic with people experiencing mild to moderate disease severity that positively impacts quality of life measures. Characteristics that impact quality of life such as confidence with balance and mobility and nonmotor symptoms of PD such as fatigue and depression are important for quality of life in PwPD. The ABC, a measurement of participant perceived

confidence with a variety of daily activities, was the only measure to reach statistical significance at EOT and EOT+4 yet MDC improvements were noted at the individual level for the ABC, PDQ-39 Summary Index, and depression measures. (Table 10, Table 11, and Table 12; Figure 9: Balance Confidence and Quality of Life and Figure 10: Depression and Fatigue)

Figure 9: Balance Confidence and Quality of Life – Group Level Averages

* p value < .05

Note: ABC=Activity Specific Balance Confidence Scale; Base=baseline; EOT=end of treatment; EOT+4=4 weeks after end of treatment; PDQ-SI=Parkinson's Disease Quality of Life Summary Index

Figure 10: Depression and Fatigue – Group Level Averages

* p value < .05

Note: Base=baseline; EOT=end of treatment; EOT+4=4 weeks after end of treatment; GDS-30=Geriatric Depression Scale; PFS=Parkinson's Fatigue Scale

Activities-specific Balance Confidence (ABC)

Confidence with activities as measured by the ABC has been correlated with turning, pace-related measures, and dynamic stability during gait (Curtz et al., 2016) which, as discussed in the previous section, have been identified as predictors of quality of life and mortality (Ellis et al., 2011). The ABC as a tool to measure response to treatment interventions has been mixed. Two recent studies in PwPD (King et al., 2015; Leavy et al., 2020) reported ABC results indicating improvements in participant's confidence with mobility but was not statistically significant and did not meet MDC. The findings from the current study found both statistically significant

changes in the ABC at EOT and EOT+4 at the group level and MDC at the individual level supporting the ABC as a sensitive measure in PwPD following LSVT BIG.

Health Related Quality of Life (HRQoL)

HRQoL was measured utilizing the PDQ39 and calculated as a summary index score which reflects the overall impact of PD on quality of life (Jenkinson & Peto, 1997; Peto et al., 1998). Impairment in HRQoL in PwPD is associated with mobility and function and is positively correlated with increasing disease severity (Schrag et al., 2000). The PDQ39 is sensitive to changes which tend to matter to the person with PD but may not necessarily be the focus of clinical assessment which is focused on impairment (Peto et al., 1998). In other words, progressive motor impairments due to increasing disease severity (i.e. tremor) is NOT predictive of worsening HRQoL but worsening physical function/mobility IS (Ellis et al., 2011).

Despite no statistically significant changes, four individuals in this cohort demonstrated improvement in their PDQ-39SI scores meeting MDC at EOT while six individuals met MDC at EOT+4 and the group mean change also met MDC at this time. Two participants demonstrated an MDC decline in HRQoL at each time point. (Table: 11)

These findings are consistent with the literature that has shown HRQoL measures to be fairly resistant to change over a short period of time (King et al., 2015; Park et al., 2014; Ridgel et al., 2009; Schenkman et al., 2012; Speelman et al., 2013). A few studies have reported improvements (Cugusi et al., 2014; Combs et al., 2013) but these interventions were more prolonged (9 weeks and 12 weeks, respectively)

supporting again, the idea that neuroplasticity changes may only be realized over a more prolonged period of time.

The mobility subdomain on the PQD-39 has been shown to be closely associated with postural control as measured by the FGA, which may provide clinicians a useful interpretation of the PDQ39 results even if no significant change is measured (Ellis et al., 2011).

This study provides insight into the complex relationship among disease related nonmotor symptoms such as depression and fatigue, disease severity, and progressive disability. Results suggest that LSVT BIG is an efficacious behavior treatment intervention that targeted mobility limitations which not only resulted in improved function but also positively impacted HRQoL for PwPD.

Parkinson's Fatigue Scale (PFS)

Fatigue is the most common non-motor symptom of PD, rated as the most disabling symptom by 33% of PwPD and within the top three most disabling by 50% of PwPD (Herlofson et al., 2017). It also has the highest negative impact on HRQoL measures and yet receives the least amount of focus in research, clinical assessment, and treatment (Herlofson et al., 2017). The pathology of fatigue in PwPD remains elusive although the basal ganglia pathways appear to be implicated, specifically the ventral striatum, caudate, and putamen and the uptake of serotonin (Friedman et al., 2016). There were no significant changes noted in levels of fatigue. Scores >3.3 fall into a category describing fatigue as a problem. The mean level of fatigue for the cohort was 2.5. There is no MDC established for the PFS but two individuals scored

above the cutoff of 3.3 at BASE and moved below the cutoff at EOT and maintained the improvement at EOT+4. No rigorous trials have been conducted yet the leading nonpharmacological treatment that has been suggested for PwPD is exercise, given that patients often report they feel energized after exercise (Friedman et al., 2016). (Table 13)

It is difficult to interpret these findings in the context of the current literature as so few studies measure fatigue. The extensive Cochrane review comparing different PT exercise intervention studies identified that although there was a wide variety of measures across all studies most were PT and PD focused (Tomlinson et al., 2012). The finding in this study is consistent with one recent trial that reported a significant improvement in perceived fatigue immediately following a high intensity boot camp (HIBC) compared with usual care (Landers et al., 2019) and the effects of a physical activity program in PwPD (Cugusi et al., 2014). Interestingly, individuals in the HIBC group continued to report lower fatigue levels at the six month follow up assessment while the usual care group reported worse fatigue. This may represent a broadly interpreted level of neuroprotection and an overlooked impact of intensive behavior treatments on one of PwPD most disabling symptoms.

Depression

The presentation is similar for depression. The prevalence of depression has been found to be as high as 36.3% for minor depression and 12.9% for major depression in PwPD (van Der Hoek et al., 2011). Unfortunately, it is estimated that only 20% of those individuals will receive treatment for their symptoms which can lead to reduced quality of life and increased risk for disability (Frisina et al., 2008;

Schrag et al., 2000). In contrast to these reports of limited treatment for depression, 80% of this cohort that reported symptoms consistent with mild depression on the GDS were receiving some type of anti-depressant medication.

Depression can be a psychosocial response to stress of living with a degenerative disease and impending disability, yet it is also thought to have a biomedical basis related to the disease process of PD itself (Frisina et al., 2008). The catecholamine system, specifically the locus coeruleus producing norepinephrine and the substantia nigra producing dopamine, has been implicated in major depression in PwPD as observed in postmortem evaluation of brain tissue (Frisina et al., 2009). Diagnosis and treatment are important early in the disease process to preserve function and quality of life.

Participants in the current study scored in the normal (n=4) and mild depression (n=5) range at BASE however at EOT and EOT+4 this had improved to n=6 in the normal range and only n=3 in the mild depression range. Depression has not been consistently measured in behavioral intervention studies. One study implementing an exercise program similar to LSVT BIG in its intensity, duration, and 1:1 therapist delivery (King et al., 2015) and another evaluating the effects of a physical activity program in PwPD (Cugusi et al., 2014) both showed significant improvement in self-reported depression levels.

Results of this study found improvements in ABC at the group level and PDQ-SI at individual level suggesting that exercise, and specifically an intensive individual intervention such as LSVT BIG, may exert small but important improvements in

confidence and quality of life while its influence on depression and perceived fatigue warrants further research.

Hypothesis 3: There will be measurable changes in sBDNF levels following LSVT BIG treatment as a result of intensive exercise.

Despite the mechanisms of BDNF not being completely understood it has been hailed as a biomarker of neuroprotection and neuroplasticity (Cotman et al., 2007) yet also linked to pathogenesis and neurodegenerative disease (Scalzo et al., 2010; Ventriglia et al., 2013).

In this cohort, resting sBDNF changed in response to the LSVT BIG exercise intervention which identified a 10.11% decline at EOT ($p=.264$) and an overall 30.94% decline from BASE to EOT+4 which was statistically significant ($p=.003$) but in the opposite direction than was expected. This was in contrast to statistically significant increases in sBDNF identified in four studies of PwPD that showed increases of 12.6%, 34%, 36%, and 22.7%, respectively (Frazzita et al., 2014; Marusiak et al., 2015; Angelucci et al., 2016; and Zoladz et al., 2014). This difference could be related to the type of exercise intervention which may have been more aerobic in nature as all four of those studies employed stationary cycle or treadmill training. (Figure 11: Serum Brain Derived Neurotrophic Factor)

Figure 11: Serum Brain Derived Neurotrophic Factor (sBDNF)

Note: Base=baseline; EOT=end of treatment; EOT+4=4 weeks after end of treatment

Hypothesis 4: There will be positively correlated changes between sBDNF level and functional mobility outcomes measures

Correlation analysis revealed weak negative relationships between sBDNF and measures that represented functional improvement (i.e. FGA, MiniBEST, step length, and ABC) and weak positive relationships between sBDNF and measures representing functional decline (i.e. UPDRS III, PFS, GDS, and PDQ-39 SI) (see Fig. 5 sBDNF Correlates).

Ventriglia et al. (2013) identified significantly decreased sBDNF associated with neurodegenerative disease such as Alzheimer's disease and related dementias

while significantly increased sBDNF was associated in PwPD with high disease severity compared with controls. They identified L-dopa as a significant contributing factor due to the medication's role in facilitating BDNF release in cortico-striatal fibers and emphasize the importance of collecting medication information when studying BDNF response. These studies were baseline measures only and did not employ any intervention to measure a response to exercise. This is in contrast to a study by Rocha et al. (2018) which identified neurotrophic factors as unchanged in PwPD. However, Rocha et al. (2018) evaluated plasma levels in contrast to serum levels which has been suggested to reflect only freely circulating BDNF while serum levels reflect stored and freely circulating BDNF (Voss et al., 2017) which can confound interpretation of results and the ability to compare results.

The current study did not include neurotypical participants for a comparison of sBDNF to PwPD. Therefore, we cannot determine if sBDNF levels were relatively high or low at BASE for the participants. Correlation analysis of sBDNF revealed only weak positive and negative relationships across all variables with the exception of the PADS-R which was a moderate negative relationship ($r = -0.627$) interpreted as higher sBDNF levels related to lower premorbid physical activity levels. This may be in line with sBDNF levels reflecting disease state such as hypothesized by Scalzo et al. (2010) who related low BDNF in early disease states of PD as a sign of pathogenesis and elevated BDNF later in the disease state as a compensatory mechanism. (Figure 5: Serum Brain Derived Neurotrophic Factor Correlates)

Neuroplasticity, Exercise Prescription and Clinical Implications

Linking behavioral and biological measures to support neuroplasticity remains challenging and open to a myriad of interpretations. The potential meaning in a single variable change (i.e. sBDNF) at a cellular level is extremely difficult to interpret. BDNF can be measured in serum, plasma, and cerebral spinal fluid in humans. BDNF is only one neurotrophic factor among several (i.e. IGF-1 and VEGF) in a cascade of responses to physiologic influences such as exercise and other confounding factors such as disease state and medication contribution. It may be that changes in BDNF are similar to neuroplastic changes that have been discussed in neuroimaging studies in response to exercise and enrichment. Increased activity and connectivity in fMRI in association with performance improvement, in a short time period, has been interpreted by some to represent an acute response representing temporary neuroplasticity (Amad et al., 2017; Bakhtiari et al., 2017; Rosenberg-Lee et al., 2018). Decreased connectivity that has been associated with ongoing performance improvement over a longer time period has been interpreted as improved efficiency of the system (Everts et al., 2017; Supekar et al., 2015; Yuan et al., 2017). These spatial and temporal responses may be at play with sBDNF where elevation in sBDNF as measure immediately following acute exercise is associated with performance improvement and decreased levels of sBDNF following chronic, longer term exercise and reflected in resting serum levels are associated with persistent performance improvements may represent an improved efficiency and decreased disease load on the system.

This study reported statistically significant improvements ($\alpha < 0.05$) across both clinical measure categories in four of the six functional mobility measures and one of the four psychometric measures but not until EOT+4. Only the ABC was significant at EOT. This delay of full effect may reflect a different temporal and spatial pattern for neuroplasticity changes to occur before they become evident as more global behavioral changes. The furthest time point in all of the LSVT BIG studies reviewed was sixteen weeks while similar intensive exercise studies assessed at twelve weeks or less (King et al., 2015; Leavy et al., 2020). Only one study included a six month follow-up time point (Landers et al., 2019) which supported improvement at EOT and then a pattern of decline by month six. This is an important note considering much of the research (and all of our clinical applications) assesses changes, whether mobility or psychometric, close to the end of a treatment intervention. These findings identify a need for more routine and longitudinal assessments.

Parkinson's disease has been described, as a "complex genetic disorder" associated with a wide array of genes that exert small effects that align and potentially trigger the cardinal signs and symptoms (Williams-Gray and Worth 2016; Weiner, Shulman, and Lang, 2013, p.28). Perhaps this multidimensional perspective in the development of the disease is one that is also pertinent in the pursuit of the treatment. We need to ensure that we are not so busy searching for the one "magic solution" that we miss out on the more realistic multifaceted solutions available. It could be that the many small effects come from a wide number of "epigenes" – nutrition, sleep, exercise, social interactions, mental engagement - each exerting a small effect until the

interventions/solutions align and facilitate the PwPD to move towards improved function, improved mental health, and better quality of life.

Exercise is one of those “epigenes”. There are several components that guide exercise as a mover of neuroplasticity. Salience, intensity, frequency, duration, and setting all come together like the ingredients in a recipe for health. A longitudinal analysis of National Parkinson Foundation Quality Improvement Initiative Data (NPFQII) concluded that PwPD who regularly exercised (>2.5 hours/week) experienced small but positive changes in HRQoL and mobility measures in contrast to those who did not exercise and experienced a decline in mobility and HRQoL (Rafferty et al., 2017). This supports the idea of regular exercise as protective of mobility and HRQoL over time.

LSVT BIG utilizes each of these key principles of neuroplasticity in such a manner as to recalibrate and steer the PwPD in the direction of restoration. It is clear from the reported outcomes in this study that LSVT BIG is an effective behavioral treatment intervention for PwPD. It is less clear as to whether it is one of those principles or the blend of all of them that contributes to the success the treatment.

Limitations

There are several limitations associated with this study. The participants were self-selected and part of a convenience sample which may limit the ability to generalize findings across populations and may represent selection bias. Individuals served as their own control but a comparison group that did not receive treatment was

not included in the sample. Since there was only one arm for treatment there was no randomization. The study had a small number of participants at $n=9$.

There are limitations inherent to a within subject multi-baseline design (A-B-A-A). One limitation is the inability to control for potential confounders which may bias the results although expanding the number of measures can sometimes assist in decreasing the impact. Another limitation is that each participant serves as their own control. A separate control group which receives no treatment would strengthen the design.

The principal investigator completing the assessments also participated in the delivery of treatment for some of the participants due to limited access to LSVT certified clinicians. Although every attempt to blind the rater to time points for assessments was made whenever possible, bias cannot be completely excluded.

A less restrictive approach was taken in setting inclusion and exclusion criteria in the recruitment process in order to promote greater ecological validity. The cohort had a normal distribution with the exception of the H&Y rating. The high distribution of participants with a H&Y score of 2 ($n=7$) reflects the ongoing challenge faced in many studies with PwPD when trying to recruit a diverse cohort. The H&Y scale was established as a convenient method of assessing disease severity by taking into account both the clinical features and progression of disability (Hoehn and Yahr 1967) and is the standard staging system used to describe patient populations second only to the MDS-UPDRS (Goetz et al., 2004). Goetz et al. (2004) described the distribution of PwPD across large cohorts with Stage 1 and Stage 5 accounting for the least number of subjects followed by Stage 4 and that most subjects (52-77%) were Stage 2 and 3.

This study reflects these identified distributions. Goetz et al., (2004) identified support for continued use of the H&Y staging as it does serve to describe PwPD, which is an important in clinical efficacy studies, and it captures important aspects of disease progression, but its limitations need to be kept in mind.

One option to address the need for an easily understood severity scale was introduced by Martinez-Martin et al. (2014) who proposed utilizing the MDS-UPDRS as a measure of disease severity and established cut-off points for each of the four parts. Applying this severity scale to the current cohort (MDS-UPDRS III: cut-off scores mild <32, moderate 33 to 58, and severe >59) identifies eight of the participants in the mild range and only one participant in the moderate range. Interestingly the two participants identified as H&Y stage 3 were both classified as mild severity. This classification of disease severity and disability rating appears more accurate in this cohort compared with the H&Y considering the PwPD identified as moderate disease severity presented as such based on actual clinical observation by this researcher/clinician in conjunction with outcome measures. However limitations exist with this approach first and foremost, the need for an MDS-UPDRS assessment to be completed and the need for further large scale validation of the cut-off values (Martinez-Martin et al. 2014).

CHAPTER 6

CONCLUSION

Recommendations for Future Research

Principles of neuroplasticity are integral to the application of behavioral interventions aimed at addressing the complex nature of Parkinson's disease. Exercise is a behavioral intervention because it exerts broad strokes on the human landscape and empowers the PwPD to modify symptoms of the disease. It requires a prescription that follows evidence-based practice. We need to employ a methodical deconstruction of exercise prescription in our research including the assessment of each component – type, mode of delivery, frequency, duration, and intensity. Evaluating LSVT BIG with an alternative dosing schedule would be an important step toward understanding the roles of dosage (intensity of exercise within one session) and duration of treatment may play in outcome.

There is not one treatment for all PwPD and treatment efficacy research needs to identify which therapy is appropriate for specific characteristics of PD. It is important to report all outcome data for responders and nonresponders. Data from “nonresponders” may support that a treatment was ineffective or may represent a PD subtype that requires different interventions. That data might also reflect stabilization and neuroprotective aspects of a treatment intervention. Complete reporting of data, even when they appear nonsignificant, can serve to guide future research directions. Although larger studies are needed, they are not always feasible or investigators may not have access to large groups of participants. Improved reporting of methodology,

exercise protocols, consistency in data collection and analysis, and use of more comprehensive measures following ICF guidelines could improve consistency across studies. This might facilitate the ability of small n studies to be evaluated in a larger context such as systematic review and meta-analysis.

Parkinson's disease has been perceived as a primary motor disease however, it needs to be kept in mind it is, in fact, a sensory-motor disease that it has many nonmotor symptoms which impact on PwPD HRQoL. More extensive psychometric measures need to be utilized both in the clinic and future research to capture important impact both the disease and treatment (i.e. exercise) may be exerting on depression, fatigue and other mental health related issues and HRQoL. Research that evaluates the role of sensory input and integration into movement will also be important to contribute to our understanding of disease progression as well as the development of new treatment interventions.

Utilization of the MDS-UPDRS III offers not only direct measures of mobility but also the ability to extract key components to classify further subtypes of PD such as tremor dominant (TD) and postural instability and gait disturbance (PIGD) (Stebbins et al., 2013), freezing of gait (FOG), and impact of dyskinesia. Integrating MDS-UPDRS III measures whenever feasible and analysis of data related to outcome measures in consideration with these subtypes may better inform clinical decision making. Freezing of gait was not assessed separately from the MDS-UPDRS III or included in the analysis. Since FOG, similar to PD subtype, can significantly impact an individual's experience with the disease including mobility and HRQoL, it will be important to integrate these measures into future studies.

In light of the delayed time frame from start of treatment to measurable functional improvement, future longitudinal studies are needed as well as recommendations for ongoing periodic clinical assessments for PwPD, especially given the progressive nature of the disease process. This will not only guide clinical practice but support the reimbursement of these interventions for PwPD.

Compliance remains a challenge, both facilitating it from a clinical perspective and measuring it from a research perspective. Future studies employing developing technologies such as smart watches and telehealth may assist in this process. LSVT BIG has been marketed primarily for PwPD, however, its employment of principles of neuroplasticity in its treatment approach may prove effective with people with a variety of neurologic disorders and future research should consider expanding into these patient populations.

Conclusion

The aim of this study was to investigate the impact of LSVT BIG on the functional mobility, quality of life, and markers of neuroplasticity in PwPD. This study is unique in its integration of neurobiological measures with comprehensive functional and psychometric measures. This study supports the use of LSVT BIG as an efficacious treatment intervention with PwPD that is associated with significant improvements in mobility, step length, confidence with balance, HRQoL measures as well as decreased reports of depression and fatigue. Results associated with sBDNF levels should be interpreted with caution since the sample was so small and further

analysis for additional neurotrophic factors, such as vascular endothelial growth factor (VEGF) and other potential anti-inflammatory markers may be warranted.

APPENDICES

APPENDIX A

Table of Measures and Timeline

Instrument	Measure	Format	Scoring	Time to complete	Time Points	ICF Level
Intake Assessment	Demographics	Interview/Questionnaire	N/A	5-10 minutes	Initial only	
ABC ^a	Balance confidence	Questionnaire*	0-1600 score divided by 100 and reported as a percentage	5-10 minutes	BASE, EOT, EOT+4	2- Activity
CIRS-G	Comorbidities	Interview/Questionnaire		5-10 minutes [#]	Initial only	
ELISA	BDNF	Blood draw		10 minutes [#]	BASE, EOT, EOT+4	
Exercise Log	Adherence to LSVT BIG	Logue sheet*		<5 minutes	Ongoing t/o study	
FGA ^a	gait	Assessment	Total score of 30; higher score better functional performance	5-10 minutes [#]	BASE, EOT, EOT+4	2- Activity
Gait Analysis ^a	Gait speed Stride length Limb speed	Wearable technology	Speed Distance Speed	15-20 minutes [#]	BASE, EOT, EOT+4	2- Activity
GDS-30 ^a	Depression	Questionnaire*	normal 0-9 mild depression 10-19 severe depression 20-30	5-10 minutes	BASE, EOT, EOT+4	1 - participation
H&Y	PD Stage	Derived from UPDRS	0-4	N/A	BASE, EOT, EOT+4	
Mini-BESTest ^a	Balance	Assessment	Max. score of 28; higher score better performance	10 minutes [#]	BASE, EOT, EOT+4	2- Activity
MOCA	Cognition	Assessment	<26/30 points	10 minutes [#]	Initial only	
MDS - UPDRS Part I	Nonmotor Experience of Daily Living	Questionnaire*	0 to 52 with a higher score is higher level of severity and disability.	5-10 minutes	BASE, EOT, EOT+4	3 – Body Structure and Function
MDS - UPDRS Part II	Motor Experience of Daily Living	Questionnaire*	0 to 52 higher score is higher level of severity and disability	5-10 minutes	BASE, EOT, EOT+4	2- Activity

^a = Primary outcome measure ; * = requires only participant time commitment; # = requires investigator assessment/involvement

Note: ABC=Activity Specific Balance Confidence Scale; Base=baseline; CIRS-G = Cumulative Illness Rating Scale; EOT=end of treatment; EOT+4=4 weeks after end of treatment; FGA=functional gait assessment; GDS-30=Geriatric Depression Scale; Hoehn and Yahr; ICF= International Classification for Functioning; MiniBEST=MiniBEST test; MOCA = Montreal Cognitive Assessment; UPDRS = Unified Parkinson's Disease Rating Scale

Table of Measures and Timeline (continued)

Instrument	Measure	Format	Scoring	Time to complete	Time Points	ICF Level
MDS -UPDRS Part III ^a	Motor Exam	Assessment	0 to 72 with a higher score indicates higher level of severity and disability.	20-30 minutes [#]	BASE, EOT, EOT+4	3 – Body Structure and Function
MDS -UPDRS Part IV	Motor Complications	Interview/Questionnaire	0 to 24 with a higher score indicates higher level of severity and disability	5-10 minutes [#]	BASE, EOT, EOT+4	3 – Body Structure and Function
PDQ-39 ^a	Quality of Life	Questionnaire*	100 points lower scores indicating better QoL	10-20 minutes	BASE, EOT, EOT+4	1 - participation
PFS-16 ^a	Fatigue	Questionnaire*	Total /16 >3.3 avg identified those perceiving fatigue to be a problem	5 minutes	BASE, EOT, EOT+4	1 - participation
PADs-R	Physical activity	Questionnaire*		15-20 minutes	Initial only	
TUG ^a	Falls risk	Assessment Wearable technology	time	N/A – within BESTest	BASE, EOT, EOT+4	2- Activity

^a = Primary outcome measure ; * = requires only participant time commitment; # = requires investigator assessment/involvement

Note: Base=baseline; IRS-G = Cumulative Illness Rating Scale; EOT=end of treatment; EOT+4=4 weeks after end of treatment; ICF= International Classification for Functioning; PADs-R = Physical Activity Disability Scale PDQ-SI=Parkinson's Disease Quality of Life Summary Index; PFS=Parkinson's Fatigue Scale TUG=timed up and go; UPDRS = Unified Parkinson's Disease Rating Scale

Summary - Time Commitment		
Study Component	Assessments	Treatment
Questionnaire's completed by participant independently (off site)	50-60 minutes	
Interview/Questionnaire's completed with researcher	15-20 minutes	
Assessments completed by researcher	60-90 minutes	
Lab work – blood draw	10-15 minutes	
LSVT BIG treatment intervention		1 hour 4x a week x 4 weeks
LSVT BIG home program		45 minutes 4x a week x 4 weeks (on days of therapy) 90 minutes 3x a week x 4 weeks (on days of no therapy)

APPENDIX B

Consent Form for Research

STUDY TITLE

LSVT BIG Exercise-Induced Neuroplasticity in People with Parkinson's Disease: An Assessment of Physiological and Behavioral Outcomes

PRINCIPAL INVESTIGATORS

Leslie Mahler, PhD, CCC-SLP
lmahler@uri.edu

Phone: 401-874-2490

Email:

Christine Clarkin, DPT
chrisclarkin@uri.edu

Phone: 401-662-5367

Email:

KEY INFORMATION

Important information to know about this research study:

- The purpose of the study is to look at how an exercise program designed for people with Parkinson's disease (called LSVT BIG) helps movement and walking.
- You need to have a diagnosis of Parkinson's disease to be in this study.
- You need to be able to walk (with or without a device) as well as stand to complete the exercises.
- You can NOT have completed the LSVT BIG treatment in the past year or have a diagnosis of a past heart attack, stroke or other neurologic diagnosis, or surgery for treatment of Parkinson's Disease such as a deep brain stimulator.
- If you choose to join the study, you will be asked to answer some questions and a therapist will do some tests related to balance and your ability to move and walk. This will take about 3 hours. This full assessment will occur two more times, the week after the LSVT BIG treatment and one last time 4 weeks later.
- You will then come to the physical therapy clinic at URI 4 times a week (for four weeks) for one hour sessions with a clinician. They will teach you exercises, movement, and walking activities. They will also give you homework you will do daily. This is an exercise program that you will end up doing twice a day, every day, for the 4 weeks (28 days).

- If you choose to join the study, you will be asked to submit a blood sample 3 times (one at each testing time point). This part is optional and will be explained in a separate consent form that will provide information regarding the blood draw and why we are asking for a blood sample. You may still join in the LSVT BIG study and decide not to do of the blood sample at any time.
- You will be asked to use as a smart watch which will record daily activity, steps, heart rate, and sleep patterns You may still join in the LSVT BIG study and not do this part or decide to stop this at any time.
- Risks or discomforts from this research: There is minimal risk associated with this study beyond those you might have with any exercise program, which can include fatigue or muscle soreness.
- This study will provide the researchers with information about the effect of this exercise treatment in patients with Parkinson’s disease. You may experience some direct benefits, which may include better movement, increased energy, decreased fatigue, improved balance, and improved quality of your walking.
- You will not be paid for your participation
- You will be provided a copy of this consent form.
- Taking part in this research project is voluntary. You don’t have to take part and you can stop at any time.

INVITATION

You are invited to take part in this research study. The information in this form is meant to help you decide whether or not to participate. If you have any questions, please ask.

Why are you being asked to be in this research study?

You are being asked to be in this study because you have a diagnosis of Parkinson’s disease, you are able to walk (with or without a device) and you can stand to complete the exercises, you have not been in an LSVT BIG exercise program in the past year, and do not have a diagnosis of a past heart attack, stroke or other neurologic diagnosis, or surgical procedure for treatment of PD such as a deep brain stimulator. You are 19 years of age or older to participate.

What is the reason for doing this research study?

People with Parkinson’s disease can have a variety of motor symptoms such as tremors, slowed movement, and decreased balance. These symptoms can lead to difficulty moving and walking and increased falls. The focus of this research is to see if an exercise program called LSVT BIG can help with these problems. Although LSVT BIG has been

advertised a lot making it a well-known treatment for people with PD, it does not have a lot of research to prove it works.

The main goal of this research is to see if LSVT BIG exercises help people move and walk better.

What will be done during this research study?

You will receive evaluations immediately before treatment, immediately after treatment, and four weeks after finishing the treatment. The treatment itself will take four weeks. The total time of the study will take about 12 weeks. There are two parts to consider when thinking about how much time it will take, the testing and the treatment.

Testing:

You will be given questions to complete at home that include topics such as confidence with movement, depression, fatigue, and activity level as well as requests for your medication and health history. This may take between 30 and 60 minutes in total to finish.

You will then be seen in the physical therapy clinic for a series of tests that include moving, walking, and balance. This may take between 1 ½ - 2 hours. Some of these tests may be videotaped.

Treatment:

LSVT BIG is an exercise delivered 1:1 by trained LSVT BIG clinicians. Each treatment session includes daily exercises similar to lunges and sidestepping, movements you normally do every day such as getting up and down from a chair or in and out of bed, and walking.

You will come to the physical therapy clinic for the LSVT BIG treatment intervention for 1 hour 4x a week x 4 weeks for a total of 16 hours. You will also perform the exercise/treatment protocol a second time on those days as well as twice a day on non-clinic days.

How will my data be used?

All data collected will be stored and analyzed here at the University of Rhode Island by staff associated with the study.

What are the possible risks of being in this research study?

There are minimal risks with participation in this study. Your risks, harms, or discomforts should be no more than those felt when doing any regular exercise program. This may include but not be limited to muscle strain or soreness, risk for falls, and risk for cardiovascular event.

What are the possible benefits to you?

You may have some direct benefits from the participating in the therapy, which may include improved mobility, increased energy, decreased fatigue, improved balance, and improved quality of your walking.

What are the possible benefits to other people?

If the results of this study show good improvement in moving and walking it would support LSVT BIG as a treatment choice for PwPD. This could help clinicians try and get more trained therapists in the exercise as well as support insurance payment for such programs

What are the alternatives to being in this research study?

Instead of being in this research study you can contact a local physical therapy clinic that offers the LSVT BIG program or any physical therapy for people with PD. This lets you get the treatment without any additional time needed to do the research testing.

What will being in this research study cost you?

There is no cost to you to be in this research study.

Will you be compensated for being in this research study?

You will not receive any compensation for participating in this research study.

What should you do if you have a problem during this research study?

If you have a problem or experience harm as a direct result of being in this study, you should immediately contact one of the people listed at the beginning of this consent form. If needed, seek immediate emergency care for this problem. Please note, it is the policy of URI not to pay for any required care. Agreeing to this does not mean you have given up any of your legal rights.

How will information about you be protected?

Steps will be taken to protect your privacy and the confidentiality of your study data. Your part in this study is confidential. HIPPA will be followed for all protected health information (PHI) collected. A participant medical record (paper) will be made and stored onsite in a locked location in the URI Physical Therapy Department. All electronic data related to wearable technology will be uploaded to a secure online platform/website made for research. All data entered into computers for analysis purposes will be de-identified (cannot identify who the information belongs to) and files and computers will be password protected.

The data will be stored in a locked cabinet in the researcher's office and will only be seen by the research team during the study and for 5 years after the study is complete.

The only persons who will have access to your research records are the study personnel, the Institutional Review Board (IRB), and any other person, agency, or sponsor as required by law. The information from this study may be published in scientific journals or presented at scientific meetings but the data will be reported as group or summarized data and your identity will be kept strictly confidential.

What are your rights as a research subject?

You may ask any questions concerning this research and have those questions answered before agreeing to participate in or during the study.

For study related questions, please contact the investigator(s) listed at the beginning of this form.

For questions concerning your rights or complaints about the research contact the Institutional Review Board (IRB) or Vice President for Research and Economic Development:

- IRB: (401) 874-4328 / researchintegrity@etal.uri.edu.
- Vice President for Research and Economic Development: at (401) 874-4576

What will happen if you decide not to be in this research study or decide to stop participating once you start?

You can decide not to be in this research study, or you can stop being in this research study ("withdraw") at any time before, during, or after the research begins for any reason. Deciding not to be in this research study or deciding to withdraw will not affect your relationship with the investigator or with the University of Rhode Island (list others as applicable). You will be provided with a list of resources regarding local therapy clinics that provide LSVT BIG and treatment alternatives.

You will not lose any benefits to which you are entitled.

Documentation of informed consent

You are voluntarily making a decision whether or not to be in this research study. Signing this form means that

- (1) you have read and understood this consent form,
- (2) you have had the consent form explained to you,
- (3) you have had your questions answered and
- (4) you have decided to be in the research study. You will be given a copy of this consent form to keep.

Participant Name:

(Name of Participant: Please print)

Participant Signature:

Signature of Research Participant

Date

Investigator certification:

My signature certifies that all elements of informed consent described on this consent form have been explained fully to the subject. In my judgment, the participant possesses the capacity to give informed consent to participate in this research and is voluntarily and knowingly giving informed consent to participate.

Signature of Person Obtaining Consent

Date

AUDIO/VIDEO ADDENDUM TO THE CONSENT FORM FOR RESEARCH

By signing this consent form, I confirm that I give my permission for photo and video recording(s) of me, to be used for the purposes listed above, and to be retained indefinitely. You may still participate in this study if you are not willing to be recorded.

Printed Name of Participant

Signature of Participant

Date

Printed Name of Person Obtaining Consent

Signature of Person Obtaining Consent

Date

ADDENDUM FOR HIPAA INFORMATION (PERSONAL HEALTH INFORMATION) ACCESS

You have rights regarding the privacy of your medical information collected before and during this research. This medical information, called “protected health information” (PHI), typically may include, depending upon the nature of this research, demographic information (like your address and birth date), the results of physical exams, blood tests, x-rays and other diagnostic and medical procedures, as well as your medical history.

By signing this consent form, you are allowing the research team to have access to your PHI. The research team includes the investigators listed on this consent form and other personnel involved in this specific study at [add additional personnel/institutions as applicable].

Your PHI will be used only for the purpose(s) described in the section “What is the reason for doing this research study?”

Your PHI will be shared, as necessary, with the Institutional Review Board (IRB) and with any person or agency required by law. You are also allowing the research team to share your PHI with other people or groups listed below all of these persons or groups listed below are obligated to protect your PHI.

You may cancel your authorization for further collection of PHI for use in this research at any time by contacting the principal investigator in writing. However, the PHI which is not included in the research data obtained to date may still be used. If you cancel this authorization, you will no longer be able to participate in this research.

- Researchers at University of Rhode Island involved in this study

You are authorizing us to use and disclose your PHI for as long as the research study is being conducted.

Printed Name of Participant

Signature of Participant

Date

Printed Name of Person Obtaining Consent

Signature of Person Obtaining Consent

Date

APPENDIX C

Consent Form for Research – Addendum for Blood Draw

STUDY TITLE

LSVT BIG Exercise-Induced Neuroplasticity in People with Parkinson's Disease: An Assessment of Physiological and Behavioral Outcomes – **Blood Draws**

PRINCIPAL INVESTIGATORS

Leslie Mahler, PhD, CCC-SLP
lmahler@uri.edu

Phone: 401-874-2490

Email:

Christine Clarkin, DPT
chrisclarkin@uri.edu

Phone: 401-662-5367

Email:

KEY INFORMATION

- **You have chosen to participate in the LSVT BIG Exercise Study and the FULL consent form regarding the study has been reviewed with you already and you have a copy of that consent form.**
- **This consent form contains information only related to the blood draws**

What will be done during this research study? – BLOOD DRAWS

You will be seen in the Kinesiology phlebotomy lab, located at 25 West Independence Way, for a blood draw on three separate occasions during the study (initial, immediately following treatment, and 4 weeks later) over the course of the 12-week study). The lab technician will draw blood by putting a needle into the vein of your arm. Two small tubes of blood will be taken (approximately 2 teaspoons). The needle stick may hurt. You will then be offered a small snack (e.g. granola bar) and drink (water, juice) when the blood draw is complete.

What are the possible risks of being in this research study? – BLOOD DRAWS

There are minimal risks associated with participation with the blood draw. There is a small risk of bruising, bleeding, fainting, and a rare risk of infection. You will be offered a snack and monitored as indicated.

How will information about you be protected? – BLOOD DRAWS

Your blood samples will have a nonidentifying study code and number to protect your privacy. They will be stored in a freezer in a secured Kinesiology lab at Independence Square until analysis. The samples may be stored and used for analysis for up to 5 years and will then be disposed of according to University policy.

Documentation of informed consent

You are voluntarily making a decision whether or not to be in this research study. Signing this form means that

- (1) you have read and understood this consent form
- (2) you have had the consent form explained to you,
- (3) you have had your questions answered and

(4) Initial next to your choice and sign below.

_____ **YES - you have decided to allow your blood to be drawn as a part of the LSVT BIG study. You will be given a copy of this consent form to keep.**

_____ **NO – you have decided NOT to allow your blood to be drawn as part of the LSVT BIG study. You will be given a copy of this consent form to keep as part of your other participation forms.**

Participant Name:

(Name of Participant: Please print)

Participant Signature:

Signature of Research Participant

Date

Investigator certification:

My signature certifies that all elements of informed consent described on this consent form have been explained fully to the subject. In my judgment, the participant possesses the capacity to give informed consent to participate in this research and is voluntarily and knowingly giving informed consent to participate.

Signature of Person Obtaining Consent

Date

APPENDIX D

LSVT BIG Summary Protocol

<i>LSVT BIG (e.g., [39])</i>
<i>Target: BIG</i>
Increased movement amplitude directed across limb motor system including gait
<i>Intensity: standardized</i>
Dosage: 4 consecutive days a week for 4 weeks (16 sessions in one month) Repetitions: minimum 8–16 repetitions/task Effort: push for maximum patient-perceived effort each day (8 or 9 on scale of 1–10 with 10 being the most)
<i>Daily exercises</i>
First half of the treatment session (30 min. or more) <i>Task 1: Maximum Sustained Movements: seated</i> 8 reps: sustain Big “stretch” floor to ceiling (10 sec hold); 8 reps: sustain Big “stretch” side to side (10 sec hold) <i>Task 2: Repetitive/Directional Movements: standing</i> 16 reps: Forward Big step – 8 each leg; 16 reps: Sideways Big step – 8 each side; 16 reps: Backward Big step – 8 each leg; 20 reps: Forward Big Rock and reach – 10 each side; 20 reps: Sideways Big Rock and reach – 10 each side <i>Task 3: Functional Component Movements</i> Patient self-identifies 5 movements he/she does in functional living every day (e.g., Sit-to-stand) Clinician and patient select one simple component of each of these movements 5 reps each of the 5 component movements “Do your movement with the same effort/bigness that you did during the daily exercises”
<i>Hierarchy</i>
Second half of the treatment session (30 min or less) (i) Designed to train rescaled amplitude/effort of movement achieved in daily exercises and functional component movements into in context specific and variable movement activities (ii) Complex multilevel tasks that progressively become more difficult over the 4 weeks and can be tailored to each patient's goals and interests (e.g., basic bathroom skills versus going out to dinner or shopping) (iii) Tasks progress in difficulty by increasing duration (maintain BIG for longer periods of time) amplitude (bigness/effort, within normal limits), and complexity of tasks (multisteps, dual processing, background noise, and attentional distracters) (iv) BIG walking is included as part of hierarchy on a daily basis. Time and distance will vary across patients, hierarchy goals, and weeks of therapy
<i>Shaping techniques</i>
Goal: train movement bigness that is healthy and good quality (i.e., no unwanted strain or pain, impingement, or awkward biomechanics) Technique: shape the quality and movement bigness through use of modeling or tactile/visual cues. “Watch me and do what I do.” Minimal cognitive loading: behavior is not achieved through extensive instructions or explanations, which are often too complex for patient to generalize outside of treatment room, but rather the patient is trained through modeling

<i>LSVT BIG (e.g., [39])</i>
<i>Sensory recalibration</i>
Treatment: focus attention on how it feels and looks to move BIG Carryover activities: start day one: daily assignments (treatment and nontreatment days); use big movements in real-life situations; (i) difficulty of the assignment matches the level of the hierarchy where the person is working; (ii) make patient accountable and probe for comments from patient that people in their daily living have said, such as, “You are moving better” Homework practice: start day one: daily assignments to practice at home (Daily Exercises and Functional Component Movements, Walking BIG); treatment days (one other time for 5–10 minutes); nontreatment days (two times for 10–15 minutes); homework book provided and patient made accountable

Fox, C., Ebersbach, G., Ramig, L., & Sapir, S. (2012). LSVT LOUD and LSVT BIG: Behavioral treatment programs for speech and body movement in parkinson disease. *Parkinson's Disease*, 2012 doi:10.1155/2012/391946

APPENDIX E

World Health Organization International Classification of Function, Disability and Health

The World Health Organization outlined the ICF in 2000 to integrate a more comprehensive perspective of disability, complement research outcome measures, and provide consistent, comparable, and universal guidance between researchers as well as on an international level. The ICF interactive model identifies three levels of human functioning: functioning at the level of body or body part, the whole person, and the whole person in his or her complete environment. These levels in turn define three functional dimensions: body functions and structures, activities, and participation that can be addressed with specific measures (World Health Organization 2000).

ICF Level 1: Participation

Participation is involvement in a life situation. Participation restrictions are problems an individual may experience in involvement in life situations (Bickenbach, Chatterji, Kostanjsek, and Ustun 2003).

ICF Level 2: Activity

Activity is the execution of a task or action by an individual. Activity limitations are difficulties an individual may have in executing activities (Bickenbach et al., 2003).

ICF Level 3: Body Structure and Function

Body functions are physiological functions of body systems including psychological functions. Body structures are anatomical parts of the body such as organs, limbs and their components. Impairments are problems in body function or structure such as a significant deviation or loss (Bickenbach et al. 2003).

APPENDIX F

Comprehensive List of Outcome Measures

Activities Specific Balance Confidence Scale (ABC) is a subjective self-reported measure of confidence in performing various ambulatory activities without falling or experiencing a sense of unsteadiness. It is a 16-item questionnaire with a 0-1600 score divided by 100 and reported as a percentage. It has a high level of internal consistency (Powell and Meyers 1995; Steffen and Seney 2008).

Cumulative Illness Rating Scale for Geriatrics (CIRS-G) is an interview-based instrument to measure medical comorbidity in relationship to disability and has been validated as an effective measure in PwPD (Visser et al., 2004).

Functional Gait Assessment (FGA) is a 10-item test with each item scored 0-3 with a total score of 30. The higher the score the higher the functional performance. It takes 5-10 minutes to administer (Weber et al., 2016).

Gait Analysis will be measured with wearable technology and include stride length, lower and upper limb speed, and over all gait speed.

Gait Speed (10-Meter walk) is the measure of time it takes to complete a 10-meter walk with the patient's preferred device. Gait speed, turning speed, and stride length have been found to be highly correlated to severity of disease and patient perception of mobility disability (Curtze et al., 2016).

Geriatric Depression Scale (GDS – 30) is a short, self-report, yes/no screening instrument for depression in the elderly (Yesavage et al., 1982). The GDS is short and easily understood, making it appropriate for use in both clinical research and routine clinical care as a screening instrument for depression in elderly PD patients (Schrage et al., 2007). It focuses on the psychological aspects and social consequences of depression, avoiding symptom overlap with medical disorders, such as PD, or aging in general. Each question on the GDS-30 can only be scored "0" or "1," for a total score of 30 with the higher score indicating higher severity of depression (normal 0-9; mild depressive 10-19; severe depressive 20-30). The instrument is not able to capture degrees of severity at the level of individual items, however, there is preliminary evidence that the overall scale may be sensitive to changes in depression severity (Schrage et al., 2007).

Hoehn & Yahr Staging (H&Y) - is a 5 point scale that describes the stage of disease from a clinical perspective from 0 – Asymptomatic, 1 – Unilateral involvement only, 2 – Bilateral involvement without impairment of balance, 3 – Mild to moderate involvement; some posture instability but physically independent; Needs assistance to recover from the pull test, 4 – Severe disability; still able to walk or stand unassisted,

and 5 – Wheelchair bound or bed ridden unless aided (Goetz et al., 2004). This is included in the MDS-UPDRS.

Mini-Balance Evaluation System Test (Mini BESTest) is a valid and reliable clinical balance scale to assess falls risk and postural control in people with PD (Duncan and Leddy 2013). It is a unidimensional test modified from the original 36 item BESTest (and different from the Brief-BESTest a 6-item test across all domains of the original test) and focuses specifically on dynamic balance (Bravini et al., 2016). It consists of 14 items with each task scored on a 3-point ordinal scale (0-2 rating) with a maximum score of 28 and a higher score indicating better performance (Franchignoni et al., 2010; Schlenstedt et al., 2015). It takes 10-15 minutes to administer and includes the TUG.

The Montreal Cognitive Assessment (MoCA) is a one-page 30-point test administered in 10 minutes intended to serve as a screen tool for cognitive impairment in a variety of patient populations covering 8 cognitive domains including visuospatial/executive functioning (5 points), memory and delayed recall (5 points), attention, concentration, and working memory (6 points), language and naming (6 points), abstraction (2 points), and orientation (6 points) (Brown et al., 2016). Initial analyses indicated that persons with 12 years of education or less tended to have worse performance on the MoCA therefore to correct for education effects 1 point is added for participants with 12 years of education or less on their total MoCA score (if <30) (Zadikoff et al., 2008). The recommended total cutoff score to detect mild cognitive impairment for people with PD (PD-MCI) is <26 with the specificity of the MoCA to exclude elderly normal controls good (87%) and sensitivity in detecting MCI excellent (90%) compared to the MMSE (18%) (Brown et al., 2016; Zadikoff et al., 2008).

(The Movement Disorder Society (MDS) Task Force for creating diagnostic procedures PwPD for dementia initially recommended the Mini-Mental State Exam (MMSE) as the most appropriate standard objective assessment of global cognitive functioning but they revised their criteria in 2012 replacing the MMSE with the MoCA (Brown et al., 2016). The measure desired in the study or clinical application, baseline status versus change over time, must be taken into consideration however, as a study released around the same time found that while the MoCA may be more sensitive to cognitive change at baseline than the MMSE, the MoCA did not appear to change over time while the MMSE did (Lessig et al., 2012). This study is utilizing the measure for baseline status only therefore the MoCA will be utilized.)

Movement Disorder Society Unified Parkinson's Disease Rating (MDS-UDRS) - Unified Parkinson's Disease Rating Scale (UPDRS) which was originally developed in the 1980s and became the most widely used clinical rating scale for PD, was revised and termed the MDS sponsored UPDRS revision (**MDS-UPDRS**) and is used as the primary international rating scale for PD clinical care and research (Goetz et al., 2008). The MDS-UPDRS has four parts, namely, I: Non-motor Experiences of Daily Living (13 items); II: Motor Experiences of Daily Living (13 items); III: Motor Examination (18 items); IV: Motor Complications (6 items). There is a 5-point range

for each item - normal (0), slight (1), mild (2), moderate (3), and severe (4) with a higher score indicating higher disability. Factor structure of the new scale has been determined to be both clinimetrically sound and clinically pertinent but it has been recommended that each of the four parts (I-IV) be reported separately and not collapsed into a single “total MDS-UPDRS” summary score (Goetz et al., 2008).

MDS-UPDRS Part I: Non-motor Experiences of Daily Living

Part I has two components: IA concerns a number of behaviors that are assessed by the investigator with all pertinent information from patients and caregivers, and IB is completed by the patient with or without the aid of the caregiver, but independently of the investigator. These sections can, however, be reviewed by the rater to ensure that all questions are answered clearly, and the rater can help explain any perceived ambiguities. It is comprised of 13 items with a 0-4 rating for a range from 0 to 52 with a higher score indicating higher level of severity and disability. It requires a 5-10 minutes to complete (Goetz et al., 2008).

MDS-UPDRS Part II: Motor Experiences of Daily Living is a self-administered survey of 13 items with a 0-4 rating for a range from 0 to 52 with a higher score indicating a higher level of severity and disability. It requires 5-10 minutes to complete.

MDS-UPDRS Part III: Motor Examination

Part III has instructions for the rater to give or demonstrate to the patient; it is completed by the rater. It is comprised of 18 items with a 0-4 rating for a range from 0 to 72 with a higher score indicating higher level of severity and disability. It requires 20-30 minutes to complete. It also includes a question regarding medication, ON/OFF state at time of exam, and a final Hoehn and Yahr stage rating (Goetz et al., 2008).

MDS-UPDRS Part IV: Motor Complications

Part IV has instructions for the rater and also instructions to be read to the patient. This part integrates patient-derived information with the rater’s clinical observations and judgments and is completed by the rater. It is comprised of 6 items with a 0-4 rating for a range from 0 to 24 with a higher score indicating higher level of severity and disability from dyskinesias. It requires 5-10 minutes to complete (Goetz et al., 2008).

Parkinson’s Disease Questionnaire-39 – Quality of Life measure (PDQ-39) is a self-report quality of life (QoL) questionnaire used to assess health-related QoL in individuals with PD. The instrument assesses QoL across 8 domains: mobility, activities of daily living, emotional well-being, stigma, social support, cognitive impairment, communication, and bodily discomfort. It takes 10-20 minutes to administer, provides a score from 0-100 with lower scores indicating better QoL, has excellent test-retest reliability, excellent internal consistency, and minimal detectable change (MDC) for each dimension identified (Hagell 2003; Hagell 2007).

Parkinson's Disease Fatigue Scale (PFS-16) is a patient-rated scale that measures fatigue, one of the non-motor symptoms associated with Parkinson's. The scale allows

the measurement of the presence of fatigue (seven items) and also its impact on daily function (nine items) and takes around five minutes to administer. It can be used to assess levels of fatigue and measure any changes that treatment or lifestyle changes may effect. The PFS-16 is available for download by healthcare professionals or not-for-profit researchers (richard.g.brown@kcl.ac.uk) to request permission for use. (Brown, Dittner, Findley, & Wessely 2005).

Physical Activity and Disability Survey (PADS-R) is a measure of physical activity in people with neurologic conditions that takes 15-20 minutes to administer (Kayes et al., 2009).

Timed Up and Go (TUG) assesses mobility, balance, walking ability, and falls risk in older adults, has good inter and intra-rater reliability, and is useful for following clinical change over time as well as predict safety with gait (Podsiadlo and Richardson 1991).

APPENDIX G

LSVT BIG 2019 Study – Participant Survey

Since participating in the BIG Program.....	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
I am moving better in my day to day activities	1	2	3	4	5
I am more confident with my day to day activities	1	2	3	4	5
Friends and family have noticed I am moving better since participating in this program	1	2	3	4	5
I have less fatigue	1	2	3	4	5
I am sleeping better	1	2	3	4	5
I am more likely to participate in social activities	1	2	3	4	5
I am likely to continue with some type of exercise after finishing the BIG program	1	2	3	4	5
I am likely to share information/recommend the program to others with Parkinson's disease	1	2	3	4	5
The Fitbit gave me helpful information about my activity and steps	1	2	3	4	5
I am likely to continue to use the Fitbit as an activity monitor	1	2	3	4	5

Rank in order of benefit (to you) the different components of the BIG program (1 = most important; 7= least important) Please choose each number only once							
The intensity of the program (high effort)	1	2	3	4	5	6	7
One on one coaching and feedback	1	2	3	4	5	6	7
The frequency of the program (attending 4x a week)	1	2	3	4	5	6	7
The frequency of the exercises (performing 2x a day)	1	2	3	4	5	6	7
The daily exercises which were challenging	1	2	3	4	5	6	7
The daily components which were functional	1	2	3	4	5	6	7
The hierarchy activities which were practical	1	2	3	4	5	6	7

The most beneficial part of the BIG program was:

The least beneficial part of the BIG program was:

What I liked most about the BIG program was:

What was most challenging about the BIG program was:

I think the program could be better if:

BIBLIOGRAPHY

- Abbruzzese, G., & Berardelli, A. (2003). *Sensorimotor integration in movement disorders*. New York: doi:10.1002/mds.10327
- ABCAM. Ab212166 Human BDNF SimpleStep ELISA® Kit [PDF]. (2019, January 25). [https://www.abcam.com/ps/products/212/ab212166/documents/ab212166_Human BDNF ELISA Kit _v2 \(website\).pdf](https://www.abcam.com/ps/products/212/ab212166/documents/ab212166_Human_BDNF_ELISA_Kit_v2_(website).pdf)
- Adkins, D.L., Boychuk, J. Remple, M.S., & Kleim, J.A. (2006). Motor training induces experience-specific patterns of plasticity across motor cortex and spinal cord. *Journal of Applied Physiology*, 10 (6), 1776-1782.
- Ahlskog, J. E. (2011). Does vigorous exercise have a neuroprotective effect in parkinson disease? *Neurology*, 77(3), 288. doi:10.1212/WNL.0b013e318225ab66
- Amad, A., Seidman, J., Draper, S. B., Bruchhage, M. M. K., Lowry, R. G., Wheeler, J., . . . Smith, M. S. (2017). Motor learning induces plasticity in the resting brain-drumming up a connection. *Cerebral Cortex (New York, N.Y.: 1991)*, 27(3), 2010-2021. 10.1093/cercor/bhw048
- Ang, E., Tai, Y., Lo, S., Seet, R., & Soong, T. (2010). Neurodegenerative diseases: Exercising toward neurogenesis and neuroregeneration. *Frontiers in Aging Neuroscience*, 2 doi:10.3389/fnagi.2010.00025
- Angelucci, F., Piermaria, J., Gelfo, F., Shofany, J., Tramontano, M., Fiore, M., . . . Peppe, A. (2016). The effects of motor rehabilitation training on clinical symptoms and serum BDNF levels in parkinson's disease subjects. *Canadian Journal of Physiology and Pharmacology*, 94(4), 455-461. doi:10.1139/cjpp-2015-0322
- Avanzino, L., Pelosin, E., Carmelo, M. V., Lagravinese, G., Abbruzzese, G., & Martino, D. (2016). Time processing and motor control in movement disorders. *Frontiers in Human Neuroscience*, 10(2016) doi:10.3389/fnhum.2016.00631
- Bakhtiari, R., Cummine, J., Reed, A., Fox, C. M., Chouinard, B., Cribben, I., & Boliek, C. A. (2017b). Changes in brain activity following intensive voice treatment in children with cerebral palsy. *Human Brain Mapping*, 38(9), 4413-4429. 10.1002/hbm.23669
- Bennie, Scott & Bruner, Kathryn & Dizon, Allan & Fritz, Holly & Goodman, Bob & Peterson, Sandra. (2003). Measurements of Balance: Comparison of the Timed

"Up and Go" Test and Functional Reach Test with the Berg Balance Scale.
Journal of Physical Therapy Science - J PHYS THER SCI. 15. 93-97.
10.1589/jpts.15.93.

Bickenbach, J., Chatterji, S., Kostanjsek, N., & Üstün, T. (2003). Ageing, disability and the WHO's international classification of functioning, disability and health (ICF). *Geneva Papers on Risk & Insurance*, 28(2), 294-303. doi:10.1111/1468-0440.00224

Braak, H., Ghebremedhin, E., Rüb, U., Bratzke, H., & Tredici, K. (2004). Stages in the development of parkinson's disease-related pathology. *Cell and Tissue Research*, 318(1), 121-134. doi:10.1007/s00441-004-0956-9

Braak, H., Rüb, U., Gai, W. P., & Del Tredici, K. (2003). Idiopathic parkinson's disease: Possible routes by which vulnerable neuronal types may be subject to neuroinvasion by an unknown pathogen. *Journal of Neural Transmission*, 110(5), 517-536. doi:10.1007/s00702-002-0808-2

Bravini, E., Nardone, A., Godi, M., Guglielmetti, S., Franchignoni, F., & Giordano, A. (2016). Does the brief-BESTest meet classical test theory and rasch analysis requirements for balance assessment in people with neurological disorders? *Physical Therapy*, 96(10), 1610. doi:10.2522/ptj.20150550

Brown, D. S., Bernstein, I. H., McClintock, S. M., Munro Cullum, C., Dewey, R. B., Husain, M., & Lacritz, L. H. (2016). Use of the montreal cognitive assessment and alzheimer's Disease-8 as cognitive screening measures in parkinson's disease. *International Journal of Geriatric Psychiatry*, 31(3), 264-272. doi:10.1002/gps.4320

Brown, K E, S L Whitney, D M Wrisley, and J M Furman. "Physical Therapy Outcomes for Persons with Bilateral Vestibular Loss." *The Laryngoscope* 111, no. 10 (2001): 1812-7

Brown, R. G., Dittner, A., Findley, L., & Wessely, S. C. (2005). The parkinson fatigue scale. *Parkinsonism and Related Disorders*, 11(1), 49-55. doi:10.1016/j.parkreldis.2004.07.007

Burke, R. E., Dauer, W. T., & Vonsattel, J. P. G. (2008). A critical evaluation of the braak staging scheme for parkinson's disease. *Annals of Neurology*, 64(5), 485-491. doi:10.1002/ana.2154

Cagnan, H., Duff, E. P., & Brown, P. (2015). The relative phases of basal ganglia activities dynamically shape effective connectivity in parkinson's disease. *Brain*, 138(6), 1667-1678. doi:10.1093/brain/awv093

- Caspersen, C. J., Powell, K. E., & Christenson, G. M. (1985). Physical activity, exercise, and physical fitness: Definitions and distinctions for health-related research. *Public Health Reports (1974-), 100*(2), 126-131.
- Castellanos, N. P., Leyva, I., Buldú, J. M., Bajo, R., Paúl, N., Cuesta, P., . . . del-Pozo, F. (2011). Principles of recovery from traumatic brain injury: Reorganization of functional networks. *NeuroImage, 55*(3), 1189-1199. doi:10.1016/j.neuroimage.2010.12.046
- Cattaneo, D., J. Jonsdottir, M. Zocchi, and A. Regola. "Effects of Balance Exercises on People with Multiple Sclerosis: A Pilot Study." *Clinical Rehabilitation 21*, no. 9 (2007): 771-81.
- Cavanaugh, J. T., Ellis, T. D., Earhart, G. M., Ford, M. P., Foreman, K. B., & Dibble, L. E. (2015). Toward understanding ambulatory activity decline in parkinson disease. *Physical Therapy, 95*(8), 1142. doi:10.2522/ptj.20140498
- Center for Disease Control. Physical Activity And Health. (2018, February 13). Retrieved June 20, 2018, from <https://www.cdc.gov/physicalactivity/basics/pa-health/index.htm>
- Cerasa, A., Fera, F., Gioia, M. C., Liguori, M., Passamonti, L., Nicoletti, G., . . . Quattrone, A. (2006). Adaptive cortical changes and the functional correlates of visuo-motor integration in relapsing-remitting multiple sclerosis. *Brain Research Bulletin, 69*(6), 597-605. doi:10.1016/j.brainresbull.2005.11.006
- Chatto, C. A., York, P. T., Slade, C. P., & Hasson, S. M. (2017). Use of a telehealth system to enhance a home exercise program for a person with parkinson disease: A case report. *Journal of Neurologic Physical Therapy, 42*(1), 1. doi:10.1097/NPT.0000000000000209
- Christiansen, C. L., Schenkman, M. L., Mcfann, K., Wolfe, P., & Kohrt, W. M. (2009). Walking economy in people with parkinson's disease. *Movement Disorders, 24*(10), 1481-1487. doi:10.1002/mds.22621
- Cleary, Kimberly, and Elena Skorniyakov. "Predicting Falls in Community Dwelling Older Adults Using the Activities-specific Balance Confidence Scale." *Archives of Gerontology and Geriatrics 72* (2017): 142-45
- Collier TJ, Kanaan NM, Kordower JH. (2011). Ageing as a primary risk factor for Parkinson's disease: evidence from studies of non-human primates. *Nat Rev Neurosci.* 2011;12(6):359–366. doi:10.1038/nrn3039

- Collier, T.J., Kanaan, N.M., and Kordower, J.H. (2017). Aging and Parkinson's disease: Different sides of the same coin? *Mov. Disord.*, 2017, vol. 32, no. 7, pp. 983–990
- Combs, S. A., Diehl, M. D., Chrzastowski, C., Didrick, N., Mccoin, B., Mox, N., . . . Wayman, J. (2013). Community-based group exercise for persons with parkinson disease: A randomized controlled trial. *NeuroRehabilitation*, 32(1), 117. doi:10.3233/NRE-130828
- Combs, S. A., Diehl, M. D., Staples, W. H., Conn, L., Davis, K., Lewis, N., & Schaneman, K. (2011). Boxing training for patients with parkinson disease: A case series. *Physical Therapy*, 91(1), 132. doi:10.2522/ptj.20100142
- Combs, S. A., Diehl, M. D., Filip, J., & Long, E. (2014). Short-distance walking speed tests in people with parkinson disease: Reliability, responsiveness, and validity. *Gait & Posture*, 39(2), 784-788. doi:10.1016/j.gaitpost.2013.10.019
- Cotman, C. W., Berchtold, N. C., & Christie, L. (2007). Exercise builds brain health: Key roles of growth factor cascades and inflammation. *Trends in Neurosciences*, 30(9), 464-472. doi:10.1016/j.tins.2007.06.011
- Creaby, M. W., & Cole, M. H. (2018). Gait characteristics and falls in parkinson's disease: A systematic review and meta-analysis. *Parkinsonism and Related Disorders*, 57, 1-8. doi:10.1016/j.parkreldis.2018.07.008
- Cugusi, L., Solla, P., Zedda, F., Loi, M., Serpe, R., Cannas, A., . . . Mercurio, G. (2014). Effects of an adapted physical activity program on motor and non-motor functions and quality of life in patients with parkinson's disease. *NeuroRehabilitation*, 35(4), 789. doi:10.3233/NRE-141162
- Curtze, C., Nutt, J. G., Carlson-Kuhta, P., Mancini, M., & Horak, F. B. (2016). Objective gait and balance impairments relate to balance confidence and perceived mobility in people with parkinson disease. *Physical Therapy*, 96(11), 1734. doi:10.2522/ptj.20150662
- Dal Bello-Haas, V., Klassen, L., Sheppard, M. S., & Metcalfe, A. (2011). Psychometric properties of activity, self-efficacy, and quality-of-life measures in individuals with parkinson disease. *Physiotherapy Canada. Physiotherapie Canada*, 63(1), 47. doi:10.3138/ptc.2009-08
- DeMaagd, George & Philip, Ashok. (2015). Parkinson's Disease and Its Management: Part 1: Disease Entity, Risk Factors, Pathophysiology, Clinical Presentation, and

Diagnosis. P & T : a peer-reviewed journal for formulary management. 40. 504-32.

Da Silva, P., Grazielle Chaves, Domingues, D. D., de Carvalho, L. A., Allodi, S., & Correa, C. L. (2016). Neurotrophic factors in parkinson's disease are regulated by exercise: Evidence-based practice. *Journal of the Neurological Sciences*, 363, 5-15. doi:10.1016/j.jns.2016.02.017

Dashtipour, K., Johnson, E., Kani, C., Kani, K., Hadi, E., Ghamsary, M., . . . Chen, J. J. (2015). Effect of exercise on motor and nonmotor symptoms of parkinson's disease. 2015 doi:10.1155/2015/586378

Desplats, P., Lee, H., Bae, E., Patrick, C., Rockenstein, E., Crews, L., . . . Lee, S. (2009). Inclusion formation and neuronal cell death through neuron-to-neuron transmission of alpha-synuclein. *Proceedings of the National Academy of Sciences of the United States of America*, 106(31), 13010. doi:10.1073/pnas.0903691106

Dinoff, A., Herrmann, N., Swardfager, W., & Lanctôt, K., L. (2017). The effect of acute exercise on blood concentrations of brain-derived neurotrophic factor in healthy adults: A meta-analysis. *The European Journal of Neuroscience*, 46(1), 1635. doi:10.1111/ejn.13603

Dittner, A. J., Wessely, S. C., & Brown, R. G. (2004). The assessment of fatigue: A practical guide for clinicians and researchers. *Journal of Psychosomatic Research*, 56(2), 157-170. doi:10.1016/S0022-3999(03)00371-4

Dontje, M. L., de Greef, M H G, Speelman, A. D., van Nimwegen, M., Krijnen, W. P., Stolk, R. P., . . . van, D. S. (2013). Quantifying daily physical activity and determinants in sedentary patients with parkinson's disease. *Parkinsonism and Related Disorders*, 19(10), 878-882. doi:10.1016/j.parkreldis.2013.05.014

Drozak, J., & Bryła, J. (2005). Dopamine: Not just a neurotransmitter. *Postepy Higieny i Medycyny Doswiadczalnej (Online)*, 59, 405.

Duncan, R. P., Leddy, A. L., Cavanaugh, J. T., Dibble, L. E., Ellis, T. D., Ford, M. P., . . . Earhart, G. M. (2013). Comparative utility of the BESTest, mini-BESTest, and brief-BESTest for predicting falls in individuals with parkinson disease: A cohort study. *Physical Therapy*, 93(4), 542. doi:10.2522/ptj.20120302

Ebersbach, G. (2014). Rehabilitative therapy in patients with parkinson's disease. *Basal Ganglia*, 4(1), 19-23. doi:10.1016/j.baga.2014.01.001

- Ebersbach, G., Ebersbach, A., Edler, D., Kaufhold, O., Kusch, M., Kupsch, A., & Wissel, J. (2010). Comparing exercise in parkinson's disease—the berlin BIG study. *Movement Disorders*, 25(12), 1902-1908. doi:10.1002/mds.23212
- Ebersbach, G., Ebersbach, A., Gandor, F., Wegner, B., Wissel, J., & Kupsch, A. (2014). Impact of physical exercise on reaction time in patients with parkinson's Disease—Data from the berlin BIG study. *Archives of Physical Medicine and Rehabilitation*, 95(5), 996-999. doi:10.1016/j.apmr.2013.10.020
- Ebersbach, G., Grust, U., Ebersbach, A., Wegner, B., Gandor, F., & Kühn, A. (2015). Amplitude-oriented exercise in parkinson's disease: A randomized study comparing LSVT- BIG and a short training protocol. *Journal of Neural Transmission; Translational Neuroscience, Neurology and Preclinical Neurological Studies, Psychiatry and Preclinical Psychiatric Studies*, 122(2), 253-256. doi:10.1007/s00702-014-1245-8
- Elbaz, A., Carcaillon, L., Kab, S., & Moisan, F. (2016). Epidemiology of parkinson's disease. *Revue Neurologique*, 172(1), 14-26. doi:10.1016/j.neurol.2015.09.012
- Ellis, T., Cavanaugh, J. T., Earhart, G. M., Ford, M. P., Foreman, K. B., & Dibble, L. E. (2011). Which measures of physical function and motor impairment best predict quality of life in parkinson's disease? *Parkinsonism and Related Disorders*, 17(9), 693-697. doi:10.1016/j.parkreldis.2011.07.004
- Ellis, T. D., Cavanaugh, J. T., Earhart, G. M., Ford, M. P., Foreman, K. B., Thackeray, A., . . . Dibble, L. E. (2016). Identifying clinical measures that most accurately reflect the progression of disability in parkinson disease. *Parkinsonism and Related Disorders*, 25, 65-71. doi:10.1016/j.parkreldis.2016.02.006
- Ellis, T., Boudreau, J. K., Deangelis, T. R., Brown, L. E., Cavanaugh, J. T., Earhart, G. M., . . . Dibble, L. E. (2013). Barriers to exercise in people with parkinson disease. *Physical Therapy*, 93(5), 628. doi:10.2522/ptj.20120279
- Ellis, T., Cavanaugh, J. T., Earhart, G. M., Ford, M. P., Foreman, K. B., Fredman, L., . . . Dibble, L. E. (2011). Factors associated with exercise behavior in people with parkinson disease. *Physical Therapy*, 91(12), 1838. doi:10.2522/ptj.20100390
- Ellis, T., de Goede, C. J., Feldman, R. G., Wolters, E. C., Kwakkel, G., & Wagenaar, R. C. (2005). Efficacy of a physical therapy program in patients with parkinson's disease: A randomized controlled trial. *Archives of Physical Medicine and Rehabilitation*, 86(4), 626-632. doi:10.1016/j.apmr.2004.08.008

- Ellis, T., Katz, D. I., White, D. K., Depiero, T. J., Hohler, A. D., & Saint-Hilaire, M. (2008). Effectiveness of an inpatient multidisciplinary rehabilitation program for people with parkinson disease. *Physical Therapy*, 88(7), 812. doi:10.2522/ptj.20070265
- Ellis, T. and Schenkman, M. (2011). Parkinson Disease Clinical Summary. APTA.org.; <https://www.ptnow.org/ClinicalSummaries/quick-detail/parkinson-disease-pd>. Accessed January 2019.
- Ertan, F S, Ertan, T, Kızıltan, G, and Uyguçgil, H. "Reliability and Validity of the Geriatric Depression Scale in Depression in Parkinson's Disease." *Journal of Neurology, Neurosurgery & Psychiatry* 76, no. 10 (2005): 1445-1447.
- Everts, R., Mürner-Lavanchy, I., Schroth, G., & Steinlin, M. (2017). Neural change following different memory training approaches in very preterm born children—A pilot study. *Developmental Neurorehabilitation*, 20(1), 14-24. 10.3109/17518423.2015.1027010
- Factor, A., S., Bennett, D., A., Hohler, M., A., Wang, M., D., & Miyasaki, M., J. (2016). Quality improvement in neurology: Parkinson disease update quality measurement set: Executive summary. *Neurology*, 86(24), 2278-2283. doi:10.1212/WNL.0000000000002670
- Farley, B. G., Fox, C. M., Ramig, L. O., & Mcfarland, D. H. (2008). Intensive amplitude-specific therapeutic approaches for parkinson's disease: Toward a neuroplasticity-principled rehabilitation model. *Topics in Geriatric Rehabilitation*, 24(2), 99-114. doi:10.1097/01.TGR.0000318898.87690.0d
- Farley, B., & Koshland, G. (2005). Training BIG to move faster: The application of the speed–amplitude relation as a rehabilitation strategy for people with parkinson's disease. *Experimental Brain Research*, 167(3), 462-467. doi:10.1007/s00221-005-0179-7
- Faul, F., Erdfelder, E., Buchner, A., & Lang, A. (2009). Statistical power analyses using G * power 3.1: Tests for correlation and regression analyses. *Behavior Research Methods*, 41(4), 1149-1160. doi:10.3758/BRM.41.4.1149
- Faul, F., Erdfelder, E., Lang, A., & Buchner, A. (2007). G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods*, 39(2), 175-191. doi:10.3758/BF03193146
- Fischer, R., & Maier, O. (2015). Interrelation of oxidative stress and inflammation in neurodegenerative disease: Role of TNF. *Oxidative Medicine and Cellular Longevity*, 2015 doi:10.1155/2015/610813

- Fishel, S. C., Hotchkiss, M. E., & Brown, S. A. (2018). The impact of LSVT BIG therapy on postural control for individuals with parkinson disease: A case series. *Physiotherapy Theory and Practice*, , 1-9. doi:10.1080/09593985.2018.1508260
- Fox, C., Ebersbach, G., Ramig, L., & Sapis, S. (2012). LSVT LOUD and LSVT BIG: Behavioral treatment programs for speech and body movement in parkinson disease. *Parkinson's Disease*, 2012 doi:10.1155/2012/391946
- Fox, C. M. (2008). Voice and Speech Disorders in Parkinson's disease and their Treatment. M. Trail (Ed.). *Neurorehabilitation in parkinson's disease : An evidence-based treatment model*. Thorofare, N.J.: SLACK Inc.
- Fox, S. H., Katzenschlager, R., Lim, S., Ravina, B., Seppi, K., Coelho, M., . . . Sampaio, C. (2011). The movement disorder society Evidence-Based medicine review update: Treatments for the motor symptoms of parkinson's disease. *Movement Disorders*, 26, S2-S41. doi:10.1002/mds.23829
- Fox, Susan H., Regina Katzenschlager, Shen-Yang Lim, Brandon Barton, Rob M. A. De Bie, Klaus Seppi, Miguel Coelho, and Cristina Sampaio. *International Parkinson and Movement Disorder Society Evidence-based Medicine Review: Update on Treatments for the Motor Symptoms of Parkinson's Disease*. Vol. 33. (2018)
- 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. doi:10.2340/16501977-0537
- Franchignoni, F., &VELOZO, C. A. (2005). Use of the berg balance scale in rehabilitation evaluation of patients with parkinson's disease. *Archives of Physical Medicine and Rehabilitation*, 86(11), 2225. doi:10.1016/j.apmr.2005.09.006
- Frazzitta, G., Bertotti, G., Riboldazzi, G., Turla, M., Uccellini, D., Boveri, N., . . . Maestri, R. (2012). Effectiveness of intensive inpatient rehabilitation treatment on disease progression in parkinsonian patients. *Neurorehabilitation and Neural Repair*, 26(2), 144-150. doi:10.1177/1545968311416990
- Frazzitta, G., Bertotti, G., Uccellini, D., Boveri, N., Rovescala, R., Pezzoli, G., & Maestri, R. (2013). Short- and long-term efficacy of intensive rehabilitation treatment on balance and gait in parkinsonian patients: A preliminary study with a 1-year followup.2013doi:10.1155/2013/583278

- Frazzitta, G., Maestri, R., Bertotti, G., Riboldazzi, G., Boveri, N., Perini, M., . . . Ghilardi, M. F. (2015). Intensive rehabilitation treatment in early parkinson's disease. *Neurorehabilitation and Neural Repair*, 29(2), 123-131. doi:10.1177/1545968314542981
- Frazzitta, G., Maestri, R., Ghilardi, M. F., Riboldazzi, G., Perini, M., Bertotti, G., . . . Comi, C. (2014). Intensive rehabilitation increases BDNF serum levels in parkinsonian patients: A randomized study. *Neurorehabilitation and Neural Repair*, 28(2), 163-168. doi:10.1177/1545968313508474
- Friedman, J. H. (2017). Misperceptions and parkinson's disease. *Journal of the Neurological Sciences*, 374, 42-46. doi:10.1016/j.jns.2016.12.059
- Friedman, J. H., Alves, G., Hagell, P., Marinus, J., Marsh, L., Martinez-Martin, P., . . . Schrag, A. (2010). *Fatigue rating scales critique and recommendations by the movement disorders society task force on rating scales for parkinson's disease*. Hoboken: doi:10.1002/mds.22989
- Friedman, J. H., Beck, J. C., Chou, K. L., Clark, G., Fagundes, C. P., Goetz, C. G., . . . Weintraub, D. (2016). Fatigue in parkinson's disease: Report from a multidisciplinary symposium. *NPJ Parkinson's Disease*, 2 doi:10.1038/npjparkd.2015.25
- Friedman, J. H., Brown, R. G., Comella, C., Garber, C. E., Krupp, L. B., Lou, J., . . . Taylor, C. B. (2007). *Fatigue in parkinson's disease: A review*. Hoboken: doi:10.1002/mds.21240
- Frisina, P. G., Borod, J. C., Foldi, N. S., & Tenenbaum, H. R. (2008). Depression in parkinson's disease: Health risks, etiology, and treatment options. *Neuropsychiatric Disease and Treatment*, 4(1), 81-91.
- Frisina, P. G., Haroutunian, V., & Libow, L. S. (2009). The neuropathological basis for depression in parkinson's disease. *Parkinsonism and Related Disorders*, 15(2), 144-148. doi:10.1016/j.parkreldis.2008.04.038
- GBD 2016 Parkinson's Disease Collaborators. Global, regional, and national burden of Parkinson's disease, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*. 2018;17:939-53.
- 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 and Related Disorders*, 6(3), 165-170. doi:10.1016/S1353-8020(99)00062-0

- Gilat, M., Lgia Silva, d. L., Bloem, B. R., Shine, J. M., Nonnekes, J., & Lewis, S. J. G. (2018). Freezing of gait: Promising avenues for future treatment. *Parkinsonism and Related Disorders*, 52, 7-16. doi:10.1016/j.parkreldis.2018.03.009
- Goedert, M., Spillantini, M. G., & Davies, S. W. (1998). *Filamentous nerve cell inclusions in neurodegenerative diseases*doi:10.1016/S0959-4388(98)80090-1
- Goetz, C. G. (2013). The parkinson's disease multidisciplinary package. *Movement Disorders*, 28(5), 565. doi:10.1002/mds.25414
- Goetz, C. G., Poewe, W., Rascol, O., & Sampaio, C. (2005). *Evidence-based medical review update: Pharmacological and surgical treatments of parkinson's disease: 2001 to 2004*. Hoboken: doi:10.1002/mds.20464
- Goetz, C. G., Poewe, W., Rascol, O., Sampaio, C., Stebbins, G. T., Counsell, C., . . . Seidl, L. (2004). Movement disorder society task force report on the hoehn and yahr staging scale: Status and recommendations the movement disorder society task force on rating scales for parkinson's disease. *Movement Disorders*, 19(9), 1020-1028. doi:10.1002/mds.20213
- Goetz, C. G., Tilley, B. C., Shaftman, S. R., Stebbins, G. T., Fahn, S., Martinez-Martin, P., . . . Lapelle, N. (2008). Movement disorder society-sponsored revision of the unified parkinson's disease rating scale (MDS-UPDRS): Scale presentation and clinimetric testing results. *Movement Disorders*, 23(15), 2129-2170. doi:10.1002/mds.22340
- Goodwin, V. A., Richards, S. H., Taylor, R. S., Taylor, A. H., & Campbell, J. L. (2008). *The effectiveness of exercise interventions for people with parkinson's disease: A systematic review and meta-analysis*. Hoboken: doi:10.1002/mds.21922
- Griesbach, G. S., & Hovda, D. A. (2015). Cellular and molecular neuronal plasticity. *Handbook of Clinical Neurology*, 128, 681. doi:10.1016/B978-0-444-63521-1.00042-X
- Gupta A, Ganesan M, Pal P, Talakkad S. Effect of partial weight-supported treadmill gait training on balance in patients with Parkinson disease. 2011 Annual Assembly of the American Academy of Physical Medicine and Rehabilitation2011; Vol. 3, issue 10:S163-4.
- Hagell, P., & Nygren, C. (2007). The 39 item parkinson's disease questionnaire (PDQ-39) revisited: Implications for evidence based medicine. *Journal of Neurology, Neurosurgery & Psychiatry*, 78(11), 1191-1198. doi:10.1136/jnnp.2006.111161

- Hagell, P., & Nilsson, M. H. (2009). *The 39-item parkinson's disease questionnaire (PDQ-39): Is it a unidimensional construct?* doi:10.1177/1756285609103726
- Hagell, P., Whalley, D., McKenna, S. P., & Lindvall, O. (2003). Health status measurement in parkinson's disease: Validity of the PDQ-39 and nottingham health profile. *Movement Disorders*, 18(7), 773-783. doi:10.1002/mds.10438
- Hariz M. My 25 Stimulating Years with DBS in Parkinson's Disease. *J Parkinsons Dis*. 2017;7(s1):S33–S41. doi:10.3233/JPD-179007
- Hass, C.J., Bishop, M., Moscovich, M., Stegemöller, E. L.,..... Okun, M. S. (2014). *Defining the clinically meaningful difference in gait speed in persons with parkinsons disease*. *Journal of Neurologic Physical Therapy*, 38 (4), 233-238. doi: 10.1097/NPT.0000000000000055
- Hayes, A. F. (2009). Beyond baron and kenny: Statistical mediation analysis in the new millennium. *Communication Monographs*, 76(4), 408-420. doi:10.1080/03637750903310360
- He, W., Goodkind, D., and Kowal, P. (2016) U.S. Census Bureau, International Population Reports, P95/16-1, An Aging World: 2015, U.S. Government Publishing Office, Washington, DC, 2016.
- Heremans, E., Nieuwboer, A., & Vercruyse, S. (2013). Freezing of gait in parkinson's disease: Where are we now? *Current Neurology and Neuroscience Reports*, 13(6), 1-9. doi:10.1007/s11910-013-0350-7
- Herlofson, K., & Kluger, B. M. (2017). Fatigue in parkinson's disease. *Journal of the Neurological Sciences*, 374, 38-41. doi:10.1016/j.jns.2016.12.061
- Hirsch, M. A., Erwin E H van, Wegen, Newman, M. A., & Heyn, P. C. (2018). Exercise-induced increase in brain-derived neurotrophic factor in human parkinson's disease: A systematic review and meta-analysis. *Translational Neurodegeneration*, 7(1), 1-12. doi:10.1186/s40035-018-0112-1
- Hirsch, M. A., Iyer, S. S., & Sanjak, M. (2016). Exercise-induced neuroplasticity in human parkinson's disease: What is the evidence telling us? *Parkinsonism and Related Disorders*, 22, S78-S81. doi:10.1016/j.parkreldis.2015.09.030
- Hoehn, M., & Yahr, M. (2011). Parkinsonism: Onset, progression, and mortality. *Neurology*, 77(9), 874. doi:10.1212/01.wnl.0000405146.06300.91

- Horak, F. B., Mancini, M., Carlson-Kuhta, P., Nutt, J. G., & Salarian, A. (2016). Balance and gait represent independent domains of mobility in parkinson disease. *Physical Therapy*, 96(9), 1364-1371. doi:10.2522/ptj.20150580
- Horváth, K., Aschermann, Z., Ács, P., Deli, G., Janszky, J., Komoly, S., . . . Kovács, N. (2015). Minimal clinically important difference on the motor examination part of MDS-UPDRS. *Parkinsonism and Related Disorders*, 21(12), 1421-1426. doi:10.1016/j.parkreldis.2015.10.006
- Isaacson, S., O'Brien, A., Lazaro, J. D., Ray, A., & Fluet, G. (2018). The JFK BIG study: the impact of LSVT BIG® on dual task walking and mobility in persons with Parkinson's disease. *Journal of physical therapy science*, 30(4), 636–641. <https://doi-org.uri.idm.oclc.org/10.1589/jpts.30.636>
- Jankovic, J. (2008). *Parkinson's disease: Clinical features and diagnosis* doi:10.1136/jnnp.2007.131045
- Janssens, J., Malfroid, K., Nyffeler, T., Bohlhalter, S., & Vanbellinghen, T. (2014). Application of LSVT BIG intervention to address gait, balance, bed mobility, and dexterity in people with parkinson disease: A case series. *Physical Therapy*, 94(7), 1014. doi:10.2522/ptj.20130232
- Jenkinson, Fitzpatrick, Peto, Greenhall, & Hyman. (1997). The Parkinson's Disease Questionnaire (PDQ-39): Development and validation of a Parkinson's disease summary index score. *Age and Ageing*, 26(5), 353-357.
- Jenkinson, C., Heffernan, C., Doll, H., & Fitzpatrick, R. (2006). The parkinsons disease questionnaire (PDQ-39): Evidence for a method of imputing missing data. *Age and Ageing*, 35(5), 497-502. doi:10.1093/ageing/af1055
- Johnston, B. (2018). Overview of exercise. Merck Sharp & Dohme, issuing body. (2013). *Merck manual (professional version)* (Professional version.. ed.). Whitehouse Station, N.J., U.S.A.: Merck Sharp & Dohme Corp; Merck Sharp & Dohme Corp. Retrieved online from <https://www.merckmanuals.com/professional/special-subjects/exercise/overview-of-exercise>
- Kahn, E., D'Haese, P., Dawant, B., Allen, L., Kao, C., Charles, P. D., & Konrad, P. (2012). Deep brain stimulation in early stage parkinson's disease: Operative experience from a prospective randomised clinical trial. *Journal of Neurology, Neurosurgery, and Psychiatry*, 83(2), 164. doi:10.1136/jnnp-2011-300008

- Kandel, E. R., Schwartz, James H (James Harris), & Jessell, T. M. (2013). *Principles of neural science* (Fifth edition.. ed.). New York: McGraw-Hill, Health Professions Division.
- Katzenschlager, R. (2014). Parkinson's disease: Recent advances. *Journal of Neurology; Official Journal of the European Neurological Society*, 261(5), 1031-1036. doi:10.1007/s00415-014-7308-9
- Kayes, N. M., Schluter, P. J., Mcpherson, K. M., Taylor, D., & Kolt, G. S. (2009). The physical activity and disability survey — revised (PADS-R): An evaluation of a measure of physical activity in people with chronic neurological conditions. *Clinical Rehabilitation*, 23(6), 534-543. doi:10.1177/0269215508101750
- Kegelmeyer, D. (2014). Parkinson EDGE Task Force Recommendations: By Disease Stage (Clinical Recommendations). Retrieved from http://www.neuropt.org/docs/default-source/parkinson-edge/pdedge-all-documents-combined.pdf?sfvrsn=bccd4f43_2
- Kessler, D., & Liddy, C. (2017). Self-management support programs for persons with parkinson's disease: An integrative review. *Patient Education and Counseling*, 100(10), 1787-1795. doi:10.1016/j.pec.2017.04.011
- Keus, S. H. J., Bloem, B. R., Hendriks, E. J. M., Bredero-Cohen, A., & Munneke, M. (2007). Evidence-based analysis of physical therapy in parkinson's disease with recommendations for practice and research. *Movement Disorders : Official Journal of the Movement Disorder Society*, 22(4), 451. doi:10.1002/mds.21244
- Khundrakpam, B. S., Reid, A., Brauer, J., Carbonell, F., Lewis, J., Ameis, S., . . . Evans, A. C. (2013). Developmental changes in organization of structural brain networks. *Cerebral Cortex*, 23(9), 2072-2085. doi:10.1093/cercor/bhs187
- Kim, S. D., Allen, N. E., Canning, C. G., & Fung, V. S. C. (2018). Parkinson disease. *Handbook of Clinical Neurology*, 159, 173. doi:10.1016/B978-0-444-63916-5.00011-2
- Kim, J., Kim, Y., & Kumar, V. (2019). Heavy metal toxicity: An update of chelating therapeutic strategies. *Journal of Trace Elements in Medicine and Biology*, 54, 226-231. doi:10.1016/j.jtemb.2019.05.003
- King, L. A., Salarian, A., Mancini, M., Priest, K. C., Nutt, J., Serdar, A., . . . Horak, F. B. (2013). Exploring outcome measures for exercise intervention in people with parkinson's disease.2013 doi:10.1155/2013/572134

- King, A., L., Wilhelm, B., J., Chen, B., Y., Blehm, B., R., Nutt, B., J., Chen, B., Z., . . . Horak, B., F. (2015). Effects of group, individual, and home exercise in persons with parkinson disease: A randomized clinical trial. *Journal of Neurologic Physical Therapy*, 39(4), 204-212. doi:10.1097/NPT.0000000000000101
- Kingsbury, A. E., Bandopadhyay, R., Silveira-Moriyama, L., Ayling, H., Kallis, C., Sterlacci, W., . . . Lees, A. J. (2010). Brain stem pathology in parkinson's disease: An evaluation of the braak staging model. *Movement Disorders*, 25(15), 2508-2515. doi:10.1002/mds.23305
- Kleim, J. A., & Jones, T. A. (2008). Principles of experience-dependent neural plasticity: Implications for rehabilitation after brain damage. *Journal of Speech, Language, and Hearing Research : JSLHR*, 51(1), 225. doi:10.1044/1092-4388(2008/018)
- Kriebel-Gasparro, A. (2016). Parkinson's disease: Update on medication management. *The Journal for Nurse Practitioners*, 12(3), e81-e89. doi:10.1016/j.nurpra.2015.10.020
- Leavy, B. Joseph, C., Löfgren, N., Johansson, H., Hagströmer, M., Franzén, E. (2020). *Outcome Evaluation of Highly Challenging Balance Training for People With Parkinson Disease: A Multicenter Effectiveness-Implementation Study*. *Journal of Neurologic Physical Therapy Journal of Neurologic Physical Therapy*. 44, 15–22 doi: 10.1097/NPT.0000000000000298
- Leddy, A. L., Crouner, B. E., & Earhart, G. M. (2011). Utility of the Mini-BESTest, BESTest, and BESTest sections for balance assessments in individuals with Parkinson disease. *Journal of neurologic physical therapy : JNPT*, 35(2), 90–97. <https://doi.org/10.1097/NPT.0b013e31821a620c>
- Lessig, S., Nie, D., Xu, R., & Corey-Bloom, J. (2012). Changes on brief cognitive instruments over time in parkinson's disease. *Movement Disorders*, 27(9), 1125-1128. doi:10.1002/mds.25070
- Lindholm, B., Nilsson, M., Hansson, O., & Hagell, P. (2018). The clinical significance of 10-m walk test standardizations in parkinson's disease. *Journal of Neurology*, 265(8), 1829-1835. doi:10.1007/s00415-018-8921-9
- Little, S., & Brown, P. (2014). Focusing brain therapeutic interventions in space and time for parkinson's disease. *Current Biology*, 24(18), R898-R909. doi:10.1016/j.cub.2014.08.002
- Little, R. J., & Rubin, D. B. (2002). Statistical analysis with missing data. New York, NY: John Wiley & Sons.

- Mahler, Leslie A.; Ramig, Lorraine O.; Fox, Cynthia (2015). Evidence-based treatment of voice and speech disorders in Parkinson disease. *Current opinion in Otolaryngology & Head and Neck Surgery*. 23(3):209-215 www.cotolaryngology.com
- Marchand, W. R., Lee, J. N., Suchy, Y., Garn, C., Johnson, S., Wood, N., & Chelune, G. (2011). Age-related changes of the functional architecture of the cortico-basal ganglia circuitry during motor task execution. *NeuroImage*, 55(1), 194-203. doi:10.1016/j.neuroimage.2010.12.030
- Marigold, Daniel S., Janice J. Eng, Andrew S. Dawson, J. Timothy Inglis, Jocelyn E. Harris, and Sif Gylfadóttir. "Exercise Leads to Faster Postural Reflexes, Improved Balance and Mobility, and Fewer Falls in Older Persons with Chronic Stroke." *Journal of the American Geriatrics Society* 53, no. 3 (2005): 416-23
- Marras C, Lang A. Parkinson's disease subtypes: lost in translation? *Journal of Neurology, Neurosurgery & Psychiatry* (2013);**84**:409-415
- Martin, John. *Neuroanatomy Text and Atlas, Fourth Edition*. US: McGraw-Hill Medical, 2012.
- Martinez-Martin, P., Skorvanek, M., Rojo-Abuin, J. M., Gregova, Z., Stebbins, G. T., & Goetz, C. G. (2018). Validation study of the hoehn and yahr scale included in the MDS-UPDRS. *Movement Disorders*, 33(4), 651-652. doi:10.1002/mds.27242
- Marusiak, J., Żeligowska, E., Mencel, J., Kisiel-Sajewicz, K., Majerczak, J., Zoladz, J. A., . . . Jaskólska, A. (2015). Interval training-induced alleviation of rigidity and hypertonia in patients with parkinson's disease is accompanied by increased basal serum brain-derived neurotrophic factor. *Journal of Rehabilitation Medicine*, 47(4), 372. doi:10.2340/16501977-1931
- Mcdonnell, M. N., Rischbieth, B., Schammer, T. T., Seaforth, C., Shaw, A. J., & Phillips, A. C. (2017). Lee silverman voice treatment (LSVT)-BIG to improve motor function in people with parkinson's disease: A systematic review and meta-analysis. *Clinical Rehabilitation*, , 269215517734385. doi:10.1177/0269215517734385
- Merck Sharp & Dohme, issuing body. (2013). *Merck manual (professional version)* (Professional version.. ed.). Whitehouse Station, N.J., U.S.A.: Merck Sharp & Dohme Corp; Merck Sharp & Dohme Corp.
- Metcalfé, V., Egan, M., & Sauvé-Schenk, K. (2019). LSVT BIG in late stroke rehabilitation: A single-case experimental design study. *Canadian Journal of Occupational Therapy*, 86(2), 87-94. doi:10.1177/0008417419832951
- Michelle, W. V., Ruchika, S. P., Kirk, I. E., Basak, C., Chaddock, L., Jennifer, S. K., . . . Arthur, F. K. (2010). Plasticity of brain networks in a randomized intervention

trial of exercise training in older adults. *Frontiers in Aging Neuroscience*, 2doi:10.3389/fnagi.2010.00032

- Millage, B., Vesey, E., Finkelstein, M., & Anheluk, M. (2017). Effect on gait speed, balance, motor symptom rating, and quality of life in those with stage I parkinson's disease utilizing LSVT BIG. *Rehabilitation Research and Practice*, 2017doi:10.1155/2017/9871070
- Miller, M. D., Paradis, C. F., Houck, P. R., Mazumdar, S., Stack, J. A., Rifai, A. H., . . . Reynolds, C. F. (1992). Rating chronic medical illness burden in geropsychiatric practice and research: Application of the cumulative illness rating scale. *Psychiatry Research*, 41(3), 237-248. doi:10.1016/0165-1781(92)90005-N
- Mirza, S., Yazdani, U., Dewey III, R., Patel, N., Dewey, R. B., Miocinovic, S., & Chitnis, S. (2017). Comparison of globus pallidus interna and subthalamic nucleus in deep brain stimulation for parkinson disease: An institutional experience and review. *Parkinson's Disease*, 2017 doi:10.1155/2017/3410820
- Moe-Nilssen, R., Nordin, E., & Lundin-Olsson, L. (2008). Criteria for evaluation of measurement properties of clinical balance measures for use in fall prevention studies. *Journal of Evaluation in Clinical Practice*, 14(2), 236-240. doi:10.1111/j.1365-2753.2007.00839.x
- Monteiro-Junior, R., Cevada, T., Oliveira, B. R. R., Lattari, E., Portugal, E. M. M., Carvalho, A., & Deslandes, A. C. (2015). We need to move more: Neurobiological hypotheses of physical exercise as a treatment for parkinson's disease. *Medical Hypotheses*, 85(5), 537-541. doi:10.1016/j.mehy.2015.07.011
- Montero, I., & Le, O. G. (2007). A guide for naming research studies in psychology. *International Journal of Clinical and Health Psychology*, 7(3), 847-862
- Morris, S, Morris, M E, and Iansek, R. "Reliability of Measurements Obtained with the Timed "Up & Go" Test in People with Parkinson Disease." *Physical Therapy* 81, no. 2 (2001): 810-818.
- Murray, M.P., Drought, A.B., & Kory, R.C. (1964). Walking patterns of normal men. *Journal of Bone & Joint Surgery*, 46A, 335-360.
- Murray, M.P., Kory, R.C., & Sepic, S.B. (1970). Walking patterns of normal women. *Archives of Physical Medicine and Rehabilitation*, 51, 637-650.
- Muthén, B., & Asparouhov, T. (2018). Recent methods for the study of measurement invariance with many groups: Alignment and random effects. *Sociological Methods & Research*, 47(4), 637-664. doi:10.1177/0049124117701488

- Muthuraman, M., Koirala, N., Ciolac, D., Pinte, B., Glaser, M., Groppa, S., . . . Groppa, S. (2018). Deep brain stimulation and L-DOPA therapy: Concepts of action and clinical applications in parkinson's disease. *Frontiers in Neurology*, 9doi:10.3389/fneur.2018.00711
- Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., . . . Chertkow, H. (2005). The montreal cognitive assessment, MoCA: A brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society*, 53(4), 695-699. doi:10.1111/j.1532-5415.2005.53221.x
- Natalia, P. R., João Paulo, S. F., Paula, L. S., Izabela Guimarães Barbosa, Mariana Soares, d. S., Paulo, P. C., . . . Antonio, L. T. (2018). Circulating levels of neurotrophic factors are unchanged in patients with parkinson's disease. *Arquivos De Neuro-Psiquiatria*, 76(5), 310-315. doi:10.1590/0004-282x20180035
- Nieuwboer, A., De Weerd, W., Dom, R., Truyen, M., Janssens, L., & Kamsma, Y. (2001). The effect of a home physiotherapy program for persons with parkinson's disease. *Journal of Rehabilitation Medicine*, 33(6), 266. doi:10.1080/165019701753236455
- Nieuwboer, A., & Giladi, N. (2013). *Characterizing freezing of gait in parkinson's disease: Models of an episodic phenomenon*doi:10.1002/mds.25683
- Nijkrake, M. J., Keus, S. H. J., Kalf, J. G., Sturkenboom, I. H. W. M., Munneke, M., Kappelle, A. C., & Bloem, B. R. (2007). Allied health care interventions and complementary therapies in parkinson's disease. *Parkinsonism and Related Disorders*, 13(3), S488-S494. doi:10.1016/S1353-8020(08)70054-3
- Nilsson, M. H., Bladh, S., & Hagell, P. (2013). Fatigue in parkinson's disease: Measurement properties of a generic and a condition-specific rating scale. *Journal of Pain and Symptom Management*, 46(5), 737-746. doi:10.1016/j.jpainsymman.2012.11.004
- Nisenzon, A. N., Robinson, M. E., Bowers, D., Banou, E., Malaty, I., & Okun, M. S. (2011). Measurement of patient-centered outcomes in parkinson's disease: What do patients really want from their treatment? *Parkinsonism and Related Disorders*, 17(2), 89-94. doi:10.1016/j.parkreldis.2010.09.005
- Nosko, D., Ferraye, M. U., Fraix, V., Goetz, L., Chabardès, S., Pollak, P., & Debû, B. (2015). *Low-frequency versus high-frequency stimulation of the pedunculopontine nucleus area in parkinson's disease: A randomised controlled trial* doi:10.1136/jnp-2013-307511

- Nutt, J. G., Siderowf, A. D., Guttman, M., Schmidt, P. N., Zamudio, J. I., Wu, S. S., . . . Nelson, E. C. (2014). Mobility, mood and site of care impact health related quality of life in parkinson's disease. *Parkinsonism and Related Disorders*, 20(3), 274-279. doi:10.1016/j.parkreldis.2013.10.004
- Ogih, O., Eisenstein, A., Kwasny, M., & Simuni, T. (2014). Back to the basics: Regular exercise matters in parkinson's disease: Results from the national parkinson foundation QII registry study. *Parkinsonism and Related Disorders*, 20(11), 1221-1225. doi:10.1016/j.parkreldis.2014.09.008
- Organization, W. H. (2010). In Üstün T. B. (Ed.), *Measuring health and disability manual for WHO disability assessment schedule WHODAS 2.0*. Geneva: World Health Organization. Retrieved from <https://www.who.int/whr/2000/en/>
- Parkinson's Foundation Economic Burden Study (2019); <https://www.parkinson.org/blog/research/economic-burden-study>; accessed 12/28/19
- Parkinson, J. (1817). An essay on the shaking palsy. London, Whittingham, and Rowland for Sherwood, Neely, and Jones. <https://archive.org/details/essayonshakingpa00parkuoft> (viewed Dec 2017).
- Pedrosa, D. J., & Timmermann, L. (2013). Review: Management of parkinson's disease. *Neuropsychiatric Disease and Treatment*, 9, 321. doi:10.2147/NDT.S32302
- Perera, S., Mody, S. H., Woodman, R. C., & Studenski, S. A. (2006). Meaningful change and responsiveness in common physical performance measures in older adults. *Journal of the American Geriatrics Society*, 54(5), 743-749. doi:10.1111/j.1532-5415.2006.00701.x
- Perry, S. I. B., Nelissen, P. M., Siemonsma, P., & Lucas, C. (2019). The effect of functional-task training on activities of daily living for people with parkinson's disease, a systematic review with meta-analysis. *Complementary Therapies in Medicine*, 42, 312-321. doi:10.1016/j.ctim.2018.12.008
- Petersen, A. M. W., & Pedersen, B. K. (2005). The anti-inflammatory effect of exercise. *Journal of Applied Physiology (Bethesda, Md.: 1985)*, 98(4), 1154. doi:10.1152/jappphysiol.00164.2004
- Peto, V., Jenkinson, C., & Fitzpatrick, R. (1998). PDQ-39: A review of the development, validation and application of a parkinson's disease quality of life questionnaire and its associated measures. *Journal of Neurology*, 245 Suppl 1, S10.

- Peto, V., Jenkinson, C., & Fitzpatrick, R. (2001). Determining minimally important differences for the PDQ-39 parkinson's disease questionnaire. *Age and Ageing*, 30(4), 299.
- Peto, V., Jenkinson, C., Fitzpatrick, R., & Greenhall, R. (1995). The development and validation of a short measure of functioning and well-being for individuals with parkinson's disease. *Quality of Life Research*, 4(3), 241-248. doi:10.1007/BF02260863
- Petrella, R. J., Payne, M., Myers, A., Overend, T., & Chesworth, B. (2000). Physical Function and Fear of Falling After Hip Fracture Rehabilitation in the Elderly. *American Journal of Physical Medicine & Rehabilitation*, 79(2), 154-160
- Petzinger, G. M., Fisher, B. E., Mcewen, S., Beeler, J. A., Walsh, J. P., & Jakowec, M. W. (2013). Exercise-enhanced neuroplasticity targeting motor and cognitive circuitry in parkinson's disease. *Lancet Neurology*, 12(7), 716-726. doi:10.1016/S1474-4422(13)70123-6
- Petzinger, G. M., Fisher, B. E., Van Leeuwen, J., Vukovic, M., Akopian, G., Meshul, C. K., . . . Jakowec, M. W. (2010). Enhancing neuroplasticity in the basal ganglia: The role of exercise in parkinson's disease. *Movement Disorders*, 25, S141-S145. doi:10.1002/mds.22782
- Podsiadlo, D., & Richardson, S. (1991). The timed "Up & go": A test of basic functional mobility for frail elderly persons. *Journal of the American Geriatrics Society*, 39(2), 142-148. doi:10.1111/j.1532-5415.1991.tb01616.x
- Postuma, R. B., Berg, D., Adler, C. H., Bloem, B. R., Chan, P., Deuschl, G., . . . Stern, M. (2016). The new definition and diagnostic criteria of parkinson's disease. *The Lancet Neurology*, 15(6), 546-548. doi:10.1016/S1474-4422(16)00116-2
- Postuma, R. B., Berg, D., Stern, M., Poewe, W., Olanow, C. W., Oertel, W., . . . Deuschl, G. (2015). *MDS clinical diagnostic criteria for parkinson's disease* doi:10.1002/mds.26424
- Powell, L. E., & Myers, A. M. (1995). The activities-specific balance confidence (ABC) scale. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 50A(1), M28. doi:10.1093/gerona/50A.1.M28
- Pringsheim, T., Jette, N., Frolkis, A., & Steeves, T. D. L. (2014). *The prevalence of parkinson's disease: A systematic review and meta-analysis* doi:10.1002/mds.25945

- Prodoehl, J., Rafferty, M. R., David, F. J., Poon, C., Vaillancourt, D. E., Comella, C. L., . . . Robichaud, J. A. (2015). Two-year exercise program improves physical function in parkinson's disease. *Neurorehabilitation and Neural Repair*, 29(2), 112-122. doi:10.1177/1545968314539732
- Qin, X., Zhang, S., Cao, C., Loh, Y. P., & Cheng, Y. (2016). Aberrations in peripheral inflammatory cytokine levels in parkinson disease: A systematic review and meta-analysis. *JAMA Neurology*, 73(11), 1316. doi:10.1001/jamaneurol.2016.2742
- Raad, J., Moore, J., Hamby, J., Rivadelo, R. L., & Straube, D. (2013). A brief review of the activities-specific balance confidence scale in older adults. *Archives of Physical Medicine and Rehabilitation*, 94(7), 1426-1427. doi:10.1016/j.apmr.2013.05.002
- Rafferty, R., M., Prodoehl, A., J., Robichaud, J., J., David, C., F., Poon, E., C., Goelz, M., L., . . . Corcos, M., D. (2017). Effects of 2 years of exercise on gait impairment in people with parkinson disease: The PRET-PD randomized trial. *Journal of Neurologic Physical Therapy*, 41(1), 21-30. doi:10.1097/NPT.0000000000000163
- Redecker, C., Bilsing, A., Csoti, I., Fogel, W., Ebersbach, G., Hauptmann, B., . . . Müngersdorf, M. (2014a). Physiotherapy in parkinson's disease patients: Recommendations for clinical practice. *Basal Ganglia*, 4(1), 35-38. doi:10.1016/j.baga.2014.03.001
- Redecker, C., Bilsing, A., Csoti, I., Fogel, W., Ebersbach, G., Hauptmann, B., . . . Müngersdorf, M. (2014b). Physiotherapy in parkinson's disease patients: Recommendations for clinical practice. *Basal Ganglia*, 4(1), 35-38. doi:10.1016/j.baga.2014.03.001
- Reeve A, Simcox E, Turnbull D. (2014). Ageing and Parkinson's disease: why is advancing age the biggest risk factor?. *Ageing Res Rev*. 2014;14(100):19–30. doi:10.1016/j.arr.2014.01.004
- Reuben, D. B., & Siu, A. L. (1990). An objective measure of physical function of elderly outpatients. *Journal of the American Geriatrics Society*, 38(10), 1105-1112. doi:10.1111/j.1532-5415.1990.tb01373.x
- Rhoda, D. A., Murray, D. M., Andridge, R. R., Pennell, M. L., & Hade, E. M. (2011). Studies with staggered starts: Multiple baseline designs and group-randomized trials. *American Journal of Public Health*, 101(11), 2164. doi:10.2105/AJPH.2011.300264

- Ridgel, A. L., Vitek, J. L., & Alberts, J. L. (2009). Forced, not voluntary, exercise improves motor function in parkinson's disease patients. *Neurorehabilitation and Neural Repair*, 23(6), 600-608. doi:10.1177/1545968308328726
- Rietdijk, C. D., Perez-Pardo, P., Garssen, J., van Wezel, R., J.A., & Kraneveld, A. D. (2017). Exploring braak's hypothesis of parkinson's disease. *Frontiers in Neurology*, 8, 37. doi:10.3389/fneur.2017.00037
- Rizzi, G., & Tan, K. R. (2017). Dopamine and acetylcholine, a circuit point of view in parkinson's disease. *Frontiers in Neural Circuits*, 11 doi:10.3389/fncir.2017.00110
- Rosenberg-Lee, M., Iuculano, T., Bae, S. R., Richardson, J., Qin, S., Jolles, D., & Menon, V. (2018). Short-term cognitive training recapitulates hippocampal functional changes associated with one year of longitudinal skill development. *Trends in Neuroscience and Education*, 10, 19-29. 10.1016/j.tine.2017.12.001
- Roush, S. E., & Sharby, N. (2011). Disability reconsidered: The paradox of physical therapy. *Physical Therapy*, 91(12), 1715. 10.2522/ptj.20100389
- Sack, I., Beierbach, B., Wuerfel, J., Klatt, D., Hamhaber, U., Papazoglou, S., . . . Braun, J. (2009). The impact of aging and gender on brain viscoelasticity. *NeuroImage*, 46(3), 652-657. doi:10.1016/j.neuroimage.2009.02.040
- Sanchez-Guajardo, V., Tentillier, N., & Romero-Ramos, M. (2015). The relation between α -synuclein and microglia in parkinson's disease: Recent developments. *Neuroscience*, 302, 47-58. doi:10.1016/j.neuroscience.2015.02.008
- Saenger, V. M., Kahan, J., Foltynie, T., Friston, K., Aziz, T. Z., Green, A. L., . . . Deco, G. (2017). Uncovering the underlying mechanisms and whole-brain dynamics of deep brain stimulation for parkinson's disease. *Scientific Reports*, 7(1), 1-14. doi:10.1038/s41598-017-10003-y
- Sapir, S., Ramig, L., Ebersbach, G., & Fox, C. (2012). LSVT LOUD and LSVT BIG: Behavioral treatment programs for speech and body movement in parkinson disease. *Parkinson's Disease*, 2012 doi:10.1155/2012/391946
- Scalzo, P., Kümmer, A., Bretas, T., Cardoso, F., & Teixeira, A. (2010). Serum levels of brain-derived neurotrophic factor correlate with motor impairment in parkinson's disease. *Journal of Neurology*, 257(4), 540-545. doi:10.1007/s00415-009-5357-2

- Schenkman, M., & Butler, R. B. (1989). A model for multisystem evaluation treatment of individuals with parkinson's disease. *Physical Therapy*, 69(11), 932. doi:10.1093/ptj/69.11.932
- Schenkman, M., Salay, J., Scherer, N., & Kohrt, W. (2004). Walking economy in patients with mild to moderate parkinsons disease. *Journal of Neurologic Physical Therapy*, 28(4), 172-173. doi:10.1097/01253086-200412000-00015
- Schenkman, M., Hall, D. A., Barón, A., E., Schwartz, R. S., Mettler, P., & Kohrt, W. M. (2012). Exercise for people in early- or mid-stage parkinson disease: A 16-month randomized controlled trial. *Physical Therapy*, 92(11), 1395. doi:10.2522/ptj.20110472
- Schenkman, M., Moore, C. G., Kohrt, W. M., Hall, D. A., Delitto, A., Comella, C. L., . . . Corcos, D. M. (2018). Effect of high-intensity treadmill exercise on motor symptoms in patients with de novo parkinson disease: A phase 2 randomized clinical trial. *JAMA Neurology*, 75(2), 219. doi:10.1001/jamaneurol.2017.3517
- Schlenstedt, C., Paschen, S., Kruse, A., Raethjen, J., Weisser, B., & Günther Deuschl. (2015). Resistance versus balance training to improve postural control in parkinson's disease: A randomized rater blinded controlled study. *PLoS ONE*, 10(10), e0140584. doi:10.1371/journal.pone.0140584
- Schrag, A., Jahanshahi, M., & Quinn, N. (2000). How does parkinson's disease affect quality of life? A comparison with quality of life in the general population. *Movement Disorders : Official Journal of the Movement Disorder Society*, 15(6), 1112. doi:AID-MDS1003>3.0.CO;2-A
- Schrag, A., Barone, P., Brown, R. G., Leentjens, A. F. G., Mcdonald, W. M., Starkstein, S., . . . Goetz, C. G. (2007). Depression rating scales in parkinson's disease: Critique and recommendations. *Movement Disorders*, 22(8), 1077-1092. doi:10.1002/mds.21333
- Schrag, A., Dodel, R., Spottke, A., Bornschein, B., Siebert, U., & Quinn, N. P. (2007). Rate of clinical progression in parkinson's disease. A prospective study. *Movement Disorders*, 22(7), 938-945. doi:10.1002/mds.21429
- Sehm, B., Taubert, M., Conde, V., Weise, D., Classen, J., Dukart, J., . . . Ragert, P. (2014). Structural brain plasticity in parkinson's disease induced by balance training. *Neurobiology of Aging*, 35(1), 232-239. doi:10.1016/j.neurobiolaging.2013.06.021

- Seppi, K., Weintraub, D., Coelho, M., Perez-Lloret, S., Fox, S. H., Katzenschlager, R., . . . Sampaio, C. (2011). The movement disorder society Evidence-Based medicine review update: Treatments for the non-motor symptoms of parkinson's disease. *Movement Disorders*, 26, S42-S80. doi:10.1002/mds.23884
- Shults, C. W. (2006). Lewy bodies. *Proceedings of the National Academy of Sciences of the United States of America*, 103(6), 1661. doi:10.1073/pnas.0509567103
- Sjödahl Hammarlund, C., Nilsson, M., & Hagell, P. (2012). Measuring outcomes in parkinson's disease: A multi-perspective concept mapping study. *Quality of Life Research*, 21(3), 453-463. doi:10.1007/s11136-011-9995-3
- Smets, E. M. A., Garssen, B., Bonke, B., & De Haes, J. C. J. M. (1995). The multidimensional fatigue inventory (MFI) psychometric qualities of an instrument to assess fatigue. *Journal of Psychosomatic Research*, 39(3), 315-325. doi:10.1016/0022-3999(94)00125-O
- Smith, B., Dalen, J., Wiggins, K., Tooley, E., Christopher, P., & Bernard, J. (2008). The brief resilience scale: Assessing the ability to bounce back. *International Journal of Behavioral Medicine*, 15(3), 194-200. doi:10.1080/10705500802222972
- Song, J., Paul, S. S., Caetano, M. J. D., Smith, S., Dibble, L. E., Love, R., . . . Allen, N. E. (2018a). Home-based step training using videogame technology in people with parkinson's disease: A single-blinded randomised controlled trial. *Clinical Rehabilitation*, 32(3), 299. doi:10.1177/0269215517721593
- Song, J., Paul, S. S., Caetano, M. J. D., Smith, S., Dibble, L. E., Love, R., . . . Allen, N. E. (2018b). Home-based step training using videogame technology in people with parkinson's disease: A single-blinded randomised controlled trial. *Clinical Rehabilitation*, 32(3), 299. doi:10.1177/0269215517721593
- Sowell, E. R., Thompson, P. M., & Toga, A. W. (2004). Mapping changes in the human cortex throughout the span of life. *Neuroscientist*, 10(4), 372-392. doi:10.1177/1073858404263960
- Speelman, A. D., van Nimwegen, M., Bloem, B. R., & Munneke, M. (2014). Evaluation of implementation of the ParkFit program: A multifaceted intervention aimed to promote physical activity in patients with parkinson's disease. *Physiotherapy*, 100(2), 134-141. doi:10.1016/j.physio.2013.05.003

- Spillantini, M. G., Schmidt, M. L., Lee, V. M., Trojanowski, J. Q., Jakes, R., & Goedert, M. (1997). Alpha-synuclein in lewy bodies. *Nature*, 388(6645), 839. doi:10.1038/42166
- 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
- Steffen, T., & Seney, M. (2008). Test-retest reliability and minimal detectable change on balance and ambulation tests, the 36-item short-form health survey, and the unified parkinson disease rating scale in people with parkinsonism. *Physical Therapy*, 88(6), 733. doi:10.2522/ptj.20070214
- Stewart, K. C., Fernandez, H. H., Okun, M. S., Jacobson, C. E., & Hass, C. J. (2008). Distribution of motor impairment influences quality of life in parkinson's disease. *Movement Disorders*, 23(10), 1466-1468. doi:10.1002/mds.22162
- Studenski, S., Perera, S., Wallace, D., Chandler, J. M., Duncan, P. W., Rooney, E., . . . Guralnik, J. M. (2003). Physical performance measures in the clinical setting. *Journal of the American Geriatrics Society*, 51(3), 314-322. doi:10.1046/j.1532-5415.2003.51104.x
- Summa, S., Basteris, A., Betti, E., & Sanguineti, V. (2015). Adaptive training with full-body movements to reduce bradykinesia in persons with parkinson's disease: A pilot study. *Journal of NeuroEngineering and Rehabilitation*, 12 doi:10.1186/s12984-015-0009-5
- Supekar, K., Iuculano, T., Chen, L., & Menon, V. (2015). Remediation of childhood math anxiety and associated neural circuits through cognitive tutoring. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, 35(36), 12574. 10.1523/JNEUROSCI.0786-15.2015
- Tan, D., Danoudis, M., Mcginley, J., & Morris, M. E. (2012). Relationships between motor aspects of gait impairments and activity limitations in people with parkinson's disease: A systematic review. *Parkinsonism and Related Disorders*, 18(2), 117-124. doi:10.1016/j.parkreldis.2011.07.014
- Tau, G. Z., & Peterson, B. S. (2010). Normal development of brain circuits. *Neuropsychopharmacology*, 35(1), 147-168. doi:10.1038/npp.2009.115
- Tomlinson, C. L., Herd, C. P., Clarke, C. E., Meek, C., Patel, S., Stowe, R., . . . Ives, N. (2001). Physiotherapy for parkinson's disease: A comparison of

techniques. *Cochrane Movement Disorders Group*, (1)
doi:10.1002/14651858.CD002815.pub2

- Tomlinson, C. L., Patel, S., Meek, C., Clarke, C. E., Stowe, R., Shah, L., . . . Ives, N. (2012). Physiotherapy versus placebo or no intervention in parkinson's disease. *The Cochrane Database of Systematic Reviews*, (8), CD002817. doi:10.1002/14651858.CD002817.pub3
- Tomlinson, C. L., Stowe, R., Patel, S., Rick, C., Gray, R., & Clarke, C. E. (2010). Systematic review of levodopa dose equivalency reporting in parkinson's disease. *Movement Disorders*, 25(15), 2649-2653. doi:10.1002/mds.23429
- Toodayan, Nadeem (2018). "James Parkinson's Essay on the Shaking Palsy, 1817–2017." *Medical Journal of Australia* 208.9: 384-86. Web.
- Trail, M., Protas, E. J., & Lai, E. C. (2008). *Neurorehabilitation in parkinson's disease : An evidence-based treatment model*. Thorofare, N.J.: SLACK Inc.
- Ueno, T., Sasaki, M., Nishijima, H., Funamizu, Y., Kon, T., Haga, R., . . . Tomiyama, M. (2017). LSVT-BIG improves UPDRS III scores at 4 weeks in parkinson's disease patients with wearing off: A prospective, open-label study. *Parkinson's Disease*, 2017doi:10.1155/2017/8130140
- Uhrbrand, A., Stenager, E., Pedersen, M. S., & Dalgas, U. (2015). Parkinson's disease and intensive exercise therapy – a systematic review and meta-analysis of randomized controlled trials. *Journal of the Neurological Sciences*, 353(1-2), 9-19. doi:10.1016/j.jns.2015.04.004
- van Der Hoek, T.,C., Bus, B. A. A., Matui, P., van Der Marck, M.,A., Esselink, R. A., & Tendolkar, I. (2011). Prevalence of depression in parkinson's disease: Effects of disease stage, motor subtype and gender. *Journal of the Neurological Sciences*, 310(1-2), 220-224. doi:10.1016/j.jns.2011.07.007
- van Nimwegen, M., Speelman, A. D., Overeem, S., van de Warrenburg, B.,P., Smulders, K., Dontje, M. L., . . . Munneke, M. (2013). Promotion of physical activity and fitness in sedentary patients with parkinson's disease: Randomised controlled trial. *BMJ (Clinical Research Ed.)*, 346(7898), f576. doi:10.1136/bmj.f576
- van Uem, Janet M. T., Marinus, J., Canning, C., van Lummel, R., Dodel, R., Liepelt-Scarfone, I., . . . Maetzler, W. (2016). Health-related quality of life in patients with parkinson's disease—A systematic review based on the ICF

- model. *Neuroscience and Biobehavioral Reviews*, 61, 26-34.
doi:10.1016/j.neubiorev.2015.11.014
- van, D. K., van Nimwegen, M., Speelman, A. D., Munneke, M., Backx, F. J. G., Donders, R., . . . Bloem, B. R. (2014). *A personalized coaching program increases outdoor activities and physical fitness in sedentary parkinson patients; a post-hoc analysis of the ParkFit trial* doi:10.1016/j.parkreldis.2014.10.004
- Ventriglia, M., Zanardini, R., Bonomini, C., Zanetti, O., Volpe, D., Pasqualetti, P., . . . Bocchio-Chiavetto, L. (2013). Serum brain-derived neurotrophic factor levels in different neurological diseases. *BioMed Research International*, 2013 doi:10.1155/2013/901082
- Vercruysse, S., Devos, H., Munks, L., Spildooren, J., Vandenbossche, J., Vandenberghe, W., . . . Heremans, E. (2012). Explaining freezing of gait in parkinson's disease: Motor and cognitive determinants. *Movement Disorders*, 27(13), 1644-1651. doi:10.1002/mds.25183
- Visser, M., Marinus, J., Van Hilten, J. J., Schipper, R. G. B., & Stiggelbout, A. M. (2004). Assessing comorbidity in patients with parkinson's disease. *Movement Disorders*, 19(7), 824-828. doi:10.1002/mds.20060
- Voss, M. W., Erickson, K. I., Prakash, R. S., Chaddock, L., Kim, J. S., Alves, H., . . . Kramer, A. F. (2013). Neurobiological markers of exercise-related brain plasticity in older adults. *Brain Behavior and Immunity*, 28, 90-99. doi:10.1016/j.bbi.2012.10.021
- Voss, M. W., Vivar, C., Kramer, A. F., & van Praag, H. (2013). Bridging animal and human models of exercise-induced brain plasticity. *Trends in Cognitive Sciences*, 17(10), 525-544. doi:10.1016/j.tics.2013.08.001
- Warraich, Z., & Kleim, J. A. (2010). Neural plasticity: The biological substrate for neurorehabilitation. *Pm&r*, 2(12), S208-S219. doi:10.1016/j.pmrj.2010.10.016
- Weber, C., Schwieterman, M., Fier, K., Berni, J., Swartz, N., Phillips, R. S., & Reneker, J. C. (2016). Reliability and validity of the functional gait assessment: A systematic review. *Physical & Occupational Therapy in Geriatrics*, 34(1), 88-103. doi:10.3109/02703181.2015.1128509
- Wei, S. -, Eisenberg, D. P., Kohn, P. D., Kippenhan, J. S., Kolachana, B. S., Weinberger, D. R., & Berman, K. F. (2012). Brain-derived neurotrophic factor val 66 met polymorphism affects resting regional cerebral blood flow and

functional connectivity differentially in women versus men. *Journal of Neuroscience*, 32(20), 7074-7081. doi:10.1523/JNEUROSCI.5375-11.2012

Weiner, W. J., Shulman, L. M., & Lang, A. E. (2013). *Parkinson's disease: a complete guide for patients and families*. Third edition. Baltimore: The Johns Hopkins University Press.

Weingarten, C. P., Sundman, M. H., Hickey, P., & Chen, N. (2015). Neuroimaging of parkinson's disease: Expanding views. *Neuroscience and Biobehavioral Reviews*, 59, 16-52. doi:10.1016/j.neubiorev.2015.09.007

Wendel, N., Macpherson, C. E., Webber, K., Hendron, K., DeAngelis, T., Colon-Semenza, C., & Ellis, T. (2018). Accuracy of activity trackers in parkinson disease: Should we prescribe them? *Physical Therapy*, 98(8), 705-714. doi:10.1093/ptj/pzy054

Williams-Gray, C. H., & Worth, P. F. (2016). *Parkinson's disease* doi://doi-org.uri.idm.oclc.org/10.1016/j.mpmed.2016.06.001

Yahr, M. D., Duvoisin, R. C., Shear, M. J., Barrett, R. E., & Hoehn, M. M. (1969). Treatment of parkinsonism with levodopa. *Archives of Neurology*, 21(4), 343. doi:10.1001/archneur.1969.00480160015001

Yesavage, J. A., Brink, T. L., Rose, T. L., Lum, O., Huang, V., Adey, M., & Leirer, V. O. (1982). Development and validation of a geriatric depression screening scale: A preliminary report. *Journal of Psychiatric Research*, 17(1), 37-49. doi:10.1016/0022-3956(82)90033-4

Yuan, W., Treble-Barna, A., Sohlberg, M. M., Harn, B., & Wade, S. L. (2017). Changes in structural connectivity following a cognitive intervention in children with traumatic brain injury. *Neurorehabilitation and Neural Repair*, 31(2), 190-201. 10.1177/1545968316675430

Zadikoff, C., Fox, S. H., Tang-Wai, D. F., Thomsen, T., De Bie, Rob M. A., Wadia, P., . . . Marras, C. (2008). A comparison of the mini mental state exam to the montreal cognitive assessment in identifying cognitive deficits in parkinson's disease. *Movement Disorders*, 23(2), 297-299. doi:10.1002/mds.21837

Zigmond, M. J., & Smeyne, R. J. (2014). Exercise: Is it a neuroprotective and if so, how does it work? *Parkinsonism and Related Disorders*, 20, S123-S127. doi:10.1016/S1353-8020(13)70030-0

Zoladz, J. A., Majerczak, J., Zeligowska, E., Mencil, J., Jaskolski, A., Jaskolska, A., & Marusiak, J. (2014). Moderate-intensity interval training increases serum brain-derived neurotrophic factor level and decreases inflammation in parkinson's disease patients. *Journal of Physiology and Pharmacology : An Official Journal of the Polish Physiological Society*, 65(3), 441.