A NOVEL NEUROREHABILITATION MODEL DESIGNED TO EXAMINE THE NEURAL PLASTICITY INVOLVED IN PARKINSON'S DISEASE.

KAROLINA ANNA BEARSS

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ABSTRACT

Parkinson's disease (PD) is a progressive neurodegenerative disorder that that is most often characterised for its motor impairments. However, people with PD (PwPD) often experience a range of mental health and non-motor issues alongside their physical symptoms. Exercise has shown to positively impact and improve PD motor symptoms, less research observations have been shown in PD mental health and non-motor symptoms. Dance is a great form of exercise which provides both aerobic and anaerobic movements. Dance is constantly changing providing a creative outlet, dance provides flexibility and balance/coordination, develops social skills thereby improving mental health, and lastly dance with music combination allows this form of exercise to be unique in that it encompasses a multisensory component that exercise alone cannot provide. My dissertation aims to understand how dance impacts PD motor, non-motor symptoms and if the changes are associated to specific brain related alterations. Using behavioral, motor and EEG approaches, I will present three separate experiments to test the effects of dance on people with PD by first studying the potential impacts of dance on short-term behavioral changes in PwPD and their overall Quality of Life (QoL) after a 12-week dance intervention. Second I will present a novel examination of the interaction of dance on both behavioural measures and electroencephalography (EEG) activity before and after the short-term (1.25 hour) course of a single dance class. The third study is a novel examination of the interaction of dance on the progression of both behavioural measures and non-motor symptoms over the long-term course of participating in multiple dance classes over a 3-year period of time. Finally, EEG activity changes over the long-term course of participating in multiple dance classes over a 3-year period of time is presented. The results of these studies strengthen the idea

of dance being an alternative or additional therapy for PwPD and also provides putative neuroplastic changes in the diseased brain.

For Evan and our baby Bearss cubs.

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Now that the serious part is over, I’d like to complete my acknowledgements with a comical relief in which Dr. Liana Brown brought to my attention on the *Top 10 Reasons a Dissertation is Harder than Having a Baby* *(source: the internet)*:

1. Three months before your due date, your supervisor doesn't say, "I want you to go back and re-do the first trimester's work."
2. Unlike advisors, you can switch doctors without having to start over.
3. Conceiving a baby is WAY more fun than conceiving a topic.
4. You know exactly how long a pregnancy takes.
5. Friends and relatives don't question whether your baby will be “useful”.
6. You don't need to explain repeatedly to friends and family what it takes to make a baby and why you're not done yet.
7. Everyone will say your baby is cute and you'll believe them.
8. Babies don't require proper footnoting or adherence to a style manual.
9. If you’re having a baby, you can freely borrow other people's stuff and not be accused of plagiarism.
10. No one will complain if your baby is too similar to another one.
11. I would like to add my own here. On the baby’s delivery date, you do not have to schedule several individual Professors on a single day and time to be present for a defense. The baby comes when it wants, and we all just have to be there!

TABLE OF CONTENTS

ABSTRACT ii
DEDICATION iv
ACKNOWLEDGEMENTS v
TABLE OF CONTENTS vii
LIST OF TABLES x
LIST OF FIGURES xi
LIST OF ABBREVIATIONS xiii

CHAPTER ONE 1
GENERAL INTRODCTION 2

1.1 PARKINSON'S DISEASE DEFINED 3
1.1.1 Basal Ganglia Loops 4
1.1.2 Nigrostriatal Degeneration 7
1.1.3 L-Dopa and DBS Treatments 11
1.1.4 Exercise Treatments 11
1.1.5 Multisensory Dance Treatments 12
1.1.6 Other Forms of Exercise Treatments 16
1.2 DANCE INDUCED NEUROPLASTICITY 18
1.3 GENERAL OBJECTIVES 18

CHAPTER TWO 20
IMPROVEMENTS IN BALANCE AND GAIT SPEED AFTER A 12 WEEK DANCE INTERVENTION FOR PARKINSON'S DISEASE

2.1 ABSTRACT 21
2.2 INTRODUCTION 22
2.3 METHODS 23
2.3.1 Participants 23
2.3.2 Measures 24
2.3.3 Procedure 24
2.3.4 Design and Statistical Analysis 26
2.4 RESULTS 27
2.5 DISCUSSION 29
2.6 ACKNOWLEDGEMENTS 30

CHAPTER THREE 31
SINGLE DANCE CLASS EFFECTS ON PARKINSON'S DISEASE MOTOR, NON-MOTOR SYMPTOMS AND RESTING STATE ENCEPHALOGRAPHY (rsEEG).

3.1 INTRODUCTION 32
3.2 METHODS 36
3.2.1 Participants 36
3.2.2 Measures 37
3.2.3 Procedure 39
3.2.3.1 Motor Testing Protocol 40

3.2.3.2 Resting State EEG (rsEEG) Testing Protocol 41
3.2.4 Design and Statistical Analysis 46
3.3 RESULTS 47
3.3.1 Positive and Negative Affect 47
3.3.2 Behavioral 48
3.3.3 rsEEG Alpha 49
3.3.4 iAPP Correlations 57
3.4 DISCUSSION 57
3.4.1 Summary 57
3.4.2 Affect and Motor Improvements 59
3.4.3 Alpha Peak Frequency and Alpha Peak Power 62
3.4.4 Limitations and Future Directions 64
3.5 CONCLUSION 65

CHAPTER FOUR 66
PARKINSON'S DISEASE MOTOR SYMPTOM PROGRESSION SLOWED WITH MULTISENSORY DANCE LEARNING OVER 3-YEARS: A PRELIMINARY LONGITUDINAL INVESTIGATION.

4.1 ABSTRACT 67
4.2 INTRODUCTION 68
4.3 METHODS 71
4.3.1 Participants 71
4.3.2 Ethical Compliance Statement 75
4.3.3 Measures 75
4.3.4 Procedure 75
4.3.5 Analysis 76
4.3.6 Data Availability 76
4.4 RESULTS 76
4.5 DISCUSSION 79
4.6 CONCLUSION 84
4.7 ACKNOWLEDGEMENTS 85
4.8 LONGITUDINAL rsEEG & FUTURE DIRECTIONS 85

CHAPTER FIVE 88
GENERAL DISCUSSION

5.1 SUMMARY OF MAJOR FINDINGS 89
5.2 LIMITATIONS 94
5.3 FUTURE DIRECTIONS 96
5.4 CONCLUSIONS 97

REFERENCES 99
APPENDICES 124

APPENDIX A: Consent Forms 124
APPENDIX B: Dance Class Exercise Description 128
APPENDIX C: MDS-UPDRS 130
APPENDIX D: MDS-UPDRS Certificate – Karolina & MDS-UPDRS Permissions 181
APPENDIX E: PANAS-X 183
APPENDIX F: PD-NMS 185
APPENDIX G: MMSE 186
APPENDIX H: Medication Questionnaire 187
APPENDIX I: EPOC Channel Electrodes 191
APPENDIX J: Nature Partnered Journal – Parkinson's Disease Appeal (Open Science Initiative) 192

LIST OF TABLES

Table 1.1. Comparison of published studies on dancing and PD using UPDRS Part III as a measure.

Table 2.1. Sample exercises featured in the dance class at NBS.

Table 3.1. Demographic and clinical characteristics of our PD and HC.

Table 3.2. Outlier rejection at visual inspection of 2-second epochs for each group, time and condition.

Table 4.1. Characteristics of people with Parkinson's disease (PwPD) in the PD-Dancer and PD-Reference groups.

LIST OF FIGURES

Figure 1.1. Motor and Non-motor Loops of the BG.

Figure 1.2. Three cortico-BG pathways. Normal and abnormal functioning of direct, indirect and hyperdirect pathways in the BG.

Figure 2.1. BBS and TUG scores at Weeks 2 and 12.

Figure 2.2. Average Frequency of QoLS items.

Figure 3.1. PRE- and POST- dance testing protocol.

Figure 3.2. Single participants topographical disposition of components from Step 8 of visual preprocessing.

Figure 3.3. A two-second epoch within channels AF3 and AF4 containing a potential **A.** eye blink and **B.** eye movement.

Figure 3.4. Positive and negative affect changes over time.

Figure 3.5. MDS- UPDRS Part III motor scores.

Figure 3.6. Global iAPF between PD and HC.

Figure 3.7. Mean alpha frequency (Hz) for each electrode.

Figure 3.8. Global iAPP between PD and HC.

Figure 3.9. Time X Group X Condition alpha peak power.

Figure 3.10. Eyes closed head maps averaged across participants in both PD and HC groups.

Figure 3.11. Mean global asymmetric alpha power changes in PD and HC PRE to POST dance class.

Figure 3.12. Mean Left and Right hemispheric asymmetry alpha power changes in PD and HC.

Figure 3.13. Lateralized dance induced increases in frontal iAPP in both PD and HC groups.

Figure 4.1. Flow chart of enrolment.

Figure 4.2. Progression of Parkinson's Disease.

Figure 4.3. Total annual rate of motor score (UPDRS III) progression across all groups and studies discussed in the text.

Figure 4.8. Visual inspection of alpha peak power(μV^2) head maps for PD-Dancers.

Figure 5.1. Impact of dance on the brain in PwPD.

LIST OF ABBREVIATIONS

AMPA - α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

AT – Argentine Tango

BBS – Berg Balance Scale

BG – Basal Ganglia

BOLD – Blood Oxygen Level Dependent

CNS – Central Nervous System

DBS – Deep Brain Stimulation

DfPD®- Dancing for Parkinson's Disease

DMN - Default-Mode Network

DLS: Dorsolateral Stratum

DMS: Dorsomedial Striatum

EB –Eye Blink

ED – Executive Dysfunction

EM– Eye Movement

EC – Eyes Closed

EEG – Electroencephalography

EO – Eyes Open

ERP – Event-Related Potential

FFT – Fast Fourier Transformation

FUS – Focused Ultrasound

GPe – Globus Pallidus Externa

GPi – Globus Pallidus Interna

H&Y – Hoehn & Yahr Scale

HC – Healthy Controls

ICA: Independent Component Analysis

iAPF – Individual Alpha Peak Frequency

iAPP – Individual Alpha Peak Power

NBS – National Ballet School

PANAS-X – Positive and Negative Affect State

PD – Parkinson's Disease

PD-NMS- Parkinson's Disease Non-Motor Symptoms Scale

PwPD – People with Parkinson's Disease

QoL: Quality of Life

rsEEG – Resting State Electroencephalography

SNc – Substantia nigra pars compacta

SNr – Substantia nigra pars reticulate

STN – Subthalamic nucleus

TMS – Transcranial Magnetic Stimulation

TUG – Timed Up and Go

MDS-UPDRS – Movement Disorder Society Unified Parkinson's Disease Rating Scale

MMSE – Mini Mental State Exam

MRI – Magnetic Resonance Imaging

NAcc – Nucleus Accumbens

NMDA- *N*-methyl-D-aspartate

VP - Ventral Pallidum

VTA - Ventral Tegmental Area

CHAPTER ONE

GENERAL INTRODUCTION

Movement disorders are clinical syndromes that are exhibited as either an excess or paucity of voluntary or involuntary movement. Imagine trying to start your morning and having difficulty with initiating brushing your teeth. Walking your usual morning path into your bathroom and then all of a sudden feeling as if you are stuck in place midway through your doorway. Not being able to simply reach for your toothbrush because your movements are slow even though you are aware and wish to move faster. Or the fact that you have difficulty brushing your teeth with accuracy because of the tremor you experience with your hands or fingers, producing nothing but disappointment in yourself from not being able to complete a simple task such as brushing your teeth like you used to. Now imagine these frustrating motor struggles impacting every aspect of your life, your routine, your entire day-ultimately negatively impacting your quality of life. This is what individuals with Parkinson's disease experience. Now imagine being able to remove or decrease these motor impairments by simply adding dancing to your weekly or daily routine. The main focus of this thesis is how the brain has adapted to this physical multisensory training and putatively repairs the damage in motor circuits, and whether dance influences other cognitive domains like attention and memory and how affect and mood changes as a function of dance.

Engaging in any type of learned voluntary movement, like dance, involves multisensory brain networks that allow the production, execution and adjustment of action. In order to execute a successful movement, multiple intermediate steps are involved, such as observing action by an exemplar (i.e., choreographer and/or teacher); perceiving and understanding each individual movement; transforming the observed action from a third-person perspective into an embodied first-person motor representation; computing motor commands to prepare and execute the action; using sensory feedback to gauge successful execution; and adjusting or reinforcing preparatory

signals accordingly to reinforce motor learning of the action (Haith et al., 2016). However, motor skills (single or a sequence of actions, which become effortless through practice, can become difficult to learn, retrieve and execute when neurological conditions disrupt the planning and control of these sequential movements. Through a series of experiments, I will demonstrate how dance incorporates several of the above operations and how these operations impact physical, social and affective symptoms in people with Parkinson's disease (PD)-ultimately exploring how dance works and possibly repairs damage or reverses degeneration.

The upcoming sections provide a general background on the research that forms the basis of the experimental chapters that follow. I will begin by describing and defining Parkinson's disease. I will then explore the many treatments used to target the symptoms of Parkinson's disease, and how motor learning of dance, induces plasticity in these brain networks and connections. By reviewing the existing literature of the impacts of dance on the brain, I will introduce the reasoning behind studying dance as an alternate to the typical Parkinson's disease treatments which will lead to the formation of the specific objectives of this proposal.

1.1 PARKINSON'S DISEASE DEFINED

Parkinson's disease is a common hypokinetic movement disorder of the central nervous system (CNS) primarily associated with dysfunction of the basal ganglia (BG) and frontostriatal circuits (Tröster & Fields, 2008). This neurodegenerative disease is the most common movement disorder and the second most prevalent disease typically affecting individuals over 55 years of age. People with PD (PwPD) face a plethora of motor impairments, including difficulties with transfers (i.e. sitting to standing), walking, and balance (Earhart, 2009; de Dreau et al., 2012), postural instability, rest tremor, muscle rigidity, freezing of gait, and asymmetric bradykinesia (Earhart, 2009; Keus et al., 2007; Heiberger et al., 2011; Gershanik,

2012; George et al., 2013). PD symptoms often result in further immobility giving rise to many non-motor symptoms including osteoporosis, muscle weakness and/or cardiovascular disease, and may ultimately lead to social isolation, low self-esteem, and decreased quality of life (QofL) (Earhart, 2009; Keus et al., 2007; Heiberger et al., 2011). In addition, PwPD may also experience cognitive impairments (Gershanik, 2012; Graybiel, 2000; Hashimoto et al., 2015; Sandoval-Rincón et al., 2015) including deficits in working memory and attention (Tröster & Fields, 2008) early in the course of their illness (Bassett, 2005), along with major depressive disorder (Hashimoto et al., 2015).

1.1.1 Basal Ganglia Loops

The BG is comprised of a distributed group of subcortical nuclei: striatum (including the caudate nucleus and putamen of the dorsal striatum and the nucleus accumbens (NAcc) of the ventral striatum), substantia nigra (SN), globus pallidus (GP), ventral pallidum (VP), subthalamic nucleus (STN), and ventral tegmental area (VTA). BG neurocircuits are broadly divided into motor and non-motor loops that are modulated by dopamine, where the motor and oculomotor loops are involved in sensorimotor control, the dorsolateral prefrontal circuit controls associative and cognitive functions while the limbic loop controls motivated behavior, reinforcement, emotions and learning (see Figure 1.1). Seeing that the BG-thalamo-cortical loops are so widespread by expanding across multiple cortical areas, and that this loop modulates BG excitability through dopamine, one can understand the impact that this loop has on both the motor and non-motor aspects of behavior especially when there is dopamine depletion within these loops.

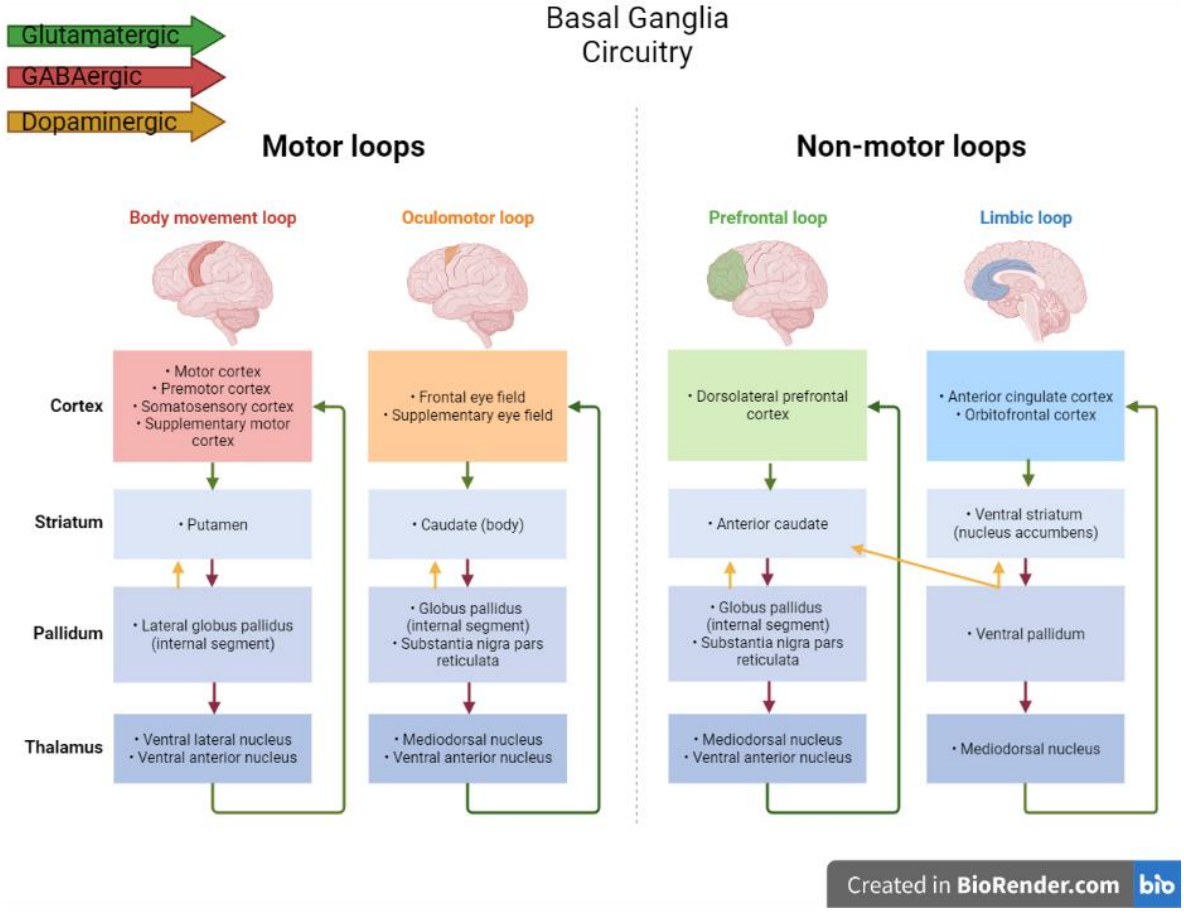

Figure 1.1. Motor and Non-motor Loops of the Basal Ganglia. BG circuits are divided into four functional loops: motor and oculomotor loops, associative/cognitive and limbic non-motor loops. Adapted from Purves et al., (2008) but recreated and structured in BioRender.com

Research has shown that anxiety and depression develop before any motor PD onset (Faivre et al., 2019) and depression affects 40-50% of PwPD (Reijnder et al., 2008). The limbic loop afferent projections include a wide range of cortical areas (including the orbitofrontal, anterior cingulate cortex and hippocampal formation) as well as subcortical structures [such as the ventral tegmental area (VTA) and amygdala] which project to the striatum including the NAcc (Figure 1.1). Within the NAcc these inputs are modulated by dopamine, and within this dopamine depletion is where some of the non-motor cardinal features of PD arise. In turn the NAcc projects onto the GPi/SN where the NAcc is under the modulatory influence of dopamine

(Lewis & Barker, 2009). A key structure for emotional processing in humans is the amygdala in fact this area along with the ventral striatum have been implicated as dysfunctional regions in mood disorders where the amygdala has been shown to be correlated with severity of depression (Remy et al., 2005). Post-mortem studies in PD have shown the PwPD have up to 20% reduction of amygdala volume and that this structure contains Lewy bodies (Harding et al., 2002) while also having reduced dopaminergic innervations (Moore, 2003). The amygdala connects with the anterior cingulate cortex, an area that is involved in many cognitive and emotional processes, in addition the anterior cingulate cortex receives strong dopaminergic innervations (Remy et al., 2005). In fact a PET study revealed the presence of hypometabolism, characterised by a decrease in brain glucose consumption and is a common feature in many neurodegenerative diseases (Zilberter & Zilberter, 2017), which was associated with depression in PwPD (Mentis et al., 2002).

Additionally, the BG is involved with the prefrontal association cortex, deemed the prefrontal loop (Figure 1.1), and plays a role in cognitive and executive functions. In fact, studies have shown that damage to the BG can produce many of the same cognitive impairments as would damage to the frontal cortex, ultimately both causing higher-order deficits (Leisman et al., 2013). PD patients exhibit executive dysfunction in symptoms of impaired working memory, planning, attention (Aarsland et al., 2011), impulse control (Leisman et al., 2013), and decreased speed of processing (Uc et al., 2005). Additionally, up to 36% of PD patients show evidence of cognitive impairment at disease onset (Foltynie et al., 2004) and cognitive symptoms are influenced by disease progression. Multiple epidemiological studies have revealed that PwPD develop dementia at 4-6 times the rate of normal aging (Aarsland et al., 2005; Hobson & Meara, 2004), and a longitudinal study of idiopathic PD, cognitive dysfunction developed much higher

than normal aging over the course of the disease and are associated with a shorter duration for dementia development (Williams-Gray et al., 2007).

The BG body movement loop includes skeletomotor circuits and is involved in sensorimotor control, where the dorsal striatum is the primary afferent structure mediating both motor and executive function. The dorsal striatum can be further subdivided into the dorsomedial (DMS) and dorsolateral (DLS) regions, which receive afferent projections from frontal- and parietal-associated cortices and sensorimotor cortices, respectively (Macpherson & Hikida, 2019). Functions of the DMS are of goal-directed motor behavior while the DLS is responsible for habit formation. We know that neuronal activity within the BG associated with motor areas of the cerebral cortex is highly correlated with parameters of movement, and thus damage to BG circuits associated with motor areas of the cortex, as seen in PD body movement loop, leads to motor symptoms of resting tremor, rigidity, bradykinesia, freezing of gait and dystonia.

1.1.2 Nigrostriatal Degeneration

The debilitating motor and non-motor symptoms that are associated with PD arise due to a loss of dopamine within the substantia nigra (SN) of the basal ganglia (BG). There is an estimated overall nigral loss of 50-60% where 70-80% dopamine neuronal loss is expected prior to the onset of any overt motor symptoms (Tröster & Fields, 2008; Graybiel, 2000). This loss of dopamine within the SN impedes on two neural pathways that work in conjunction with one another while producing opposite net effects on the targeted thalamus in order to release movement, ultimately allowing for fluid control of movement: the direct and indirect striato-pallidal pathways.

The normal functioning of the BG involves a proper balance in firing between the activity of these following pathways. The direct pathway involves the striatum, globus pallidus internus (GPi), thalamus and the motor cortex (Figure 1.2 A). The aim of the direct pathway is to initiate movement or stimulate movement by selectively facilitating certain motor (or cognitive) programs in the cerebral cortex that are adaptive to the current task. The direct pathway connections start with neurons in the striatum that make inhibitory connections with neurons in the GPi. The GPi neurons in turn make inhibitory connections on neurons in the thalamus. Thus, the firing of GPi neurons inhibits the thalamus, making the thalamus less likely to excite the cortex. In a healthy BG, when the direct pathway striatal neurons fire, however, they inhibit the activity of the GPi neurons. This inhibition releases the thalamic neurons from inhibition allowing them to fire to excite the motor cortex leading to stimulation of movement. The net effect of the motor cortex exciting the direct pathway further excites the motor cortex producing a positive feedback loop.

The indirect pathway involves the striatum, globus pallidus externus (GPe), subthalamic nucleus (STN), thalamus and the motor cortex (Figure 1.2 A). The indirect pathway inhibits muscle movement by simultaneously inhibiting the execution of competing motor programs, ultimately leading to preventing any unwanted movements from occurring. Here the striatal neurons make inhibitory connections to the GPe where it makes inhibitory connections to cells in the STN, which in turn make excitatory connections to cells in the GPi. In a healthy BG, when the indirect pathway striatal neurons fire, however, they excite the activity of the GPi neurons. This excitation increases thalamic neuron inhibition preventing them to fire in order to excite the motor cortex leading to prevention of movement. The net effect of the motor cortex exciting the indirect pathway is to inhibit the motor cortex, producing a negative feedback loop.

Meanwhile the SN is working in the background fine tuning these movements and neural communications within the direct and indirect pathways by using dopamine to either further excite the thalamus (direct pathways) or further inhibit the thalamus (indirect pathway).

The cortico-STN-GPi/substantia nigra pars reticula (SNr) hyperdirect pathway conveys strong excitatory signals from the cortex to the GPi/SNr with faster conduction velocity than the direct and indirect pathways (Nambu, 2008). Thus, GPi activity is influenced by signals through the hyperdirect, direct, and indirect pathways (Figure 1.2 A). The hyperdirect pathway seems to be important for inhibiting irrelevant motor programs and/or changing motor plans (Nambu et al., 2002).

Any upset of the balance between the direct and indirect pathways results in complicated motor dysfunctions. In PD where there is a loss of dopamine in the SN, the nigrostriatal pathway excites the direct pathway and inhibits the indirect pathway, the loss of this input tips the balance in favor of activity in the indirect pathway (Figure 1.2 B-C). Thus, the GPi neurons are abnormally active, keeping the thalamic neurons inhibited. Without the thalamic input, the motor cortex neurons are not as excited, and therefore the motor system is less able to execute the motor plans in response to the individuals volition. Damage to the BG in PD causes excessive inhibition of the thalamo-cortical nuclei leading to difficulty initiating movements and once the movements are initiated they tend to be abnormally slow.

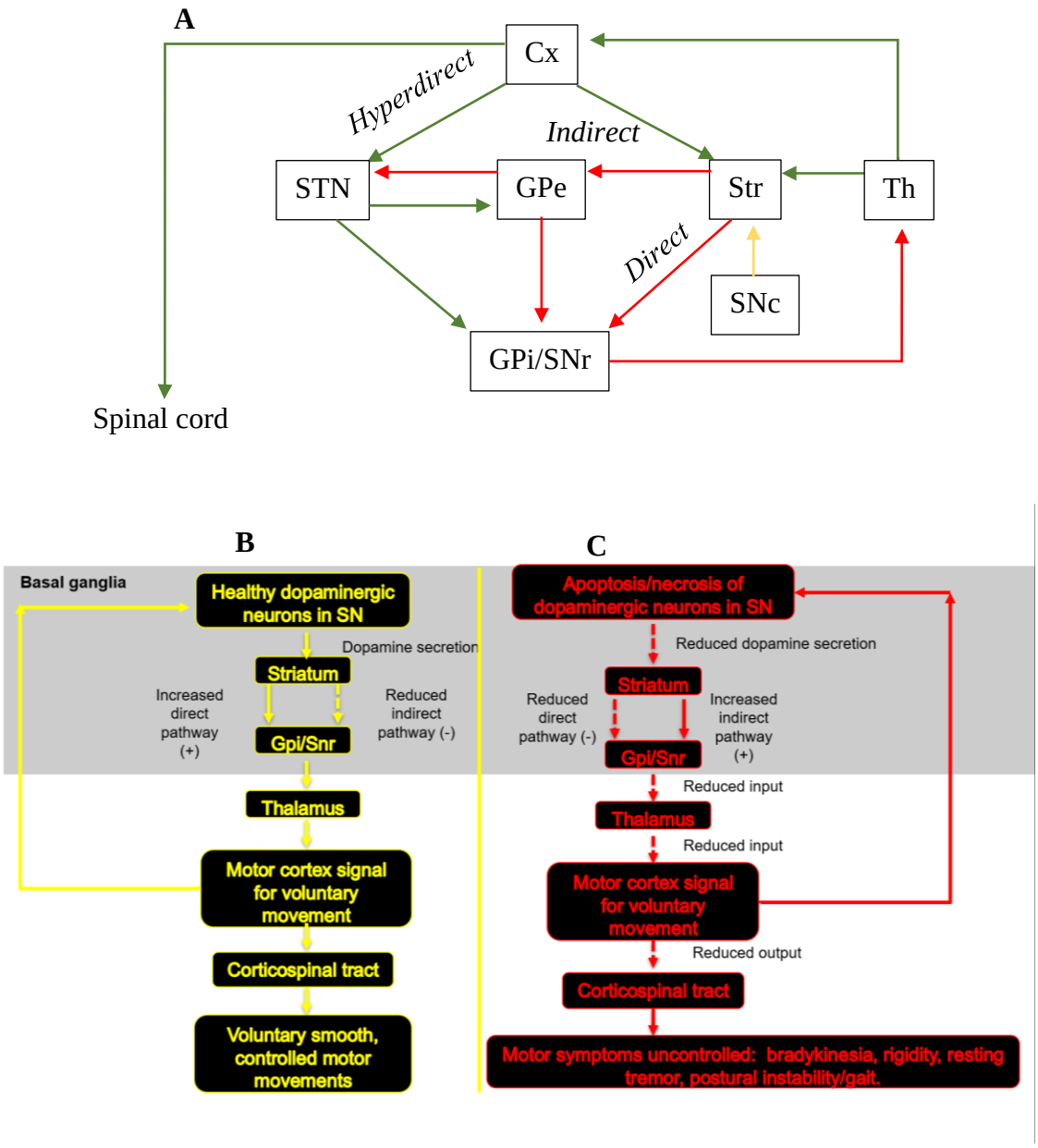

Figure 1.2. A. Three cortico-BG pathways. Green arrows represent excitatory glutamatergic projections, red arrows represent inhibitory GABAergic projections and yellow arrows represent dopaminergic projections. B. normal and C. abnormal functioning of direct (Cx-Str-GPi/SNr), indirect (Cx-Str-GPe-STN-GPi/SNr) and hyperdirect (Cx-STN-GPi/SNr) pathways in the BG. Cx, cerebral cortex; GPe, globus pallidus externus; GPi, globus pallidus internus, SNr, substantia nigra pars reticula, STN, subthalamic nucleus, Str, striatum, Th, thalamus.

1.1.3 L-Dopa and DBS Treatments

Pharmacological treatments, such as L-Dopa replacements, and surgical interventions, such as deep brain stimulation (DBS) and focused ultrasound (FUS), are typical treatments for PD that ultimately aim to restore the equilibrium between the direct and indirect striato-pallidal pathways. Dopamine replacements such as levodopa and carbidopa are precursors for dopamine, which allows them to cross the blood-brain barrier whereas dopamine itself cannot. L-Dopa treatment is used to increase dopamine concentrations in the SN, however these treatments come with adverse side effects such as hallucinations, delusions, confusion, depression, anxiety, agitation, nightmares, and cognitive 'frontal' effects (Tröster & Fields 2008). Due to dopamine replacements targeting SN to increase dopamine, this treatment seems to mainly target and reduce motor symptoms associated with PD, leaving the non-motor symptoms untreated. DBS is limited to PwPD who have severe symptoms, and for whom medications no longer work not all PwPD are good candidates for this highly invasive procedure. This surgical treatment also targets the motor symptoms of PD thus ignoring the non-motor symptoms that exist (Earhart, 2009; de Dreu et al., 2012). Finally, FUS is a fairly new, non-invasive procedure that uses magnetic resonance image (MRI) paired with ultrasound technology to precisely target areas in the BG, such as the thalamus, that help with improvements in tremor by providing focal lesions (Lipsman et al., 2013). Although FUS provides a safe alternative to the highly invasive DBS, it does not alleviate all other PD motor symptoms and again the non-motor symptoms are ignored.

1.1.4 Exercise Treatments

To date, there is no evidence based physiotherapy guidelines for PwPD, thus a wide range of physiotherapy techniques are currently used to treat PD with little difference in treatment effects across them (Tomlinson et al., 2012). Most physiotherapy programs target only

the motor symptoms of PD with no improvements shown in quality of life measures after physiotherapy (Tomlinson et al., 2012). Being that PD is such a complex disorder, physiotherapy treatments in the form of exercise programs seem to only be effective for a few motor symptoms (such as balance and speed) while ignoring the other motor symptoms (i.e.: tremors) and non-motor symptoms of PD. In addition, the benefits of physiotherapy are not long-term; disease symptoms tend to worsen and the disease process resumes after short-term benefits have abolished. Recently, research focus has shifted from standard physiotherapy exercises to dance programs due to the lack of compliance and regular participation from PD during physiotherapy. Additionally, dance is an enjoyable alternative to regular physiotherapy and has been found to improve adherence to a physical multifaceted exercise (Heiberger et al, 2011; Hackney et al., 2007).

1.1.5 Multisensory Dance Treatments

Dance requires skilled movements to be precisely coordinated with external auditory stimuli (i.e., music and/or verbal instruction) resulting in expertise that is multimodal in nature while maintaining a high level of physical performance. Dance is a planned, structured, novel activity that is a complement to other PD treatments, it helps individuals stay active and improves overall mobility, quality of life as well as providing an additional support group for all those involved (PwPD and caregivers). Patients often complain about difficulties with walking, mobility, posture, and balance as PD advances. These symptoms may improve with dance exercises. In fact, research has shown that people who dance habitually over their lives are known to have better balance and less variable gait in comparison to non-dancers (Verghese, 2006; Zhang et al., 2008). Additionally, dance-based balance training has been shown to be successful in improving balance in elderly individuals (Federici et al., 2005). Dance also could

enhance strength and/or flexibility while improving cardiovascular functioning. These are important areas that have been identified as being vital for an exercise program designed for PwPD (Keus et al.,2007).

One the earliest studies compared a 6-week period of dance/movement therapy to a traditional exercise program (i.e.: treadmill walking). The authors observed improvements in movement initiation in the dance group but not in the exercise group (Westbrook & McKibben, 1989). From these first studies arose the Mark Morris Dance Group and the Brooklyn Parkinson Group collaborated to develop "Dance for PD". This dance program continues to be offered on a weekly basis and a study of this class suggests that it positively impacts quality of life in PwPD (Westheimer, 2008). Other research examined the effects of partnered dance on PD symptoms, with specific emphasis on Argentine Tango (AT). The research has shown the PwPD demonstrated significant improvements in balance, as evidenced by an average improvement of 4 points on the Berg Balance Scale, with a twice weekly, 10-week tango program (Hackney et al, 2007). In addition, after the study ended, nearly half of the tango group continued to participate in ongoing classes but none of the exercise group members continued in the exercise program-indicating a higher level of interest in continuing to participate in tango dance (Hackney et al., 2007). Not only has dance shown to improve the motor and quality of life in PwPD, there are multiple studies that speculate about the ways that dance may be exerting its influence on neural mechanisms and these published studies, along with their interventions and study descriptions are summarised in Table 1.1 below

Table 1.1. Published studies on dancing and PD using UPDRS Part III as a measure: 7 studies that included no control group or no other intervention group, 5 studies that had a true no control/no intervention group, and 10 studies that labeled their control group as other intervention group/RCT study.

UPDRS III Published Studies (N=21)						
Study		**Duration (months)**	**Total N**	**PD Dancers (n)**	**PD Control/No Intervention (n)**	**PD Other Intervention (n)**
No Control Group but Other Intervention Group (n =7; 33.3%)	Heiberger et al., (2011)	3	11	11		
	Hackney et al., (2009)	0.5	12	12		
	Marchant et al., (2010)	0.5	11	11		
	Shanaham et al., (2015)	2	9	9		
	McKay et al., (2017)	0.75	22	22		
	Lihala et al., (2020)	2	9	9		
	Sowalsky et al., (2017)	0.25	1	1		
Average		**1.3**	**10.71**	**10.71**		
Chapter 4 Project (Bearss & DeSouza, 2021)		***~40***	***32***	***16***	***16***	
True Control/No Intervention Group (n =5; 23.8%)	Duncan & Earhart, 2012	12	35	16	19	
	Duncan & Earhart, 2014	24	10	5	5	
	Foster et al., (2013)	13	52	26	26	
	Hackney & Earhart, 2009	3.25	61	31	17	13
	Lukšys & Griškevičius, 2016	2	24	14	10	
Average		**11.05**	**30.6**	**15.2**	**15.4**	
Chapter 4 Project (Bearss & DeSouza, 2021)		***~40***	***32***	***16***	***16***	

Other Interventions Group (n=10; 47.6%)	McKee & Hackney, 2013	3	33	24		9
	de Bruin et al., 2010	3.25	22	11		11
	Hackney & Earhart, 2009	3.25	31	14		17
	Rocha et al., 2017	2	21	10		11
	Hackney et al., 2007	3.25	19	9		10
	Volpe et al., 2013	6	24	12		12
	Romenets et al., 2015	0.5	33	18		15
	Delabary et al., 2020	6	20	10		10
	McNeely et al., 2015	3	16	8		8
Average		3.4	24.3	12.9		11.4
Overall Average		4.6	22.7	13.5	15.4	11.6
Chapter 4 Project (Bearss & DeSouza, 2021)		***~40***	***32***	***16***	***16***	

1.1.6 Other Forms of Exercise Treatments

In addition to Multisensory Dance treatments, there are many other types of physical exercises that exist for the PD population and these activities range in various forms. The effectiveness of each individual exercise regimen will differ depending on various factors such as current PD symptom state and overall health, motivation, previous activity level and disease severity thus a variety of activities and the different forms may provide an overall well-rounded benefit to impede the widespread PD symptomology that normally increases over the course of the disease. One form of exercise for PwPD are aerobic based exercises that aim to challenge one's cardiovascular system and these include walking, biking, running, and swimming (van der Kolk et al., 2019). There is also the existence of strength training exercises which involve the use of your body weight in order to help build muscle mass and strength and flexibility training is incorporated to help improve muscle length and range of motion as posture (Ramazzina et al., 2017). Finally, activities which focus on balance and agility training combine the above three training techniques of aerobic exercise, strength and flexibility in forms of dance, boxing (Combs et al., 2013), Tai chi (Yang et al., 2014), yoga or Pilates (Kwok et al., 2019), and golfing (Bliss et al., 2021). Additionally, there is a form of low intensity exercise referred to as Sensory training (Sangarapillaie et al., 2021) that requires participants to complete exercise with their eyes closed. Sensory training exercises suggest that this form of exercise allows for sustained levels of dopamine in the BG, improving overall PD severity and that the beneficial effects are long terms in nature (Sangarapillai et al., 2020).

The existence in the variability of interventions adopted for the treatment of PD with exercise is beneficial to treat a particular PD symptom or at most lesson a few PD symptoms. However, more complex interventions which combine more than one type or form of exercise

demonstrate to be most favorable interventions by improving PD symptom outcomes. Dance is one of these favorable interventions as it incorporates aerobic, strength and flexibility training but in addition adds a multisensory training that other forms of therapy do not provide consistently. The important difference in where dance involves sensory training is what essentially produces the most favorable outcome in significant improvements seen in motor, mood, cognition, and behavior ultimately leading to improved quality of life. Being that dance is so multifaceted in the type of exercise and movement forms that it offers, which in turn allows for a more diversified population thus making dance for everyone.

1.2 DANCE INDUCED NEUROPLASTICITY

Dance research has shown that performance of tango movements to a metered and predicated beat was associated with increased activation of the putamen (Brown et al., 2005), an area that normally shows reduced activation in PwPD. Research has shown that the use of music and partnered movement may serve as auditory, visual and somatosensory cues which may bypass the diseased basal ganglia and as such utilize undisturbed alternate pathways all of which serve to facilitate movement (Cunnington et al., 1995; Debaere et al., 2003). In addition to the rhythmic auditory cues, dance involves much foot work and foot/leg involvement, these may serve as visual cues and help with the reduction of gait variability normally seen as a symptom in PwPD (Baker et al., 2008). Experienced ballet dancers have shown experience-dependent plasticity of alpha (8-12 Hz) and beta (13-30 Hz) activity during action observation (Di Nota et al., 2017). Dance includes a combination of physical activity and sensory enrichment, which has been shown to have the largest and a sustaining effect on adult neuroplasticity in comparison to regular physical exercise. In fact, studies have shown that dance training is superior to conventional physical exercise in inducing brain plasticity in the elderly in areas such as the cingulate cortex, insula, corpus callosum and sensorimotor cortex (Rehfeld et al., 2018).

Much remains to be studied including the neural mechanisms by which dance conveys benefit to those with PD and the long-term effectiveness of dance as a potential additional therapy on these neural mechanisms in PwPD.

1.3 GENERAL OBJECTIVES

I will present a series of investigations that evaluate the impact of short- and long-term dance practice on the effects of behavioral, motor, non-motor and resting state EEG (rsEEG)

changes in PwPD and healthy controls. In my first project, I aim to show PD symptom improvements in balance and gait after participation in short-term (1-day) and long-term (12-weeks) dance programs. This study will be the first to show quality of life (QoL) enhancements following a dance intervention that was one-third shorter in duration (15-hours total), in comparison to previous studies. In this first project, the definition of short-term was based on data emerging from a single day of dance participation (after a 75-minute dance class) while long-term was defined as the completion of a 12-week dance term program. My second project will further add to that of project 1, where I will demonstrate improvements in behavioral, motor, and non-motor functions, improved affect and changes in rsEEG as a function of a single dance class (75-mins). The third project follows sixteen PwPD for up to three years showing reduced disease progression as measured with all levels of the MDS-UPDRS paired with rsEEG changes.

The results of these studies will provide critical information to help inform the efficacy of dance programs to alleviate motor, cognitive and neurophysiological impairments in PwPD.

CHAPTER TWO

IMPROVEMENTS IN BALANCE AND GAIT SPEED AFTER A 12-WEEK DANCE INTERVENTION FOR PARKINSON'S DISEASE

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2.1 ABSTRACT

Preliminary research suggests dance is beneficial for people with Parkinson's Disease and can serve to complement conventional medical treatments. There are many types of dance classes however, the Dance for Parkinson's Disease model has shown rapid growth in participant attendance and interest over time. Unlike other studies where the description of the dance program has been rather vague, this model has clear principles and a specific structure which has led to more research in this model over others. Whilst preliminary research has demonstrated that this intervention is potentially quite effective, what remains unknown is the specific length of dance intervention required, measured in weeks and hours, until improvements are seen in motor impairments and quality of life in Parkinson's Disease. Methods: We aimed to replicate and extend previous findings where enhancements were shown on short-term motor (1-day) and quality of life in Parkinson's Disease. We conducted a 12-week pilot study using the Dance for Parkinson's Disease model. This study was a quasi-experimental, non-controlled study of nine (9) participants, who completed 2 motor (Berg Balance Scale and Timed Up and Go) and quality of life questionnaires (Quality of Life Scale and questionnaire of wellbeing) before and after the second and twelfth class. Results: Balance and gait improvements in short-term (1-day) and long-term (12-weeks) in the Berg Balance Scale. No improvements in quality of life were observed. Enhancements were observed in one-third (34%) less dance intervention duration (15 hours), than previous studies. Conclusions: Participation in dance classes, improved motor symptoms in both short (1-day) and long-term (12-week) durations. Overall, quality of life did not change.

Keywords: Plasticity Dance; Learning; Social; Quality of life

2.2 INTRODUCTION

Parkinson's Disease (PD) is described as a hypokinetic movement disorder of the central nervous system primarily associated with dysfunction of the basal ganglia (BG). This subcortical structure plays a prominent role in motor learning, particularly in the late stage of learning where movement sequence retrieval is more implicit and habitual. Difficulty in executing habitual movement is a distinct feature of PD.

Levodopa, the primary pharmacological medicine for PD, has multiple limitations in its intervention. Only a few motor symptoms of PD are temporarily treated, there is a decreased efficacy of drug treatment as PD progresses, symptoms become progressively resistant to levodopa (Hely et al., 2000), non-motor symptoms of PD are ignored, and finally adverse side-effects such as depression, anxiety, hallucinations and dyskinesia arise as a result of levodopa use. Due to these various limitations, research within this field has shifted its attention to other forms of interventions, such as dance therapy, intended to improve daily functioning and quality of life by teaching and training PD patients' compensatory movement strategies while providing a positive social atmosphere. Various dance classes have shown to alleviate motor symptoms of people with PD (Heiberger et al,. 2011; Westheimer, 2008:Houston & McGill, 2013; Mandelbaum & Lo, 2014; Volpe et al., 2013; Westheimer et al., 2015). We studied dance classes using the Dance for PD (DfPD®) model first conceived by Westheimer (2008); this model, a collaboration of the Mark Morris Dance Group (MMDG) and the Brooklyn Parkinson Group (BPG), posits an artistic model in its aims and conception for those with PD (and their caregivers) that has been implemented worldwide. DfPD® classes target PD specific symptoms related to balance, cognition, motor skill, depression and confidence in physical function. Our study intended to examine the shortest dance session (12-weeks; 15 hrs) in novel PD-dancers

compared to studies of 8-months (Heiberger et al., 2011) and 17-months (Westheimer, 2008) to date. Westheimer (2008) employed a similar dance program over 17-months, and reported long-term QoL benefits. Heiberger et al., (2011) employed an 8-month dance program to examine short-term effects on motor control after one dance class and studied long-term effects of QoL.

This study aimed to replicate short-term (1-day) motor improvements (Heiberger et al., 2011) and extend research to examine long-term motor (12-week) and QoL measurements (at weeks 2 and 12) following participation in weekly DfPD® classes. Unlike previous DfPD® studies (Heiberger et al., 2011; Westheimer, 2008) that reported findings after 8-months (Heiberger et al., 2011) and 17-months (Westheimer, 2008), the present study looked at the effects of a dance program that is on average 34% shorter in dance intervention duration. We hypothesized, both short-term (1-day) and long-term (at 12-weeks, 15 hrs) motor improvements and increases in QoL scores from baseline (week 2) to week 12.

2.3 METHODS

2.3.1 Participants

Fourteen individuals initially volunteered for the study; five did not complete the entire protocol, before and after class testing during weeks 2–12, due to personal reasons and absences. Thus, a total of nine PD volunteers completed a new Dancing with Parkinson's Program at Canada's National Ballet School (NBS); Hoehn and Yahr (H&Y) range = asymptomatic to severe (0–4), $M_{H\&Y} = 0.8$ ($M_{age} = 67.78 \pm 6.14$ yrs; $n_{Males} = 5$; average length of disease diagnosis = 5.56 years; range = 0–17 years). Written informed consent was obtained using an approved protocol from York University's Ethics Board (2013-211) (Appendix A).

2.3.2 Measures

The Berg Balance Scale (BBS) [32,33] (n = 5) and the Timed Up and Go (TUG) (n = 5) test were employed for this study as a measure of motor performance. The BBS is comprised of 14 tasks, measuring different functions of balance and posture that are common to daily living. Each task is judged by the experimenter on an ordinal scale ranging from 0 to 4 (Hashimoto et al., 2015), and evaluated as either a factor of time to complete, or quality of execution. With this measure, a total score of 56 reflects perfect balance. TUG is a timed measurement (in seconds) of movement sequencing, gait, and balance control. This test requires a participant, on request, to rise from a seated position, walk 3 m (indicated by a marking on the floor), turn around, return to the seat, and sit back down. Two QoL questionnaires (n = 9) were administered: the Quality of Life Scale (QoLS) from Oregon Health and Sciences University and a post dance class questionnaire of wellbeing developed by Westheimer (2008) and Heiberger et al., (2011) was used. Repeated-measure comparisons for the BBS and QoLS were analyzed using the Wilcoxon sign-ranked test. TUG scores were analyzed using a paired samples t-test.

2.3.3 Procedure

Motor assessments (BBS and TUG) were conducted on two separate occasions; the class of week 2 (class 2) and the class of week 12 (class 12). On both occasions participants were tested before (Pre) and after (Post) dance class. Testing was conducted at week 2, instead of week 1 as attendance is usually higher after the initial class as most participants are returning from their summer vacations and the study is explained in class 1, causing it to be of shorter duration in dance training when compared to the remaining classes in weeks 2 – 12.

For the QoLS, questions 17 and 18 appeared on the questionnaire at week 12. A weekly 75-min dance class for 12-weeks was instructed by two NBS DfPD® trained faculty. Classes

commenced with a seated warm-up on chairs, followed by ‘‘barre’’ work, and ended with dancing across the floor exercises, choreography was also learned each week with the aim to have a performance on week 12 (see Table 2.1).

Table 2.1. Sample exercises featured in the dance class at NBS.

Exercise	Description	Purpose
Danced name introduction	Stating your name with a corresponding dance movement. The rest of the class first watches before repeating the participants name and movement. Standing or seated.	Feeling welcomed and welcoming everyone in the class. Practicing skills of choreographing on the spot.
Tendus	Pressing the feet along the floor until the leg is fully extended. Arms follow a similar extension motion. Seated.	Warming up the feet and lower leg, while working on strengthening the core.
Shuffle dance	A series of shuffles, stamps, and ankle inversions. Seated.	Facilitating flexibility and mobility in the ankles and knees.
Magic dance	Dancing with an imaginary ball and scarf, while exploring a range of motion. Seated.	An opportunity for vivid imagery and creative interpretation.
Rainfall cannon	Simulating the sounds of an approaching rainstorm using various body parts as percussion instruments. Seated.	Practicing movement initiation by waiting to execute a movement in proper sequence.
Winning the poker game	Rising slowing from a chair while moving in a celebratory manner.	Practicing rising from a seated position in a safe manner.
Painter and Sculptor mirrored pairs	A paired improvisation dance, done face to face. One partner would lead while the other mirrored their painting motion. This dance finished with a series of intertwined sculpture-like poses. Seated and standing aspects.	Mirroring a partner in a detailed fashion, and practicing creative movement initiation by improvising and developing unique poses.
Pliés in parallel and second position	Holding on to the back of a chair, pliés (bending of the knees) and rises were done in parallel (feet together) and apart. Standing.	Developing strength and balance while standing and increasing range of motion in the legs.

Lunging side to side	While holding onto the back of the chair, transferring weight from side to side with legs in a wide pronated position and "brandishing a fist" at a neighbouring participant. Standing.	Finding a core centre for balance by lunging off balance and returning to a central position.
Waltz	Waltz step performed first on the spot and the travelling. Standing.	Safely dancing through space, and physically embodying the triplet rhythm of a waltz.
Shy to confident shuffle dance	A standing variation of the seated shuffle dance, where the movements are done first in a demur and small manner, but gradually increase in confidence until they are gregariously expressed.	A fun way of practicing moving with confidence and with clear intention.
The "Showdown Hoedown" dance	Approximately a 2 minute choreography done facing a partner, first dancing as advisories in the "showdown" and then together as companions in the "hoedown." Standing.	Challenging participants to recall a lengthy piece of choreography with multiple sections and changes of direction

2.3.4 Statistical Analysis and Design

The experiment was a within-subjects design. The independent variables were Time (class 2 and class 12) and Condition (Pre or Post). The dependent variables were Motor Assessments (using the BBS and TUG) and quality of life (using the QoLS and questionnaire of wellbeing).

An initial inspection of compliance and clinical characteristics will be examined in the PD dance group prior to conducting the following statistical analyses. Compliance was defined as participants who completed the entire dance class duration of 12-weeks. Repeated-measure comparisons for the BBS and QoLS will be analyzed using the Wilcoxon sign-ranked test. TUG scores will be analyzed using a paired samples *t*-test.

2.4 Results

The results for BBS showed long-term improvements (after 12-weeks of dance involvement) on balance scores for those measured after class on week 2 (n = 5; Mdn = 50) and after class on week 12 (Mdn = 53.5), $Z = -2.02$, $p = 0.022$, $r = 0.91$, one-tailed (Figure 1A); the same was found for those measured before class on week 12 (n = 7; Mdn = 53) and after class on week 12 (Mdn = 54) $Z = -2.39$, $p = 0.009$, $r = 0.90$, one-tailed (Figure 1B). A significant decrease in time to complete the TUG was also found when comparing the measures after class on week 2 ($M = 10.2$, $SEM = 0.93$) and after class on week 12 ($M = 8.18$, $SEM = 0.47$), $t(4) = 2.25$, $p = 0.044$, $r = 0.75$, one-tailed (Figure 1C). No significant decrease in time was found for those performing the TUG before ($M = 9.26$, $SEM = 0.67$) and after class on week 12 ($M = 8.85$, $SEM = 0.54$), $t(6) = 0.90$, $p = 0.20$, one-tailed.

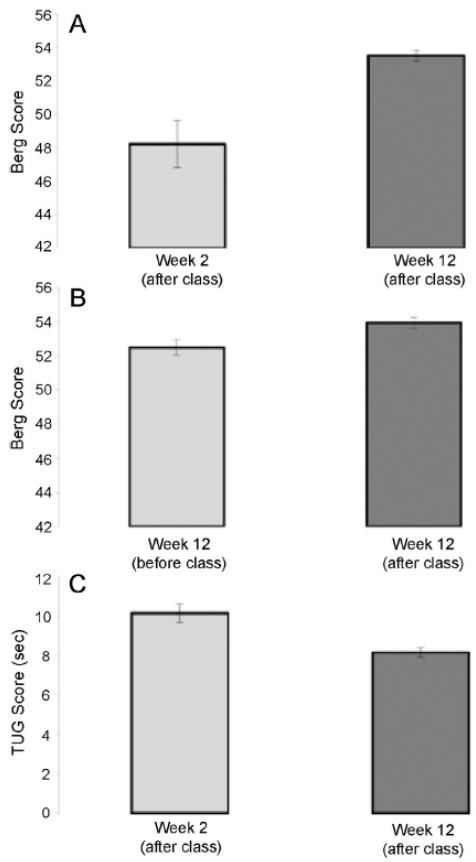

Figure 2.1. A. Parkinson's participants' mean scores for the BBS questionnaire performed after week 2 and week 12 (n = 5; Wilcoxon sign-Ranked test $p < 0.05$, one-tailed). Error bars represent standard error of the mean (SEM) for all bar graphs **B.** Parkinson's participants 'mean scores for the BBS questionnaire performed before and after the last dance class (n = 7; Wilcoxon sign-Ranked test $p < 0.05$, one-tailed). **C**. Parkinson's participants' mean scores for the TUG test performed after week 2 and 12(n = 5; paired samples t-test $p < 0.05$, one-tailed).

The total score for the QoLS (n=9) showed no significant change from the end of week 2 (Mdn = 85.6) to week 12 (Mdn = 87) $Z = -0.14$, $p = 0.45$, one-tailed. However, when assessing each item individually, there were significant changes for item 3 (rating relationships with parents, siblings, and other relatives – communicating, visiting, helping) and for item 9 (learning – attending school, improving understanding, getting additional knowledge). Item 3 resulted in a significant reduction in score from class 2 (Mdn = 6.00) to class 12 (Mdn = 5.00) $Z = -1.90$, $p = 0.029$, $r = 0.63$, one-tailed, while item 9 significantly increased from class 2 (Mdn = 5.00) to class 12 (Mdn = 5.00) $Z = -2.449$, $p = 0.007$, $r = 0.81$, one-tailed (Figure 2.2).

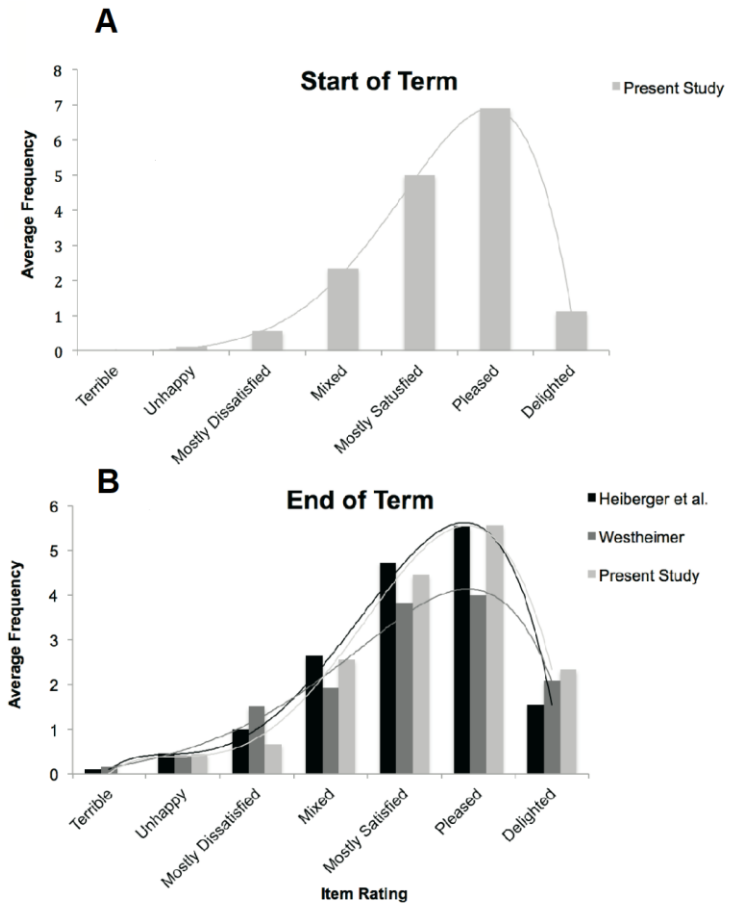

Figure 2.2. Average ratings for the QoL items when measured at the beginning of the dance term (A) and at (B) the end of the dance term for all 3 studies. For the above figures, the frequency of each rating was summed and then divided by the number of participants who responded to each questionnaire. There was no significant difference in rating frequencies between the studies (Heiberger et al. (2011) n=11, Westheimer (2008) n=12, and the present study n=9; Pearson's chi-square test, p >0.05, two-tailed).

2.5 Discussion

With BBS and QoL, an increase in score represents enhanced balance and enhanced QoL, respectively. The TUG task is measured in seconds, and a decrease in time to complete the TUG indicates an improvement of gait speed and ambulation. As hypothesized, results revealed, for the first time, long-term changes in 15 h of participation in a 12-week DfPD1 program in both balance performance and gait speed, as BBS numbers increased and time to complete TUG

decreased at week 12 in comparison to week 2. These findings replicate Heiberger's et al., (2011) short-term improvements (1-day) in balance when evaluated before and after a class.

Unlike previous studies (Tröster & Fields, 2008; de Dreu et al., 2012) where QoLS were provided once, our study performed a before and after sampling and found that there were no improvements from week 2 to week 12 which may be due to the fact that our QoL baseline scores were measured at week 2, and thus the participants have already been exposed to the group and the model itself which may have increased their QoL scores. Follow-up studies should measure QoL prior to registration before having experience with the DfPD1 program and the research being conducted. Results in our study add to those in Westheimer (2008) 20 h dance study, where motor improvements, in balance and gait, are seen as early as 15 h into dance class. In summary, although long-term changes, as defined as 12-weeks of dance involvement, in balance and gait were found, a parallel degree of change for overall QoLS scores did not occur from week 2 to week 12. QoLS may have potentially already increased after just two weeks of dance class, what is more important for future studies is to uncover the mechanisms (Sandoval-Rincón et al., 2015), such as neural or structural changes, that underlie these behavioural changes.

2.6 Acknowledgements

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CHAPTER THREE

SINGLE DANCE CLASS EFFECTS ON PARKINSON'S DISEASE MOTOR, NON-MOTOR SYMPTOMS AND RESTING STATE ENCEPHALOGRAPHY (rsEEG).

3.1 INTRODUCTION

Dance has been characterised as a multi-dimensional exercise, where it offers an enriched environment due to the simultaneous auditory and visual sensory stimulation, musical and social interaction, memory, motor learning, emotional perception, expression and interaction. All of these characteristics of dance evokes a widespread activity of numerous brain regions. Dance has been shown to have positive short-term benefits on motor functioning for people with Parkinson's Disease (PwPD), which was shown in Chapter Two above, using a short 12-week dance program (Heiberger et al., 2011; Westheimer, 2008; Bearss et al., 2017).

Alpha rhythms (8 – 13 Hz) have been the longest studied brain oscillations since their discovery in the late 1920's by Hans Berger, and this rhythm is by far the strongest electrophysiological signal measured from the human waking brain in both the occipital and frontal cortex regions (Halgren et al., 2019; Da Silva et al., 1973). Alpha is the most dominant in electroencephalogram (EEG) events during quiet wakefulness, relaxed state and with eyes closed (EC) where alpha amplitude is at its highest. In contrast, alpha amplitude is reduced when mental effort is applied or during feelings of sleepiness or drowsiness (Goldman et al., 2002). EEG is non-invasive and records the electrical field produced by neural electrical activity in the brain. EEG has good temporal resolution and high test-retest reliability, which is increasingly recognized as a fundamental hallmark of cortical integrative functions. It has been shown that quantifying EEG rhythms could provide an important biomarker for a lot of neurological disorders, including PD.

Alpha rhythms have been theorized to play a key role in fundamental top-down cognitive processes such as attention (Saalmann et al., 2012), working memory (Jensen et al., 2002), functional inhibition (Peterson & Voytek, 2017) and perception (Samaha & Postle, 2015). However, its physiology and the underlying circuits and neural structure(s) which generate alpha

rhythms are poorly understood and continue to be scientifically controversial. Studies have suggested the thalamus to be the primary alpha pacemaker (Lőrincz et al., 2009) whereas other studies have pointed to infragranular layers driven by layer V pyramidal cells (Van Kerkoerle et al., 2014). Following the hypothesis that the thalamus houses these waves one would thus predict abnormal alpha waves seen in rsEEG in PwPD due to the over inhibition of the thalamus seen in their thalamocortical network (as described in Figure 1.1. B). Multiple studies have examined differences seen in alpha waves between PwPD and controls during performance of specific tasks; where the results remain inconsistent due to the variable differences in task performance between these studies. What remains consistent in the literature between the differences in PwPD and healthy controls, even with differences in task performance, is PwPD consistently have a lower individual alpha peak frequency (iAPF) (Moazami-Goudarzi et al., 2008). Lower frequencies are suggested to be abnormal (i.e.: neuropathologic) and is a probable consequence of the over inhibition of the thalamus reflected in rsEEG.

Additionally, Stoffers et al., (2007) showed that during resting state magnetoencephalographic (MEG) recordings in early stage, untreated PD patients, cortical activity exhibited higher alpha power compared to controls. This slowing of neural activity in the cortex in PwPD can be traced back to the complex connectivity starting in the substantia nigra (SN), going through the BG and finally affecting the thalamocortical network – areas affected by the depletion of dopamine levels in PwPD (as described in Figure 1.1.B).

Vardy et al., (2011) examined the relationship between neural slowing and disease severity during rest and motor performance for PwPD and healthy age-matched controls, as motor symptoms are one of the classical characteristics in PD. Their results showed that PD patients displayed slowing of neural activity, in which cortical activity has higher relative power

in the lower alpha frequency. Interestingly, the authors also showed that there was an alpha decrease in power and median frequency which was correlated with increases in motor movement scores on the UPDRS Part III. Finally, they showed that UPDRS Part I mental score correlated the least with the change in relative power during movement and the most during resting state and that the median frequency motor score (Part III) was significantly correlated with neural slowing during movement. Whereas the mental functioning (Part I) and activities of daily living (Part III-ADL) scores were significantly correlated during resting state. These findings suggest that PD progression results in prominent slowing of neural activity in the motor cortex during motor performance and that the slowing is modulated by motor activity (Vardy et al., 2011). The differences seen during resting state and movement suggests that different mechanisms are responsible for neural slowing in PwPD. Perhaps the abnormal activity in the subthalamic nucleus (STN) causes a change in cortical power displaying itself in PD cognitive and motor symptoms (Brown, 2007). That is, changes in cortical alpha could be mediated by different (partly overlapping) brain networks that are more specific for motor tasks reflected by the UPDRS motor score or for cognitive aspects reflected by UPDRS mental functioning and ADL scores (Vardy et al., 2011).

Executive dysfunction (ED) is a well-known non-motor cognitive impairment in PwPD, where deficits in internal control of attention, set shifting, planning, inhibition, conflict resolution, impairment in dual-task performance, and a range of decision-making and social cognition tasks is seen ultimately affecting their goal directed behaviors (Teramoto et al., 2016). Reciprocally interconnected frontal and parietal regions join with the BG and thalamus to deliver executive function cognitive processes. Being that the thalamocortical pathways are affected in PwPD, one would expect differences in rsEEG following new and challenging environmental

situations. ED in many PwPD develop into overt dementia and cognitive dysfunction interfering with activities of daily living and ultimately affecting their QoL (Bosboom et al., 2006).

The aim of our current study was to extend the findings of Chapter Two, by examining the effects of dance on both motor and non-motor functioning; and to further extend these findings by correlating these effects to onsite recordings of rsEEG, which we collected immediately before and after participation in a single dance class (1.25 hour). With the growing number of studies indicating positive benefits of recreational exercise for PD patients, such as improved gait speed, strength, balance, and QoL (Earhart, 2009; Bearss et al., 2017), combined with the knowledge that dance therapy results in more significant improvements than other types of exercise and/or no exercise (Westbrook & McKibben, 1989) our next step in this line of research was to examine brain-related plasticity as a function of dance for PD, as few studies have examined the neural correlates of dance class participation in PwPD (Karpati et al., 2015; Li et al., 2015). To date, no studies investigating the effects of dance on PD and rsEEG exist in the literature (except for results shown in a graduate student's thesis (Levkov, 2015) and in a pilot study on volunteers with depression Barnstaple & DeSouza, 2017).

OBJECTIVES AND HYPOTHESES

The present study is a novel examination of the interaction of dance on both motor measures and electro-cortical activity before and after participating in a single dance class. The aim of this study was to determine the short-term global electrophysiological changes (specifically in alpha band frequency) in conjunction with changes in positive and negative affect and motor scores as a result of participating in a single dance class between PwPD and age-matched healthy controls (HC). Precisely, I hypothesized less motor impairment, improved mood (i.e.: increase in positive

affect and decrease in negative affect scores), and an overall increase in averaged alpha band frequency in PwPD after participation in a single (75 minute) dance class.

3.2 METHODS

3.2.1 Participants

Seventeen PwPD with mild-severity disease ($M_{H\&Y}$= 1.31, *SD*= 1.01); (M_{age} = 68.82, SD = 8.95, N_{Males} = 12, $M_{DiseaseDuration}$= 5.45, *SD*= 5.08) and 19 healthy controls (HC) (M_{age} = 52.78, *SD* = 17.30, N_{Males} = 6) were tested on various measures (see below) both before (PRE) and after (POST) participating in a 1.25-hr dance class for the Dance with Parkinson's program at Canada's National Ballet School. All participants were compensated $25/hour for their time and involvement in the study.

Table 3.1 depicts the demographic and clinical characteristics of the study participants. There were significant differences between our PD and HC groups on the variables of Age: $t(32) = 2.922$, $p = 0.006$ (2-tailed), where our PD group was significantly older than our HC; Gender: $\chi^2(1)= 5.46$, p = 0.022, where there were more males in our PD group; and PD-NMS scores: $t(19) = 3.78$, $p = 0.001$ (2-tailed), where PD group showed significantly more non motor symptoms associated with Parkinson's in comparison to HC. This is an expected finding as we would expect our PD group to have more non-motor symptoms that are associated with the disease. There was no significant difference between PD and HC in MMSE scores $t(22) = .073$, $p = 0.943$ (2-tailed), indicating that the two groups were comparable in their cognitive mental states. Levodopa medication ON/OFF state was recorded for each PD participant which mark's the participants clinical state and is defied as being in an "ON STATE" when the PD medication has a good response and being in an "OFF STATE" when patient's experience a poor response in spite of taking their PD medication (as taken from the MDS-UPDRS assessment).

Table 3.1. Demographic and clinical characteristics of our PD and HC. Significant differences were seen in age, gender and PD-NMS scores between PD and HC groups.

Demographics	PD (n=17)	HC (n=19)	Test Value	Statistical Result
Age (years)	*M* = 68.82, *SD* = 8.95	*M* = 52.78, *SD* = 17.30	$t(32) = 2.92$	$p = 0.006$**
Gender	5 F/12 M	13 F/6 M	$\chi^2(1) = 5.46$	$p = 0.022$**
MMSE (0-30)	*M* = 27.69, *SD* = 2.06	*M* = 27.64, *SD* = 1.63	$t(22) = .073$	$p = 0.943$
PD-NMS (0-30)	*M* = 8.83, *SD* = 2.44	*M* = 4.00, *SD* = 3.43	$t(19) = 3.78$	$p = 0.001$**
Disease Duration (years)	*M* = 5.45, *SD* = 5.08	-	-	-
Levodopa ON/OFF State PRE/POST	PRE : 10 ON/1 OFF/6 N/A	-	-	-
	POST: 11 ON/1 OFF/5 N/A			

3.2.2 Measures

The Mini Mental State Exam (MMSE), a widely used cognitive screening test (Appendix G), was administered at PRE testing to help determine whether the participant is capable of continuing to participate in the study. MMSE includes tests of orientation, attention, memory, language and visual-spatial skills that are asked and rated by the experimenter. One point is given for each question if the answer is correct for a maximum total score of 30. Any participant with MMSE at or above 26 is presumed competent and would be deemed eligible to continue with testing. Initially we had 18 PwPD but one participant scored 24 on the MMSE and was thus excluded from the study.

Participants were also tested using the standardized Unified Parkinson's Disease Rating Scale (UPDRS) revised by the Movement Disorder Society (MDS) (Appendix B). This scale is used to follow the course of PD and consists of a total of 50 questions divided into four sections that require independent completion by people affected by PD and their caregivers. UPDRS is the most widely used scale in the literature to determine treatment-related benefits in PwPD. The subsections are broken down into the following: Part I: non-motor experiences of daily living (13 items); Part II: motor experiences of daily living (13 items); Part III (18 items): motor examination; and Part IV (6 items): motor complications. For the purposes of Project 2 which focuses on motor changes, only Part III (motor examination) was administered and scored by the experimenter. Part III (motor examination) contains 18-items that are composed of several subitems with right, left, or other body distribution scores that have ratings of 0 (normal or no problems) to 4 (severe); these items are then summed where higher overall Part III scores indicate greater motor impairment or severity.

Positive and Negative Affect Schedule (PANAS-X) was used before (PRE) and after (POST) the dance class (Appendix E). The PANAS-X is a self-rated 60 words scale that describes different feelings and emotions. It assesses 11 specific affects: Fear, Sadness, Guilt, Hostility, Shyness, Fatigue, Surprise, Joviality, Self-Assurance, Attentiveness, and Serenity that emerge from within the broader general dimensions of positive (10-items) and negative (10-items) emotional experience. Likert- scale ratings are of 1 (very slightly or not at all) to 5 (extremely). Participants completed the form before where they are asked to *"indicate to what extent they have felt this way during the past week"* and after *"indicate to what extent they feel <u>after</u> the class"*. Scores were summed for general positive items where higher scores indicate greater positive mood and for general negative items where higher scores indicate greater

negative mood. The PANAS-X is a popular tool used to measure feeling and emotions in research trials and is a fast questionnaire to complete (about 10 minutes) and thus was suitable for this project, as there were many assessments that were given to the participants at two time points (PRE and POST) in a single day-which can be tiresome for the participants.

PD Non-motor Symptoms (PD-NMS) questionnaire was used as it highlights non-motor issues that may not be obviously linked to PD by the person experiencing them (Appendix F). The questionnaire consists of 30 questions which ask whether the participant has experienced any of the following NMS within the past month. Answers are provided as either a Yes or No response and total YES and NO responses were then tallied for final scores indicative of NMS experiences.

Finally, rsEEG both PRE and POST dance training was assessed to detect any neural rhythm changes. The procedures and structure are described in detail below.

3.2.3 Procedure

Participants (whether PD or Controls) that volunteered for the study completed rsEEG, MDS-UPDRS (Part III), MMSE and PANAS-X within the hour before and after a single dance class (Figure 3.1). Each week, two participants were tested before the dance class simultaneously, one participant conducted the rsEEG first, while the second participant completed the remaining paper and pen questionnaires (MMSE, PANAS-X and PD-NMS) and the MDS-UPDRS (Part III) first, and then they would switch to complete the other tests once the first was completed, thus allowing for counterbalancing. This procedure was repeated after the dance class. The EEG testing room was located in a quiet, dark room at the NBS library, and the questionnaire/motor testing room was located in a carpeted conference room at NBS.

Participants were initially provided with the consent form and were asked to take their time to read through it in its entirety (Appendix A).

Figure 3.1. PRE- and POST- dance testing protocol. Effectiveness of dance for motor and non-motor symptoms were tested before (PRE) and after (POST) a single dance class using behavioral measures such as the standardized MDS-UPDRS (Part III), H&Y, and PANAS-X. MMSE and PD-NMS were measured only once during testing. EO represents Eyes Open and EC represents Eyes Closed eye state conditions for the rsEEG testing component.

rsEEG was used to measure neurophysiological changes associated with participating in a single dance class. The rsEEG task involved 3 minutes of eyes closed (EC) and 3 minutes of eyes open (EO), presented in random order.

3.2.3.1 Motor Testing Protocol

The Movement Disorder Society- Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III consists of a rater administered and evaluated motor examination to assess the motor signs of PD. The rater administering the assessment was previously trained with the MDS-UPDRS online tutorials and completed a test which followed with a certificate of completion (my certificate can be found in Appendix D followed by permission to use the MDS-UPDRS for the styudy). Part III of the UPDRS contains 18 items, including speech, facial expression, simple hand, arm, foot, and leg movements, rising from a chair, gait, freezing, and various tremors. The 18 items allow scoring of right and left sides of body or other body distribution scores, for a total

of 33 scores. From these, a total MDS-UPDRS (Part III) score was calculated, with a lower score determining a lower severity of motor impairment.

3.2.3.2 Resting state EEG (rsEEG) Testing Protocol

Resting state EEG (rsEEG) measurements were obtained using the Emotive EPOC 14 channel wireless neuroheadset and recorded using accompanying TestBench software (Emotive Systems, Inc., 2012 San Francisco, CA). Active electrodes were placed according to the international 10-20 system and include AF3, AF4, F3, F4, F7, F8, FC5, FC6, P7, P8, T7, T8, O1 and O2 and reference electrodes at P3/P4, common mode sense (CMS-left mastoid), and driven right leg (DRL-right mastoid) (Appendix I). The data was sampled at a rate of 128 Hz per channel with 16-bit ADC resolution and 0.02 to 45 Hz resolution with digital notch filters at 50 Hz and 60 Hz. Data is then sent to the computer by utilizing a USB dongle, communicating using the 2.4 GHz band. Felt tip pads were moistened with saline solution prior to placement in each electrode. Participants were instructed to remain as still and as relaxed as possible, and to let their mind wander during the recording. rsEEG was collected in two 3 minute epochs, once with eyes open (EO) and once with eyes closed (EC). The purpose of EO and EC conditions is that arousal activity is dependent on these conditions; where arousal is higher in EO conditions. Separating EO and EC conditions allowed me to narrow in on changes in brain activity while eliminating any arousals from having the eyes open. Specifically, alpha frequency in EEGs is dominant (higher) in healthy individuals during an EC resting state condition allowing me to differentiate any potential differences between the healthy control group and that of PwPD both at baseline and after dance class participation. Order of EO and EC conditions were randomized for all participants. POST testing, the participant was asked what they had been thinking about

during the 6 minutes, and this was recorded on a note pad by the experimenter in order to help identify any possible abnormalities that may be seen during the data cleaning phase (such as a sneeze that will be indicative as noise at a particular time in the EEG data and referring to the notes will help clarify that). Stimuli on the computer screen during rsEEG showed a picture of either EC or EO and the corresponding written instructions were presented using MediaLab (v2012.4.119, Blair Jarvis for Empirisoft Co., New York, NY). Data markers were recorded in the data and sent from MediaLab to TestBench via Virtual Serial Port Driver (Version 7.1, Eltima Software, 2013, Bellevue, WA).

Preprocessing of EEG data was conducted offline using Matlab (Version 7.10.0.99 R2010a, The Mathworks, Inc., Natick, MA) with the addition of the Fieldtrip toolbox (Oostenveld et al. 2011). Steps taken for data pre-processing was as follows (as taken from [53]):

Step 1: The .edf files from TestBench were converted to .mat files.

The data was converted from a 3D matrix (Channel, Samples, Epochs) to a 2D matrix (Channel, Samples) because a single Epoch was recorded for each participant and thus this dimension could be dropped. This was done in order to utilize Matlab software.

Step 2: Data markers were identified.

The Eltima software allows numerical markers to be sent to the EMOTIV software during recording. At the start of the EO rsEEG segment, the number 98 will appear in the data. At the start of the EC rsEEG segment, the number 100 will appear in the data. The order identified the start of each segment (via numbered marker), and the point 180 seconds after each segment began.

Step 3: Epoch segmentation: redefining in to EO and EC segments.

The data was then epoched in to a 3-minute EO segment and a 3-minute EC segment.

[1]Step 4: Epoch segmentation: redefining in to 2-second bins.

Each 180-second rsEEG segment was redefined in to 2 second bins, creating 90, 2 second bins for each rsEEG segment (EO and EC).

Step 5: Preprocessing for visualization

A two pass Butterworth filter was applied from 1 Hz - 50 Hz. Demean (baseline correction) and detrend (removal of mean value or linear trend) corrections will be applied.

Step 6: Visual inspection and data checking

Each 2-second epoch of data was visually inspected using variance, amplitude maximums and max z values. Using these values, visually obvious outliers in the data were rejected. Please refer to Table 3.2 which depicts the rejected outliers for the groups, time and condition.

Table 3.2. Visual inspection of rejected outliers in 2-second epochs for each group, time and condition.

	PD		**Controls**	
	PRE	**POST**	**PRE**	**POST**
EO	15.3 ± 8.1	14.6 ± 7.8	11.7 ± 5.4	12.3 ± 6.3
EC	14.4 ± 7.6	12.7 ± 7.2	10.8 ± 5.7	11.5 ± 6.6

Overall, for PD in EO condition there was a total of 149.4 ± 16.2 seconds (2.49 minutes) and for EC condition 151.2 ± 15.2 seconds (2.52 minutes) of useable rsEEG data in the PRE dance time. For the Control groups in EO condition there was a total of 156.6 ± 10.8 seconds (2.61 minutes) and for EC condition 158.4 ± 11.4 seconds (2.64 minutes) of useable rsEEG data in the PRE dance time.

Overall, for the PD in EO condition there was a total of 150.8 ± 15.6 seconds (2.51 minutes) and for EC condition 154.6 ± 14.4 seconds (2.58 minutes) of useable rsEEG data in the

[1]Steps 4 – 10 were completed for each participant and for each PRE- and POST- dance .mat files.

POST dance time. For the Control groups in EO condition there was a total of 155.4 ± 12.6 seconds (2.59 minutes) and for EC condition 157 ± 13.2 seconds (2.62 minutes) of useable rsEEG data in the POST dance time.

Step 7: Independent Component Analysis (ICA)

To further clean the data, the raw signal was mathematically divided in to 14 independent components depending on naturally recurring variances in the data. The first few components house the largest variances, and are typically where artifacts such as eyes blinks, eyes movements, and/or noise are found.

Step 8: Visual inspection of the topographical disposition of the components

Topographic dispositions of each component were visually inspected for possible artifact profiles (Figure 3.2) such as eye blinks, eye movements, or noise.

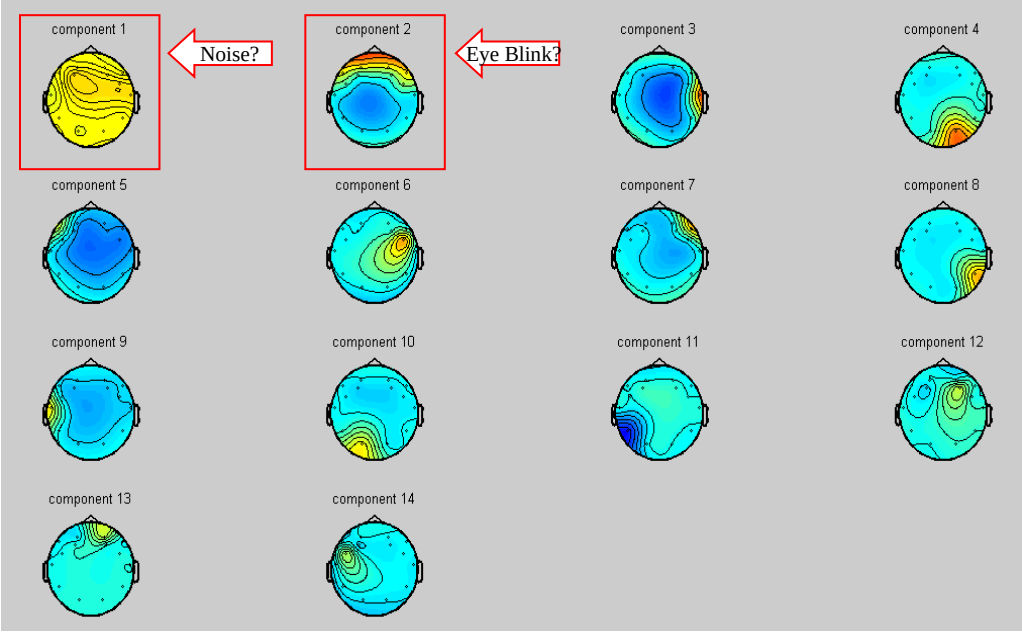


Figure 3.2. Example data from a single participants topographical disposition of components from Step 8 of visual preprocessing. Components 1 to 14 created by ICA. All components were visually inspected for potential eye movements (EM), eye blinks (EB) or noise profiles. In this example we would flag Component 1 as potential aberrant signal noise which is characterised as a single solid color over entire topographical head map and Component 2 would be flagged as

potential EB characterised as a centralized hotspot in the frontal region. An EM, not seen here, is characterised by a hot spot and an ipsilateral cold spot in the frontal region.

Step 9: Component Inspection

Using channels AF3 and AF4 (black and blue lines depicted in Figure 3.3 below), each 2-second epoch within identified components of interest (Step 8) was further inspected for EB, EM or noise.

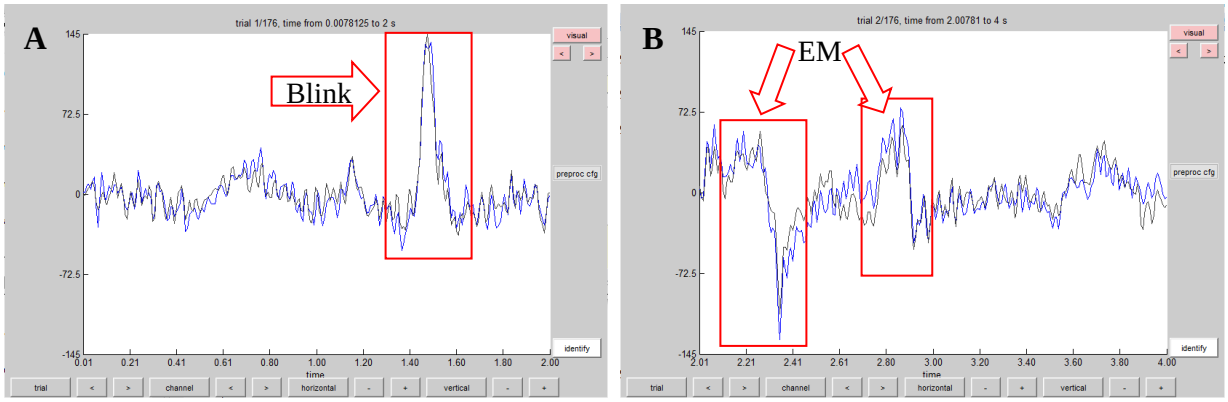


Figure 3.3. A two-second epoch within channels AF3 and AF4 containing a potential **A.** blink and **B.** eye movement. These will be further investigated within Component 2 (Figure 3.2) in Step 9 of preprocessing.

When a two-second epoch containing any of the artifacts is identified, the specific epoch is then further examined within each identified component from Step 8. In this example, we would further investigate the EB and EM within Component 2. This step is completed in order to ensure that the previously identified components of interest do in fact contain these artifacts, before their removal in following Step 10. For each potential artifact identified in Step 8, a minimum of four, two-second epochs containing this artifact was identified before a component is removed.

Step 10: Component removal

Components containing confirmed artifacts were removed from the data, and a component rejected .mat file was created.

Step 11: Re-reference

To clean the signal further, the average signal across all electrodes was then computed and subtracted from each electrode, for each time point.

Step 12: Frequency Analysis – Power Spectra Computed

A multitaper Fast Fourier Transformation (FFT) was applied, in which the entire spectrum for the entire data length was analyzed. Frequencies of interested were organized in to 0.5 Hz increments from 1 Hz to 50 Hz, and a Hanning window will be applied in order to correct for leakage in the FFT.

Step 13: Alpha Peak Search

The alpha frequency peak (y-axis) and associated power (x-axis) was identified for each subject for EO and EC separately, for each individual electrode in the PRE- and POST-dance rsEEG. Data was then exported to SPSS for statistical analyses.

3.2.4 Design and Statistical Analyses

All iAPP values were log transformed before undergoing any statistical tests in order to be able to use *normal* statistical measures. Statistical analyses were conducted offline using SPSS (Version 20, IBM Corp, 2011, Armonk, NY). Both alpha peak frequency (Hz) and absolute alpha power (μV^2) significant changes over time were calculated using two separate three-way repeated measures ANOVAs. Condition (PRE to POST), Electrodes (fourteen) and Group (PD and HC) as factors. Condition and Electrode were the within subject factors and Group as the between-subject factor. To explore global right (R) versus global left (L) hemisphere significance from PRE to POST dance class, a three-way repeated measures ANOVA was used, using Hemisphere (R and L), Time (PRE to POST) and Group (PD and HC)

as factors. Time and Hemisphere were within subject factors and Group as a between subject factors. To further analyse the significance, a two-way repeated measures ANOVA in each group as conducted, using Hemisphere and Time as factors.

Separate two-way repeated measure ANOVA were conducted for each dependent variable. The independent variables were Group (PD and HC) and Time (PRE or POST) where group is a between-subject factor and condition was the within-subject factor. The dependent variables were Motor Assessments (MDS-UPDRS Part III), positive and negative affect (PANAS-X), non-motor symptoms of PD (PD-NMS), and electro-cortical alpha changes (rsEEG). In addition, alpha peak frequency was correlated with changes in UPDRS Part III motor scores in order to reveal if the motor changes are associated with any alpha band changes. If and when main effects of interactions were determined to be significant, pairwise comparisons were conducted to determine the direction of the effect.

3.3 RESULTS

3.3.1 Positive and Negative Affect

A 2 (Group) X 2 (Time) repeated measures ANOVA revealed that mean scores in PANAS-X negative affect decreased over time for both groups, as demonstrated by a significant main effect of time [$F(1,30) = 30.30$, $p < 0.01$] and a medium effect size ($\eta^2 = 0.50$) as observed in Figure 3.4A. There were no other significant main effects or interactions ($p > 0.05$).

The repeated measures ANOVA for positive affect revealed an increase in overall positive scores over time [$F(1,30) = 10.27$, $p < 0.01$] with a medium effect size ($\eta^2 = 0.26$). Also, the interaction of Time x Group showed a significant interaction, [$F(1,30) = 6.529$, $p = 0.016$] and a small effect size ($\eta^2 = 0.18$), seen in Figure 3.4B. Pairwise comparisons showed that positive affect

scores significantly increased in the HC group only from PRE (M = 34.81, SD = 1.87) to POST (M = 39.25, SD = 2.16) dance class, and not in the PD group ($p > 0.05$).

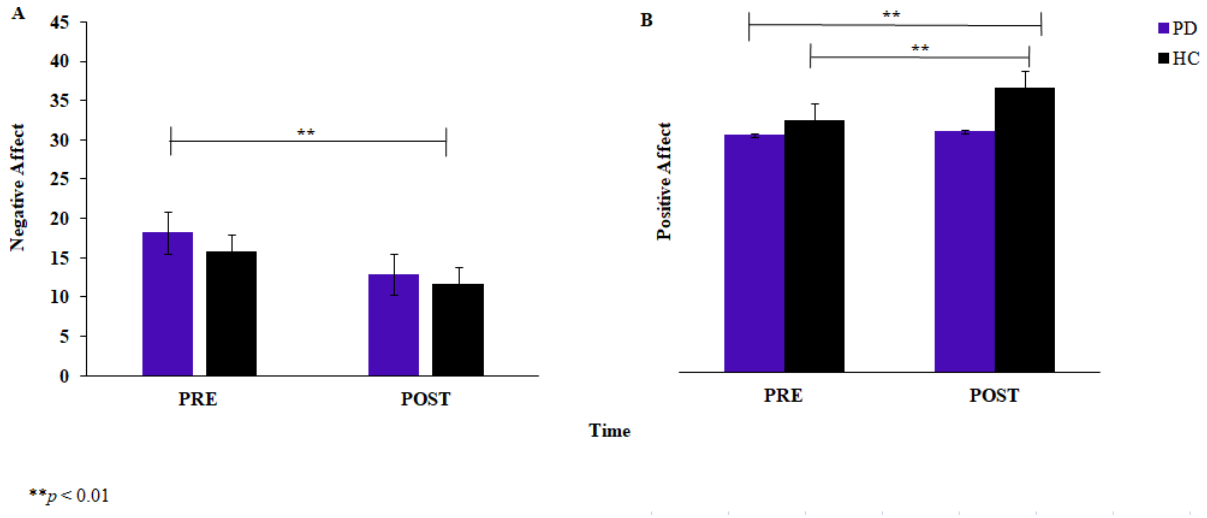


Figure 3.4. Positive and negative affect changes over time. **A.** Significant decreases were observed in overall negative affect in both the PD and HC groups over time, $F(1,30) = 30.30$, $p < 0.01$, with a medium effect size, $\eta^2 = 0.50$. **B**: Significant increases were found in positive affect scores over time. A significant interaction between Time x Group $F(1,30) = 6.529$, $p = 0.016$ revealed a significant increase in positive affect scores in the HC group only from PRE to POST. Bars represent standard error of the mean (SEM). **Significance at $p < 0.01$.

3.3.2 Behavioral

MDS- UPDRS Part III motor scores were higher in PD group (M= 20.88, SD= 1.44) than the HC group (M= 3.00, SD= 1.36) [$F(1,34) = 84.80$, $p < 0.001$] with medium effect size (η^2= 0.71). Significant differences were found between PRE and POST time, where overall PRE UPDRS scores were higher (M= 13.05, SD= 1.54) in comparison to POST UPDRS scores (M= 10.83, SD= 1.26), [$F(1,34) = 31.21$, $p < 0.001$] with medium effect size (η^2= 0.48). Additionally there was a significant interaction between Time X Group, where post hoc analysis revealed that PD had a significantly higher UPDRS scores before dance (M= 22.94, SD= 1.58) in comparison

to after class (M= 18.82, SD= 1.29) [$F(1,34) = 50.907$, $p < 0.001$] with a medium effect size (η^2= 0.60). No significant differences were seen in the HC group p= 0.56.

There was a significant difference in H&Y scores between the two groups [$F(1,34) = 72.679$, $p < 0.001$], where PD group had higher H&Y score (M= 1.29, SD= 0.11) than HC (M= 0.00, SD= 0.10). There were no significant differences found in H&Y scores with regards to time, PRE versus POST dance class.

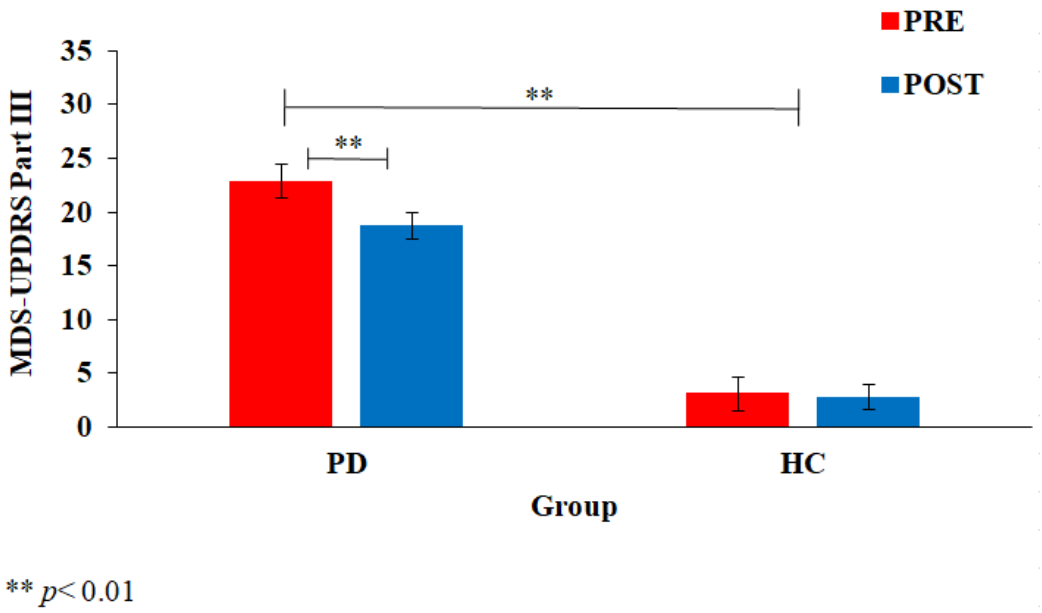


Figure 3.5. MDS- UPDRS Part III motor scores. PD group motor scores decreased after a single dance class. Bars represent standard error of the mean (SEM). **significance at $p < 0.01$.

3.3.3 rsEEG Alpha

After completing rsEEG data pre-processing for alpha peak power and frequency analysis, our PD group had an N= 13 and HC group size was N= 15 that was used for statistical analysis. Participants were excluded due to either too noisy of a signal, incomplete full 6-minute data set in either PRE or POST testing time, or missing data for either PRE or POST testing time.

Global Alpha Peak Frequency (Hz)

A 2 (Group) x 2 (Condition) x 2 (Time) x 14 (Electrode) repeated measures ANOVA revealed a main effect of Group $F(1, 26) = 8.880$, $p = 0.006$, $\eta^2=0.255$, in which Controls exhibited a higher iAPF (M= 9.10, SD= 0.186) when compared to individuals with PD (M= 8.28, SD= 0.200) (Figure 3.6 and Figure 3.7), a main effect of Condition $F(1,26) = 4.906$, $p = 0.036$, η^2= 0.159 where EC (M= 8.80, SD= 0.163) had a higher alpha peak frequency than EO condition (M= 8.58, SD= 0.127). No other main effects of Time, Electrode or interactions were found to be significant ($p > 0.05$).

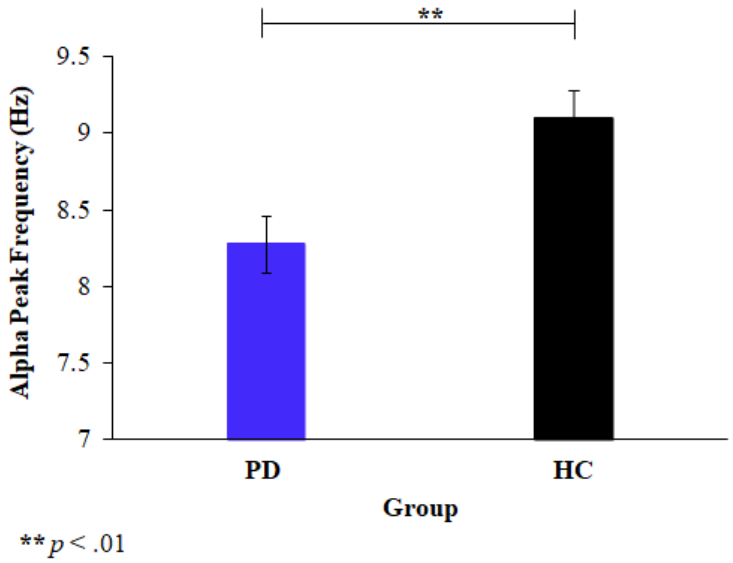


Figure 3.6. Healthy Controls (HC) showed a higher global iAPF when compared to PD when averaged across all electrodes. Bars represent standard error of the mean (SEM). **significance at $p < 0.01$.

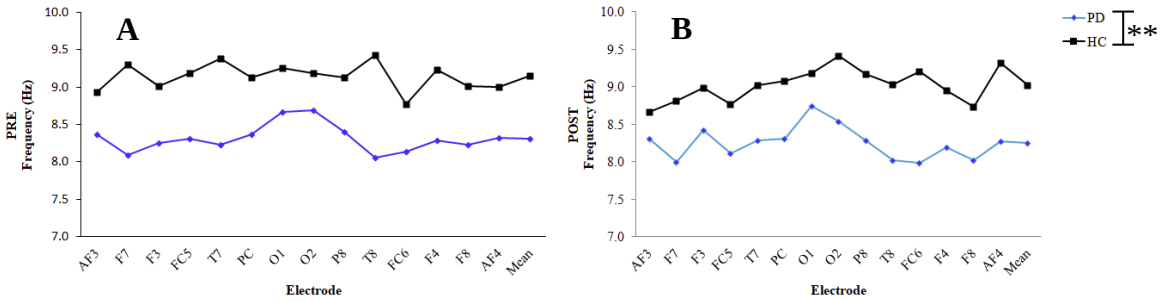


Figure 3.7. Mean alpha frequency (Hz) for each electrode **A**. PRE and **B**. POST dance class for PD and HC. **significance at $p < 0.01$.

Global Alpha Peak Power (logμV^2)

A 2 (Group) X 2 (Condition) X 2 (Time) X 14 (Electrode) repeated measures ANOVA revealed a main effect of Electrode $F(5.247, 136.411) = 11.881$, $p < 0.001$, $\eta^2=0.314$, a main effect of Time $F(1, 26) = 6.864$, $p = 0.014$, $\eta^2=0.209$ where alpha peak power was higher POST dance class (M= .321, SD= 0.088) in comparison to PRE dance class (M= .146, SD= 0.079), a main effect of Condition $F(1, 26) = 14.870$, $p < 0.001$, $\eta^2=0.364$, where EC had a higher alpha peak power (M= .348, SD= 0.091) in comparison to EO (M= .119, SD= 0.072). A main effect for Group was approaching significance $F(1, 26) = 3.286$, $p = 0.081$, $\eta^2=0.112$, where PD had higher alpha peak power (M= .373, SD= 0.112) than HC's (M= .095, SD= 0.105) (Figure 3.8). There was a two-way interaction between Condition and Electrode $F(4.656, 121.066) = 8.503$, $p < 0.001$, $\eta^2=0.246$.

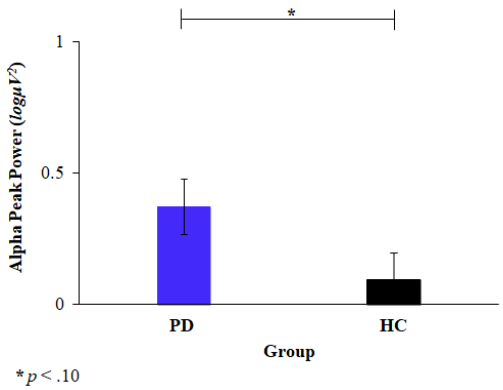


Figure 3.8. Healthy Controls (HC) showed a lower global iAPP when compared to PD when averaged across all electrodes. Bars represent standard error of the mean (SEM). *Significance at $p < 0.10$.

Even though there were no interaction effects for Condition x Time x Group, there were main effects for each of these variables and thus the interactions were investigated further. When examining the Condition by Time within each Group, PD showed no significant increases in alpha peak power from PRE to POST in either EC ($p_B = 0.344$) or EO ($p_B = 0.430$). However, HC's showed significant increases in alpha peak power from PRE to POST in both EC ($p_B < 0.05$) and EO ($p_B < 0.05$) (Figure 3.9). When examining the Group by Condition within each Time, PD showed increases in alpha peak power when compared to controls in only the EO condition ($p_B < 0.05$) PRE dance class (Figure 3.9), no significant changes in alpha peak power were observed post dance class in either the EO ($p_B = 0.518$) or EC ($p_B = 0.190$) conditions between the two groups. Lastly, when examining the Time by Condition within each Group, where our PD group showed stronger alpha peak power in EC over EO only in the PRE time point ($p_B < 0.05$), whereas our HC's showed stronger alpha peak power in EC over EO in both PRE ($p_B < 0.001$) and POST ($p_B < 0.05$) dance class (Figure 3.9). Refer to the corresponding head maps below for a visual comparison of the EC condition, as the EC condition was the focal interest of comparisons (Figure 3.10).

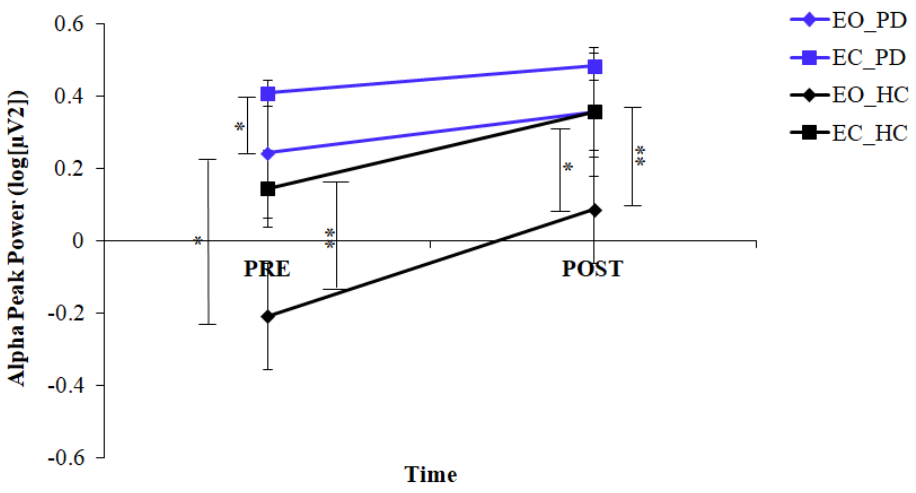


Figure 3.9. Time X Group X Condition alpha peak power (averaged across all 14 channel electrodes). Bars represent standard error of the mean (SEM). Blue lines are PD, black lines are HC's, diamond shape is for EO condition and square is for EC conditions. Significance at $^{**}p < 0.001$ and $^{*}p < 0.05$.

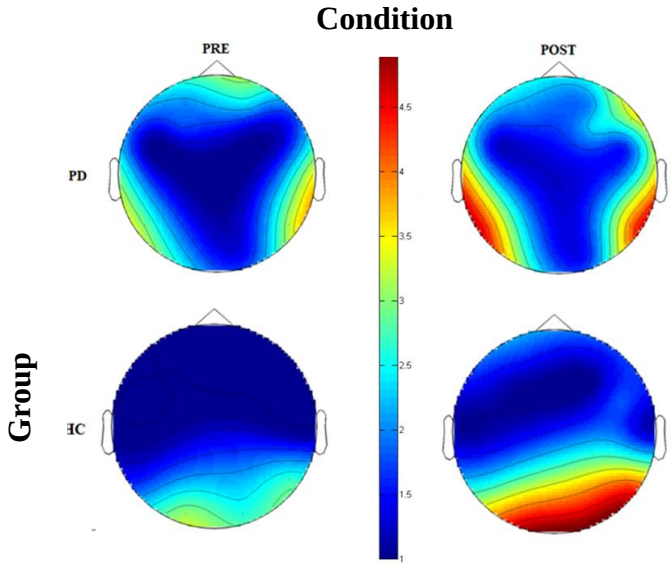


Figure 3.10. Eyes closed head maps averaged across participants in both PD and HC groups. PRE condition is on the left and POST condition is on the right. Middle bar represents $log\mu V^2$ range in alpha peak power.

Left and Right Hemisphere Asymmetry ($log\mu V^2$)

In order to determine whether there was an existence of hemispheric asymmetry a three-way repeated measures ANOVA of 2 (Hemisphere) X 2 (Time) X 2 (Group) was conducted and revealed no significant difference (p = 0.541). However, a main effect of Time $F(1, 26) = 8.269$, $p = 0.008$, η^2=0.241 where difference between left and right hemispheric asymmetry was greatest after the dance class (M= 1.30, SD= 0.380) in comparison to before (M= .678, SD= 0.363). An approaching significant interaction between Time and Group $F(1, 26) = 3.590$, $p = 0.069$, η^2=0.121 and a pairwise comparisons revealed that hemispheric asymmetry was greater POST class than PRE in only the HC's ($p_B < .05$) and no difference in hemispheric asymmetry was seen between PRE and POST in PD (p = 0.509) (Figure 3.11).

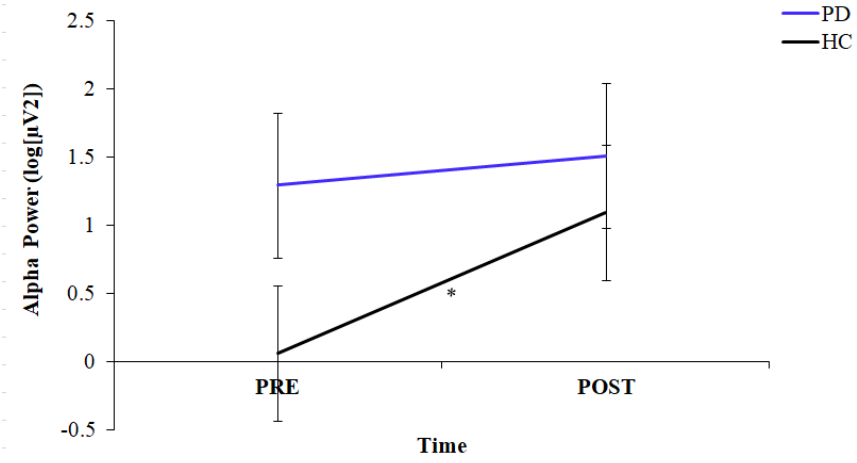


Figure 3.11. Mean global asymmetric alpha power changes in PD and HC PRE to POST dance class. Bars represent standard error of the mean (SEM). Blue lines are PD, black lines are HC's, diamond shape is for EO condition and square is for EC conditions. Significance at * $p < 0.10$.

Even though there was a non-significant interaction effects between the variables of 2 (Hemisphere) X 2 (Time) X 2 (Group), there were main effects for some of these variables, as stated above, as such the interactions were explored further. When examining the Hemisphere by Time within each Group, PD and HC's showed no difference in hemispheric asymmetry for

alpha power from PRE to POST in either Left or Right hemisphere in both groups ($p > 0.05$). When examining the Hemisphere by Group within Time, HC's showed an increase in alpha power Left hemispheric asymmetry from PRE to POST ($p_B < 0.05$) as well as an increase in Right asymmetry from PRE to POST ($p_B < 0.05$), depicted in Figure 3.12. Finally, when examining Time by Group within Hemisphere, PD and HC's showed no difference in Left and Right hemispheric asymmetry in either the PRE or POST time points ($p > 0.05$).

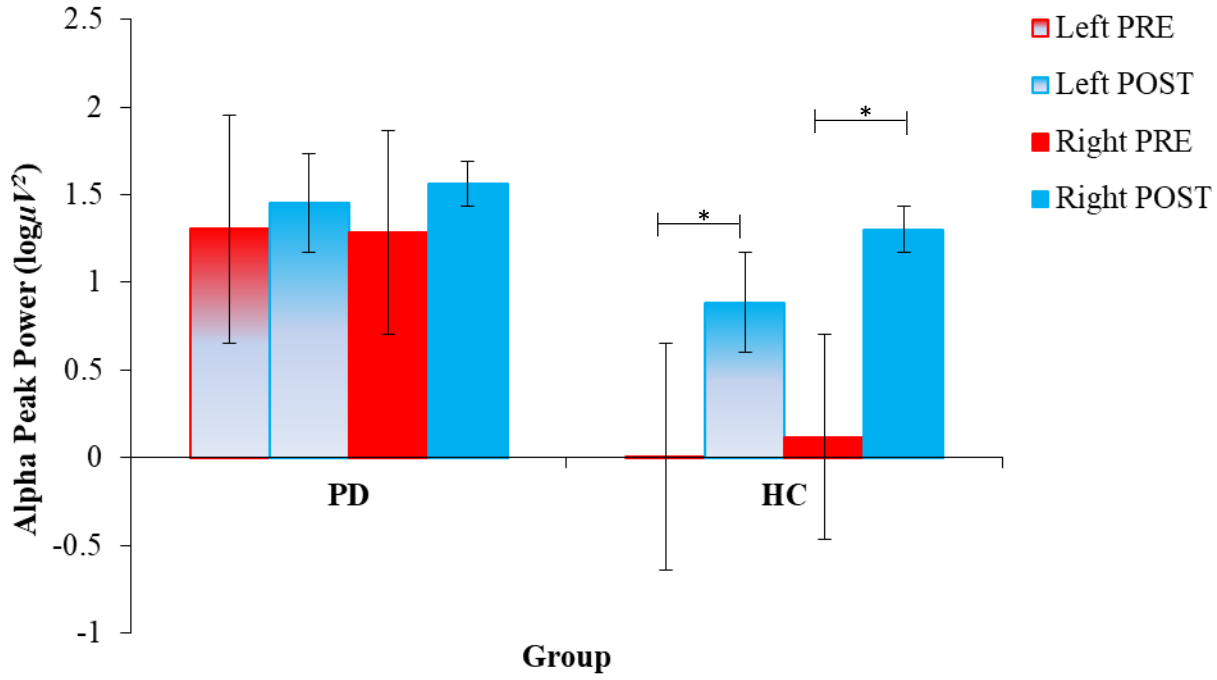


Figure 3.12. Mean left (gradient fill) and right hemispheric asymmetry alpha power changes in PD and HC. Bars represent standard error of the mean (SEM). Blue bars are POST, red bars are PRE. Significance at * $p < 0.05$.

Anterior Individual Alpha Peak Power ($log\mu V^2$)

To evaluate an existence of frontal asymmetry that may have arisen from dance participation, an averaged anterior alpha power in the EC condition was computed for the left (comprising of electrodes AF3, F7, F3 and FC5) and right (comprising of electrodes AF4, F4, F8

and FC6) anterior hemispheres (refer to Appendix H for electrode numbering and placement). A 2 (Time) X 2 (Group) X 2 (Hemisphere) repeated measures ANOVA revealed a significant main effect of Time $F(1, 26) = 7.018$, $p = 0.014$, $\eta^2=0.213$ and a Condition $F(1, 26) = 13.280$, $p = 0.001$, $\eta^2=0.338$ where EC was higher than EO. Even though there was no significant difference found between the two groups ($p = 0.258$), the two groups were still evaluated separately with the intent of uncovering any anterior changes in iAPP that were dance induced. Thus, for each group a 2 (Hemisphere) X 2 (Time) repeated measures ANOVA was conducted. In our PD group, there was no significant Hemisphere X Time interaction $F(1, 12) = .586$, $p = 0.459$, $\eta^2=0.2047$, however because the purpose of this analysis was to evaluate asymmetric changes in anterior alpha power, I continued to investigate any pairwise comparisons. The results for our PD group revealed no significant differences in right or left anterior alpha peak power from PRE to POST dance class. The Control group displayed a significance for the effect of Time $F(1, 14) = 9.457$, $p =0.008$, $\eta^2 = 0.403$). Even though the interaction of Hemisphere X Time was not significant $F (1, 14) = 2.006$, $p =.179$, $\eta^2 = 0.125$) the exploratory pairwise comparisons showed increases in the left hemisphere from PRE- to POST- dance class ($p_B < 0.05$), and no significant increases in the right hemisphere ($p_B = 0.158$) (Figure 3.13).

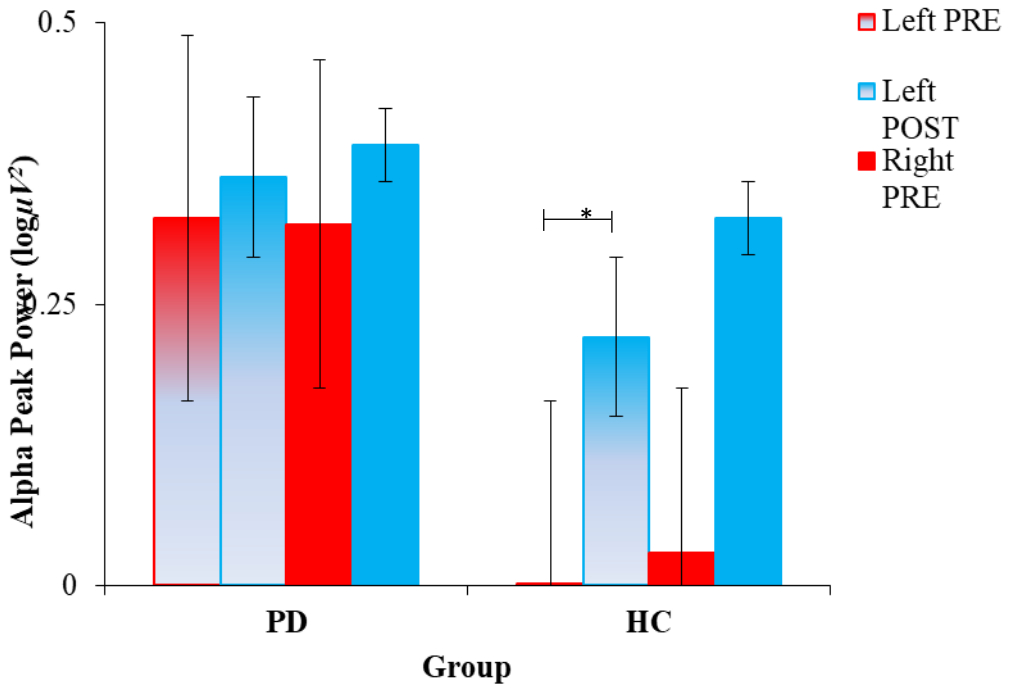


Figure 3.13. Lateralized dance induced increases in anterior/frontal iAPP in both PD and HC groups. Bars represent standard error of the mean (SEM). Blue bars are POST, red bars are PRE. Left anterior is gradient while right anterior is solid colors. Significance at * $p_B < 0.05$.

3.3.3 Individual Alpha Peak Power Correlations

Global and anterior iAPP difference values (POST – PRE dance class, left and right hemispheres separately) were correlated with changes in $UPDRS_{avg}$, $PANAS_{Positive}$ and $PANAS_{Negative}$ scores within both the PD and in the Control groups. A two-tailed Pearson's correlation revealed no significant correlations for either group, for any of the behavioral measures.

3.4 DISCUSSION

3.4.1 Summary

In this chapter we examined changes in positive and negative affect scores (using PANAS-X), motor PD symptoms (using UPDRS motor examination part III), rsEEG for alpha peak frequency (Hz) and alpha peak power (μV^2) in both PD and HC groups from participation in a

single1.25-hr dance class (PRE to POST comparisons). Results indicated that POST dance class there was an overall decrease in negative affect scores in each PD and HC groups, and an overall increase in positive affect scores between PD and HC's. Additionally, HC's exhibited an increase in positive affect scores from PRE to POST the dance class.

Motor scores in UPDRS III were higher in PD than the HC group. Overall, motor scores were higher PRE class in comparison to POST between the PD and HC's. Motor scores decreased POST dance class in the PD group from PRE dance class.

Global examination of alpha peak frequency (Hz) revealed that overall HC's exhibited a larger alpha peak frequency in comparison to the PD group and that EC condition displayed larger alpha peak frequency than the EO condition. Dance did not alter alpha peak frequency in the PD group in either EC or EO conditions and PD group did not display any eye state dependent modulation of alpha peak frequency.

Global examination of alpha peak power ($log\mu V^2$) increased POST dance class, was greater in the EC than EO condition, larger in PD group than the HC's. Further examination by each group revealed that alpha peak power was larger in the EO in our PD group than the EO condition in HC group, PRE alpha peak power was larger for EC than for PRE EO only in the PD group.

Examining the asymmetry in alpha peak power from left to right hemisphere there was a larger difference in left and right hemisphere asymmetry POST class than PRE in HC group only. HC group exhibited an increase in alpha peak power in both the left hemisphere and right hemisphere from PRE to POST dance class. No differences in alpha peak power were observed in the PD group.

Anterior alpha peak power was greatest after dance class and within the EC condition. Our healthy controls showed greater anterior alpha peak power only in the left hemispheres from before

to after dance class. No difference in either anterior left or anterior right, before to after dance class was seen in our PD group.

3.4.2 Affect and Motor Improvements

We were able to show improvements in positive affect after dance class participation in only our healthy control group and not our PD group. Actually, our PD dancers remained nearly identical from PRE to POST dance class in their positive mood. This finding is somewhat consistent with our initial hypothesis, except for our PD dance group where we hypothesized that positive affect would improve after the dance class in this group. In addition, the results showed an overall decrease in negative affect after the dance class, which was consistent with our initial hypothesis.

It is well known that exercise arouses emotional responses through the endorphin system, where a "feel good high" is produced after an amazing hard workout while at the same time providing natural pain relief (Devi, 2019). In addition, research has shown that music also elicits emotional and physiological responses (Dunbar et al., 2012; Sevdalis & Keller, 2011; Koelsch, 2015) and plays a role in brain synchrony (Janata & Grafton, 2003). With dance, your body and brain get to enjoy the combination of exercise, music and fun while providing overwhelming positivity, greater self-esteem and confidence and a sense of bonding through partner work. Historically, the BG was best known for its relevance in implications on motor functions and motor control based on the neuropathology of movement disorders and the fact that the BG pathways output primarily to the motor cortex (Turner & Desmurget, 2010). However, our understanding of the role and functions of the BG has evolved, from being known exclusively for motor function to a more complex set of functions that mediate the full range of goal-directed behaviors, including emotions, motivation, and cognition (Haber & Knutson, 2010). Several brain regions are involved

in an identifiable reward circuit including the nucleus accumbens (NAcc), a part of BG structure, which seems to be at the center of this reward circuit (Haber & Knutson, 2010). Additionally, the BG includes the caudate nucleus (CN) where it projects to the amygdala along with the NAcc, amygdala is involved in emotional processing (Banich & Compton, 2011). Damage to the central hub of the reward circuitry pathway and/or the emotional processing pathways due to a loss of dopaminergic innervation could account for the significant increase in positive affect seen in only the PD group. PD participants verbal feedback after the dance class stated that most felt tired and exhausted after being so active in the 1.25-hr dance session and as such they indicated that this exhaustion impacted their *General Positive Affect Dimension Scales* of measuring "active", "alert" and "attentive" post-dance states. Due to the fact that they felt drained, exhausted and tired after dancing, their activity level may have been low from being physically tired, not being as alert and attentive because they were mentally drained and had low attention because their mental capability was filled up during the dance class. As such, even though their positive affect scores did not increase that did not necessarily mean that they were not happier, but more so of the fact that their exhaustion may have dominated the positive feelings after the class while still feeling a sense of enjoyment and happiness which was verbally expressed by the participants following the dance class and also indicative in the decrease in negative affect scores which may be indicative of improved mood. These results reaffirm the positive impact that dancing has for not only individuals affected with PD but also for older aged adults as well.

Research has already shown that balance is improved in both elderly (da Silva Borges et al., 2014) and PD populations (Hackney & Earhart, 2009) who participate in dance classes. Our study is the first to look at motor improvements following a single dance class (1.25-hours) in PD and HC elderly population. Our results support the initial hypothesis that motor scores would

decrease after the dance class in our PD group. UPDRS Part III motor scores decreased after a single dance class indicating an overall PD motor symptom immediately improvement in our PD group whereas our HC group remained indifferent between after the class. Exercise has been shown to reduce motor symptoms, improve PD drug efficacy, and is potentially neuroprotective (Xu et al., 2010). Dance challenges autonomous physical and emotional expression by stimulating many sensorimotor systems (visual, auditory, somatosensory, and vestibular) through whole body movement in complex environments and tasks. Studies generally support teacher-led classes with visual and auditory cueing or music (rhythmic) entrainment (Batson, 2010) because these cues help regulate steady-state locomotor movements and as such PwPD discover new motor abilities and developing adaptive strategies during dance involvement that can then be then transferred to the demands of everyday tasks. A single- case pilot study conducted by Batson et al., (2014) investigated fMRI brain changes following a 1-week (5 consecutive days of 1-h classes) of improvisational dance intervention and showed changes in the BG community with increased long-range connections where the default-mode network (DMN) displayed increased long-range connectivity (Buzsáki, 2006), particularly between the BG and the cortical motor centers. Prior to the intensive training, the BG appeared in isolation from other regional connections, however post intervention there was a greater shared network community with the motor cortex where this change may be indicative of neuroplasticity changes that arise from dance and are thus revealed in the observable and measurable PD motor symptoms directly impacting mobility and providing motor improvements. While the underlying brain mechanisms describing these changes is unclear, previous researchers suggest that improved movement following dance participation may be due to increased multisensory cueing and more autonomic movement patterns (due to the music rhythmic cueing with step repetition and coordination).

3.4.3 Alpha Peak Frequency and Alpha Peak Power

Brain rhythms, also known as oscillations, are linked with numerous cognitive functions and grouped into several oscillatory bands (Buzsáki, 2006). Oscillatory alpha-band activity is linked to processes such a perception (Benwell et al., 2017), attention (Keitel et al., 2019), and working memory (Bonnefond & Jensen, 2012). Alpha power has been shown to be both inversely related to both blood-oxygen-level dependent (BOLD) signal (Scheeringa et al., 2016) and cortical excitability (Haegens et al., 2011) with functional inhibition of cortical regions that are responsive to information that is irrelevant to the task at hand (Jensen & Mazaheri, 2010). Few studies have examined brain functional correlates of dance interventions (Batson et al., 2014) and no studies to date have investigated the brain structural correlates of dance-based therapies. We know that abnormal oscillatory activity occurs within the BG in PwPD. This abnormal activity is modified by the stimulation of different cerebello–thalamo–cortical structures, restoring normal unsynchronized activity in the BG circuitry and reducing the clinical symptoms of PD. There is much research done on deep brain stimulation techniques, which is therapy where areas of the BG are stimulated at high frequencies, in order to explore the causal links with motor movement and manipulation of alpha oscillations. This research has shown that suppressing alpha and beta band activity across widespread areas such as the sensorimotor cortex and STN can alleviate PD motor symptoms (Luoma et al., 2018). In humans, STN activity is coherent with EEG recorded over the sensorimotor areas of the brain (Fogelson et al., 2006). Our PD dancers did exhibit higher alpha power in comparison to our HC, and this higher alpha power may explain a link to PD motor impairment where previous research has shown that higher alpha power is associated with greater motor impairment. Contrary to previous research, our PD group did show higher alpha power in the EO condition over the EC condition, and no difference in

global alpha peak power was seen in our PD group indicating no change in alpha oscillation following the dance class.

Our PD group displayed a global slowing of iAPF in comparison to our HC's. This result has been consistent to previous research that showed PwPD have impairments with executive functions such as working memory and attention where lower iAPF is correlated to lower scores in cognitive performance in these areas (Angelakis et al., 2004). Because our PD group showed lower iAPF in both EO and EC conditions this may be reflective of PD impairment in underlying brain networks that are responsible for cognitive performance in areas such as executive function. We have also demonstrated that individuals with PD do not show eye state dependent modulation of iAPF peaks in which the EO condition elicits a lower iAPF than the EC condition. This result could be explained by the dopaminergic deficiency at the retinal level where it behaves as though it is improperly dark-adapted in PwPD. Or the fact that visual acuity in PD is a well –established risk factor for the presence of visual hallucinations in PD and thus this could be reflective in our PD groups higher iAPF as seen in the EO condition that was not observed in the EO condition of the HC's (Archibald et al., 2009). Further, structural degeneration of the retina has been reported in PD and these changes have been shown to be associated with retinal dark-light adaptation (Archibald et al., 2009) which could also help to explain the no difference seen in our EC and EO conditions within our PD group.

When examining anterior (or frontal) iAPP, anterior asymmetry (left versus right) and its relationship to emotional state our results indicated that HC had greater iAPP in the left anterior hemisphere after the dance class where PwPD dancers did not show any anterior hemispheric differences or asymmetry from before or after the dance class. Anterior EEG activity reflects prefrontal cortex activity and one's ability to regulate emotions using strategies of control and

emotion expression (Grecucci et al., 2013). Greater iAPP tends to be associated with positive emotions and enhanced emotion regulation processes, this result could be implying that the increases seen in the left anterior hemisphere of our HC's was due to the positive emotions elicited by participation in the dance class and this was in fact shown and supported in the PANAS-X positive affect score increases for our HC group after the dance class (see section 3.3.1 above). Our PD dancers however showed no difference between PRE and POST dance class for both the left or right hemispheres, indicating no change in alpha power as a function of dance in the left and right anterior hemispheres. Although, PD dancers did have and overall negative affect decrease in their PANAS-X scores after the dance class, they did not exhibit any increases in alpha power frontal asymmetry, and this could be due to the idea that we did not directly measure any depression based scores previous to dance participation in our PD group. Therefore, this finding remains unconfirmed in the hypothesis of whether the PD dancers previously suffered from depression and whether that would then be depicted in their rsEEG anterior left and right alpha peak power asymmetry. One would expect that if experiencing depression, then alpha peak power would be higher in the right hemisphere given that this hemisphere is responsible for avoidance related negative emotions like sadness, fear and anxiety, and as such expect that decreases in anterior left hemisphere, being that this hemisphere is responsible for positive emotions and control.

3.4.4 Limitations and Future Directions

Future studies on the brain and behavioral correlates of dance interventions are required in order to further understand and validate the true promise of dance therapy, precisely research that includes both brain function and structure is required in order to have a more complete understanding of the neural correlates of dance. Further, showing alpha rhythm alterations and

changes in motor and non-motor PD symptoms over a longer period of time of dance participation should be explored in order to show if these changes last for a longer period of time and if so, do these changes further improve over time and how. In addition, what would be useful to understand is which types of patients respond best to dance therapy and why. This is the objective of my third chapter and study, which explores motor and non-motor PD symptom changes over a period of over 3-years of dance involvement.

3.5 CONCLUSION

This study reports motor and affective improvements consistent with initial hypothesis and previous studies, which reaffirm the positive impact that dancing has for not only individuals affected with PD but for older aged adults as well. As PD symptoms are multi-faceted, this study supports that the dance environment improves a variety of PD symptoms and does so in a very short time frame (i.e., after a single 1.25-hr dance class) and may provide an alternative beneficial treatment for individuals with PD.

CHAPTER FOUR

PARKINSON'S DISEASE MOTOR SYMPTOM PROGRESSION SLOWED WITH MULTISENSORY DANCE LEARNING OVER 3-YEARS: A PRELIMINARY LONGITUDINAL INVESTIGATION.

Bearss, K. A., & DeSouza, J. F. X. (2021). Parkinson's Disease Motor Symptom Progression Slowed with Multisensory Dance Learning over 3-Years: A Preliminary Longitudinal Investigation. *Brain Sciences*, *11*(7), 895.

The final publication is available at https://doi.org/10.3390/brainsci11070895

4.1 ABSTRACT

Parkinson's disease (PD) is a neurodegenerative disease that has a fast progression of motor dysfunction within the first 5 years of diagnosis, showing an annual motor rate of decline of the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) between 5.2 and 8.9 points. We aimed to determine both motor and non-motor PD symptom progression while participating in dance classes once per week over a period of three years. Longitudinal data was assessed for a total of 32 people with PD using MDS-UPDRS scores. Daily motor rate of decline was zero (slope = 0.000146) in PD-Dancers, indicating no motor impairment, whereas the PD-Reference group showed the expected motor decline across three years ($p < 0.01$). Similarly, non-motor aspects of daily living, motor experiences of daily living, and motor complications showed no significant decline. A significant group (PD-Dancers and PD-Reference) by days interaction showed that PD who train once per week have less motor impairment ($M = 18.75$) than PD-References who do not train ($M = 24.61$) over time ($p < 0.05$). Training is effective at slowing both motor and non-motor PD symptoms over three years as shown in decreased scores of the MDS-UPDRS.

Keywords: multisensory therapy; motor symptoms; Parkinson's disease; neurorehabilitation; longitudinal

4.2 INTRODUCTION

Parkinson's disease (PD) is referred to as a movement disorder because of the associated tremors, stiffening or rigidity of movements, slowing of movements (bradykinesia) and postural instability (balance). However, PD also affects many other body symptoms not associated to movement such as anxiety, depression, dementia and mild memory and thinking problems as well as executive dysfunction (ED). The progression of these PD motor (Lang & Lozano, 1998; Tan et al., 2021) and non-motor (Chaudhuri et al., 2007; Martinez-Martin et al., 2011) symptoms negatively impact function and quality of life (QoL). Studies have shown beneficial effects of gait speed, balance, locomotion and aspects of quality of life from various styles of dance classes: including dance that incorporates ballet, jazz, contemporary, theater and choreography, as well as a well-developed dance curriculum known as Dance for Parkinson's Disease (DfPD) classes (Heiberger et al., 2011; Westheimer, 2008; Houston & McGill, 2013; Volpe et al., 2013; Westheimer et al., 2015; Bearss et al., 2017; dos Santos Delabary et al., 2020). Dance offers an enjoyable, multidimensional enriched environment where involvement in such a task provides dancers with the necessary tools to enhance balance, coordination, flexibility, imagery, imitation, creativity, rhythm, memory and learning—all of which contribute to improvements in motor symptoms (Heiberger et al., 2011; Westheimer, 2008; Houston & McGill, 2013; Volpe et al., 2013; Westheimer et al., 2015). In addition, dance enhances social connection, reduces stress and tension, and boosts confidence and self-esteem leading to an overall improvement in mood (Mandebaum & Lo, 2014; Westheimer et al., 2015). In addition, research on dance in PD has shown improvements in patient-caregiver QoL (Giménez-Llort & Castillo-Mariqueo, 2020) thus we encouraged the caregivers to enrol in the class.

Research on the effects of dance for people with PD (PwPD) has mainly focused on short-term (Hackney & Earhart, 2009; Batson, 2010; Cameron et al., 2013; Hackney & Earhart, 2010; McKee & Hackney, 2013; de Bruin et al., 2010; Hackney & Earhart, 2010) functional outcomes in motor (Heiberger et al., 2011; Westheimer, 2008; Bearss et al., 2017) and non-motor (Bearss et al., 2017; Hackney & Earhart, 2009) symptoms. A few studies in PD have investigated longer intervention periods ranging from six months (Batson, 2010; Hackney & Earhart, 2009), twelve months (Duncan & Earhart, 2012; McGill et al., 2019; McGill et al., 2019; Foster et al., 2013) or as long as two years (McRae et al, 2018; Duncan & Earhart, 2014). No research to date has examined how long-term participation in dance (greater than 12-weeks) impacts disease progression greater than two years. The longest research to date is a 2-year study by McRae et al., (2017), which evaluated QoL, self-efficacy, the effect of DfPD classes on daily activities outside of class and functional mobility in PD participants volunteering in DfPD. They found that DfPD classes positively impacted both social and emotional function outside of the classes, and that motor functioning affects QoL through self-efficacy (McRae et al., 2018). Although this study demonstrated the positive influence dance has on social and emotional function in PwPD, it lacked using a motor rating assessment that is most widely applied in PD such as the Movement Disorders Society—Unified Parkinson's Disease Rating Scale (UPDRS Part III motor scale). In addition, research has yet to show how continuous participation in dance class impacts the progression of PD motor and non-motor symptomology.

A study conducted by Duncan and Earhart (2014) (Duncan & Earhart, 2014) used UPDRS Parts I through III, respectively. The results showed lower scores for all three UPDRS measures at 12- and 24-month follow-up in the five Argentine tango participants in comparison to five PD patients in the control group. To date, Duncan and Earhart's (2014) research is the

only longitudinal study which utilizes the UPDRS as its assessment tool. Our study is the most up to date longitudinal follow-up seen in this field of research that was last updated by Duncan in 2014. Since Duncan and Earhart's (2014) study used the same assessment tools as our current study (all parts of the UPDRS) over a long period of time, thus we are treating Duncan and Earhart's (2014) study as a precedent to help shape and guide our current study. With that, our study not only expands the time duration of this line of research to include data for over a three-year period (over one year longer than Duncan and Earhart's (2014) study) but it also increased the sample size to sixteen (16) PwPD dance trained participants (an increase of 220% in sample size).

The first aim of this current preliminary report is to evaluate our PD-Dance cohort through an interim period on progression of the motor and non-motor PD symptoms while participating in weekly DfPD classes for over three years. Ultimately, the results of this small-scale preliminary study will allow us to investigate whether using our current outcome measures of all parts of the UPDRS will be feasible to use in a future randomized controlled trial (RCT) leading to our second goal of the study.

To date, research on the progression of cardinal features of PD has shown large variability amongst PD. In a study with average follow-up of approximately six years, Jankovic and Kapadia (2001) assessed overall functional decline in people with PD while on medication, using the UPDRS parts I–III, respectively. Results indicated an annual progression of motor symptoms of 0.704% or total UPDRS III scores of 1.34–1.58, with motor symptoms typically the most affected by PD as the disease progresses (Jankovic & Kapadia, 2001). In addition, the authors concluded that age of onset of PD impacts the rate of progression of PD symptoms, such that those with an older age of onset (>57 y) had a more rapid progression of PD in comparison

to those with a younger age of onset (Jankovic & Kapadia, 2001). Another study exhibited fast progression of motor dysfunction within the first five years, with annual rates of progression of the UPDRS III (motor function) score from 5.2 to 8.9 (Parkinson Study Group, 2004).

In most research investigating progression of PD symptoms, disease progression rates have been defined as the difference between a baseline score and the last score on various measures annually tested (Parkinson Study Group, 2004; Chan & Halford, 2001). Our study is the first to follow PwPD over a 3-year period during weekly dance participation, providing additional information regarding the nature of progression of motor and non-motor PD symptoms. Our research goal is to create a long-term neurorehabilitation strategy that combats the symptoms of PD. As such, we utilize a multisensory activity which incorporated the use and stimulation of several sensory modalities in the dance environment including vision, audition, tactile perception, proprioception, kinesthesia, social organization and expression, olfactory, vestibular and balance control—all senses which may influence many of the mood, cognitive, motor and neural challenges faced by people with PD. Over the past four years we have followed and collected data from people with PD while they learned choreography, which is designed to be adaptable to the disease stage and current PD symptoms for those living with PD.

4.3 MATERIALS AND METHODS

4.3.1. Participants

Participants who had a minimum of two testing sessions between the October 2014 and November 2017 were included in the study. Therefore, a total of sixteen PwPD; mild-severity ($M_{H\&Y}$ = 1.3, SD = 0.9), (N_{Males} = 11, $M_{DxYears}$ = 5.5, SD = 4.5) agreed to an ongoing, longitudinal, weekly participation consisting of a 1.25-h DfPD® class at Canada's National Ballet School (NBS) and Trinity locations in Toronto, Ontario, over a 3-year period and thus had

longitudinal data included in this report. These 16 initial volunteers remained in our study during the course of the staggered 3-year data collection period and thus we had a 0% drop out rate for our study. The ethical protocol was approved by York University and written informed consent was obtained prior to data collection. There are no ethical concerns for this study. Fifteen PD-Dancers provided their age and age at PD onset. Of the sixteen participants, 13 were diagnosed with PD >57 years of age, where the average age at diagnosis was 63.9 (*SD* = 11.5). Overall DfPD exercises for each PD dancer were recorded in hours and shown in Table 1. Exercise for this current study was defined as any activity that provides both aerobic and anaerobic movements.

Since the PD non-dance group was impossible to select from our population of PD-Dancers and under the limit of non-exercise related conditions, a reference group, consisting of 16 non-dance PD participants were chosen from a larger PD cohort from the Parkinson's Progression Marker Initiative (PPMI). It is a longitudinal research project mandated to identify PD markers funded by the Michael J. Fox Foundation for Parkinson's Research (MJFF) and related funding partners (www.ppmi-info.org/fundingpartners). These 16 PD-Reference group participants were matched on the means of age and gender (N_{Males} = 11), Hoehn and Yahr (H and Y) score (mild-severity, $M_{H\&Y}$ = 1.6, *SD* = 0.5) and disease duration to our PD-Dancers group (Table 1), and thus formed our longitudinal PD-Reference non-dance group that would define the baseline standards in our study.

In order to capture weekly exercises for the PD-Reference non-dance group, we used a subsection of the Physical Activity Scale for the Elderly (PASE) called Leisure Time Activity. PASE is a reliable, validated and dependable questionnaire used to measure physical activity assessment in older adult populations while relating physical activity to fall and fracture risks as

well as gait and balance characteristics, all of which are prominent symptoms of PD. Focusing on questions 4b and 5b, which ask how many hours per week did the subject engage in either ballroom dancing, aerobic dance or both, we are able to conclude that 13 of the PD subjects (3 subjects did not have data for the PASE) did not engage in any form of dance throughout the duration of the study (Table 4.1).

Table 4.1. Characteristics of people with Parkinson's disease (PwPD) in the PD-Dancer and PD-Reference groups.

PD-Dancers					**PD-Reference**					
Subject	**Age**	**Age Onset**	**H&Y**	**Total hours in DfPD® exercises**	**Subject**	**Age**	**Age Onset**	**H&Y**	**PASE Activity (hrs.)**	
									Q. 4b (ballroom dance)	**Q. 5b (aerobic dance)**
10x	70	67	2	107	3002	68	60	2	0	0
10x	66	64	1	125	3018	61	55	2	0	0
10x	76	73	0	124	3021	64	58	2	0	0
10x	70	66	1	116	3028	76	71	2	0	0
10x	83	82	2	173	3051	72	64	2	0	0
10x	52	37	2	64	3810	67	58	1	-	-
10x	59	50	2	113	3958	76	69	1	-	-
10x	73	70	2	105	3962	69	63	1	-	-
10x	77	77	3	17	4076	72	66	2	0	0
11x	58	58	0	84	40690	72	65	2	0	0
11x	61	50	1	83	40693	72	66	1	0	0
12x	68	67	1	122	40740	69	65	1	0	0
13x	73	71	1	24	40916	77	65	2	0	0
14x	-	-	1	50	50175	62	57	1	0	0
15x	77	67	0	35	51971	66	62	2	0	0
16x	68	60	1	17	57090	74	72	2	0	0

Mean	*68.73*	*63.93*	*1.25*	*85.53*		*69.81*	*63.50*	*1.63*	*0.00*	*0.00*
SD	*8.41*	*11.54*	*0.86*	*45.24*		*4.93*	*4.95*	*0.50*	*0.00*	*0.00*

4.3.2. Ethical Compliance Statement

The study was approved by the Office of Research Ethics (ORE) committee at York University (REB#2013-211 and 2017-296). Prior to any data collection, written informed consent was obtained from each participant.

4.3.3. Measures

UPDRS scores for non-motor aspects of daily living (Part I), motor experiences of daily living (Part II), motor examination (Part III) and motor complications (Part IV) were used to assess motor and non-motor PD symptoms. Motor examination was assessed before participation in the 1.25 h, weekly DfPD class, while the remainder UPDRS Parts I, II and IV were assessed once after each dance class. Motor assessments were video recorded and labeled as non-identifying terms in order to blind our 7 or 8 raters who were trained on scoring the UPDRS using the online training program: a certificate exam developed by The International Parkinson and Movement Disorder Society (MDS). Research has shown that reviewing exercises to assess the motor part of the UPDRS can improve the reliability of the measures in the UPDRS scoring across the raters (McKee & Hackney, 2013). Each trained rater conducted each UPDRS motor assessment, and this the average UPDRS motor score was based across all of the same raters.

4.3.4. Procedure

Sixteen subjects trained in a weekly 1.25-h DfPD class for a total of 82,111 [range/subject = 1027 to 10,391] minutes of training. Classes began with live music during the seated warm-up, followed by "barre" work, and ended with moving across the floor; choreography was also learned for an upcoming performance (see Bearss et al., 2017 for dance class details). UPDRS III was videoed and scored by 7–8 MDS-trained experimenters. UPDRS I, II and IV were self-reported on a paper and pen basis.

4.3.5. Analysis

Linear mixed effects model analysis allowed us to account for individual variability (n = 16) while simultaneously accounting for sixty dance training sessions and was our predefined analysis plan. Data were analyzed using SPSS (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. IBM Corp, Armonk, NY, USA). An average slope was generated for each subsection of the UPDRS by calculating the slope of each individual participant across time and then averaging across subjects' slopes, creating an average slope of each individual participant and the corresponding linear fit which then was compared to a slope of zero.

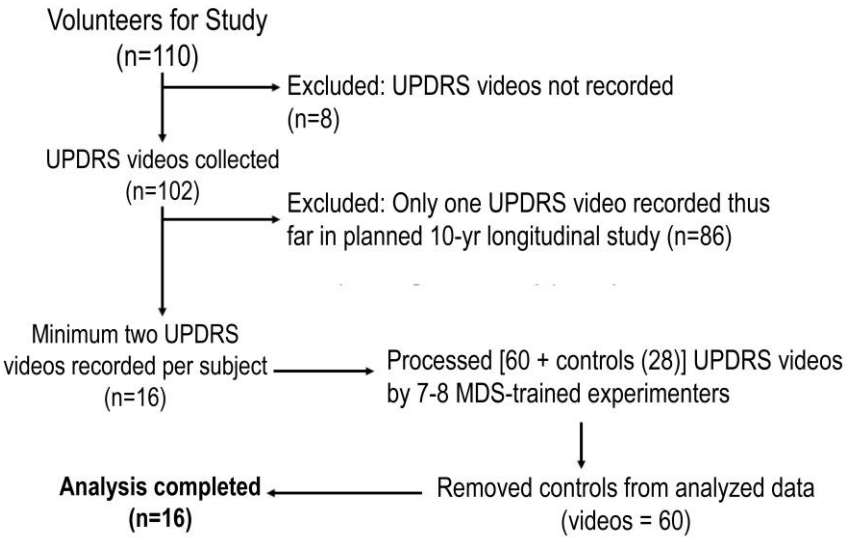
4.3.6. Data Availability

The data is available upon request. As part of our groups Open Science policy.

4.4. RESULTS

UPDRS videos were recorded for three years which were then sorted to the 16 subjects who fit our longitudinal criteria of having two sessions (total 60 videos with a mean of 3.75 sessions/subject (range 2–6); Figure 4.1).

Figure 4.1. Flow chart of enrolment.



As with many neurodegenerative diseases, the majority (69%) of participants in the PD-Dance group were male. As such, the PD-Reference group was well balanced in the gender demographic variable to ensure no gender differences would arise, influencing the results. Each subject's averaged UPDRS III score for each dance session was plotted and lines were drawn for all 16 subjects across all the time points that were recorded (Figure 4.2A). As noted in Table 4.1, the total amount of DfPD exercise (in hours) differed across our PD-Dancers within the 3-year data-collection period as not all of the 16 participants were scheduled for consistent data collection within this 3-year time frame. The average slope across all 16 subjects was then computed and plotted (thick blue line in Figure 4.2A). There is no motor impairment (UPDRS part III) across time ($p = 0.817$) with a daily rate (slope) of 0.000146, which is non-significant from a slope of zero. Surprisingly, non-motor aspects of daily living (I) across time ($p = 0.329$) with a daily rate of –0.0072, motor experiences of daily living (II) across time ($p = 0.540$) with a daily rate of –0.000298, and motor complications (IV) across time ($p = 0.390$) with a daily rate of –0.0000069 also did not show any impairment across time in our dance trained PD group; Figure 4.2D—see dashed, dotted blue lines).

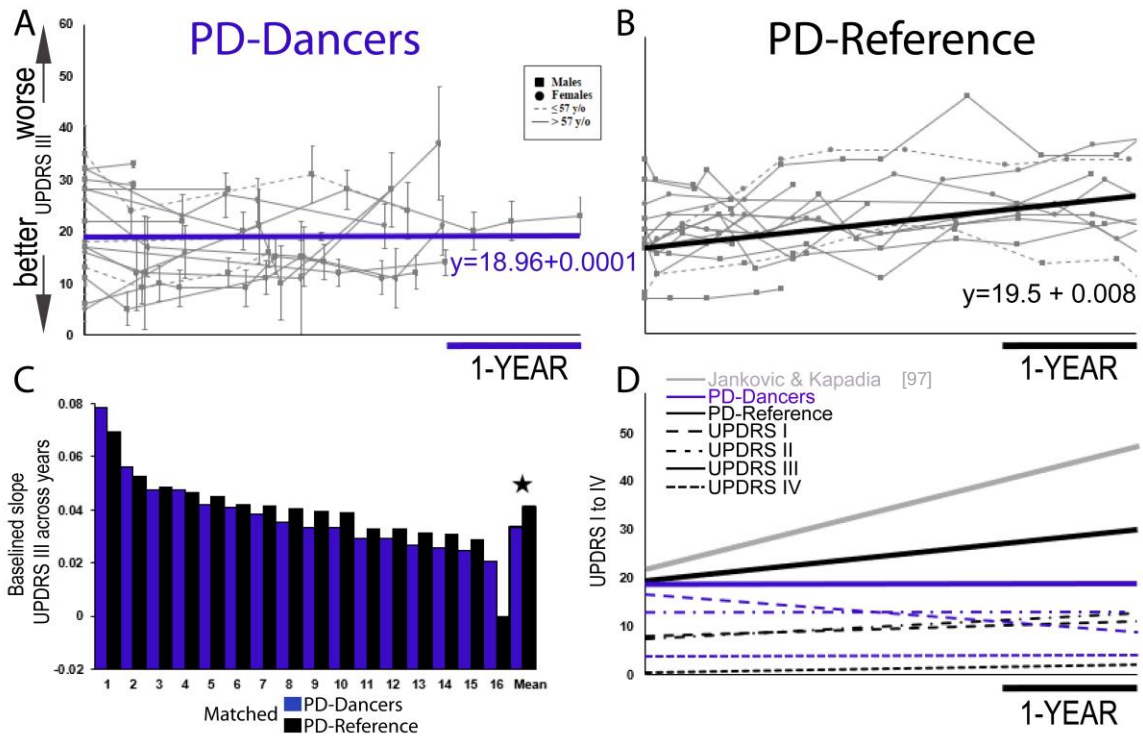


Figure 4.2. Progression of Parkinson's disease: PD-Dancer average slopes are indicated by blue color lines and all PD-Reference slopes are represented by black lines. (**A**) PD-Dancer (n = 16) scores for UPDRS part III (motor examination) across 3 years. Squares (circles) represent scores for males (females); dashed lines indicate participants ≤ 57 years of age at diagnosis, and solid lines indicate age of diagnosis at >57 years of age. Error bars represent the standard error across each experimenter (7–8) scoring for an individual testing session. Solid black line indicates average slope of 0.000146% rate of decline. (**B**) Matched PD-Reference (n = 16) scores for UPDRS part III (motor examination). Solid black line indicates average slope of 0.008% annual motor rate of decline. Same conventions as Figure 1A, except there are no error bars from UPDRS III data since it was rated by one Movement Disorder Society (MDS) experimenter. Only 3 years of data is displayed. (**C**) Baselined individual slopes for all 16 PD-Dancers and 16 PD-References sorted from largest to smallest slopes. (**D**) Summary of all UPDRS I–IV scores. Grey line indicates Jankovic and Kapadia (2001) UPDRS III annual rate of decline.

A significant group (PD-Dancers and PD-Reference) by days interaction showed that PwPD who train weekly have less motor impairment (M = 18.75, SD = 7.82) than PD-Reference who do not train (M = 24.61, SD = 9.67) and over time ($p < 0.05$). To get the motor score change over years, we computed all UPDRS III scores from days into years where we then performed the mixed effects analysis on the GROUP (PD-Dancers and PD-Reference) by years interaction. From this model, we determined that PwPD who train once per week had an overall annual

slower rate of change in motor scores when compared to PwPD who do not train ($\beta = -2.93$, $t = -3.35$, $p < 0.01$) (Figure 4.2). In addition, as expected from the previous literature [106,109], PD-Reference showed motor impairment (UPDRS III) across time ($p < 0.01$, Figure 4.2B) with a daily rate (slope) of 0.008. In addition, PD-Reference UPDRS I and II showed disease progression of PD over time ($p < 0.005$) with a daily rate (slope) of 0.0017, and ($p < 0.01$) with a daily rate (slope) of 0.0027 in subjects who did not dance. Whereas PD-Reference UPDRS IV showed no progression ($p = 0.365$) with a daily rate (slope) of 0.0008 (Figure 4.2D). Figure 4.2C display's individual slopes for both groups, PD-Dancers (blue bars) and PD-Reference (black bars), respectively, that were baselined to the lowest slope score in the PD-Reference data set. Mean slopes were plotted at the end of the graph, indicating a significant difference between the two groups where PD-Dancers had less motor impairment than PD patients who do not train in dance ($p < 0.05$) Hedges' $g = 0.67$ indicating a medium effect.

4.5. DISCUSSION

This study is the first to show that neither the motor nor the non-motor PD symptoms progress in this disease with participation in longitudinal neurorehabilitation training over three years (of our 10-year on-going project). This is markedly different from all previous studies, which showed annual rates of decline for PD increasing at a slope rate of 0.704%/y (Jankovic & Kapadia, 2001) or 5.2–8.9/y within the first 5 years (Parkinson Study Group, 2004). Additionally, we confirmed this continual decline in a new cohort—our matched PD non-dance group (PD-Reference), where for the duration of the study these subjects had zero hours of exercise involving dance as measured by questions 4b and 5b of the PASE. Considering demographics, our PD sample had a mean disease duration of 5.54 years ($SD = 4.52$) which would make our population vulnerable to a rapid symptom decline within the first 5 years

(Parkinson Study Group, 2004). Most importantly, our PD subjects average age at PD diagnosis was 63.93 years (*SD* = 11.54) and according to Jankovic's study (Jankovic & Kapadia, 2001), those who are >57 years of age at disease onset should show the most rapid motor decline. Remarkably, our dancing participants did not demonstrate this disease progression; however, our matched PD-Reference did show this reported PD disease progression. We further modeled our data and computed that after completing 1000 days of training our PD dancers will have a UPDRS III motor score of 19.07 whereas our PD-Reference will score 28.27. Our data further showed that training in dance would slow the rate of PD motor impairment progression, as measured by the UPDRS III, by close to 3 points annually in comparison to our PD subjects who did not train (Figure 4.3). Since motor PD symptom progression has been shown to be the fastest within the first 5 years (Parkinson Study Group, 2004) of diagnosis, we expanded these motor scores to 5 years and displayed the results across all studies and groups in Figure 4.3. The results in Figure 4.2 indicate that training in dance for 1 year will have a 3-point lower UPDRS III score in comparison with no training; these differences in scores increase after 5 years where no training leads to a 15-point higher motor score in comparison with those who do train. These results support previous findings in the literature which indicate fast motor progression within the first 5 years of PD (Parkinson Study Group, 2004); however, what is of importance here is that this rapid motor progression is not shown with consistent weekly training, and motor impairment progression remains much slower. The reasons for our findings could be due to the additive effects of training, socialization, support and group dynamics that putatively occur within and around the classes (Heiberger et al., 2011; Westheimer, 2008; Bearss et al., 2017; Hackney & Earhart, 2010; Chan & Holford, 2001; Israili & Israili, 2018; Shanahan et al., 2017;

Rocha et al., 2017). Our future studies will continue to examine this cohort with these as dependent measures where possible.

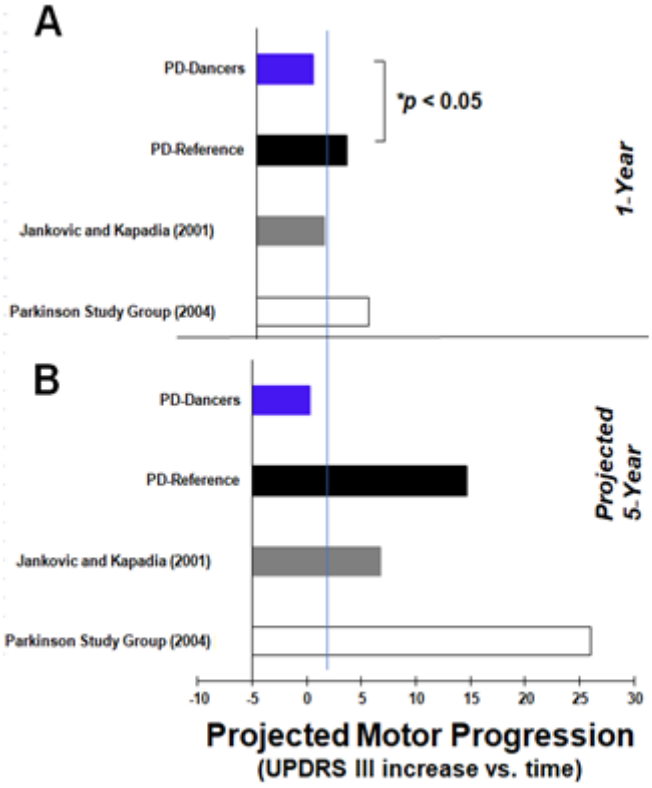


Figure 4.3. Total annual rate of motor score (UPDRS III) progression across all groups and studies discussed in the text. Based on reported values with Jankovic and Kapadia (2001) the annual rate of progression during the ON-state is quoted. Motor scores after (**A**) 1 year are plotted based on available data and (**B**) 5 years are projected for each group based on current slope measurements.

A growing body of evidence demonstrates that high-intensity interval training (HIIT) can serve as an effective alternate to traditional PD exercise programs, inducing similar or even superior physiological adaptations in healthy individuals and diseased populations (Allen wet al., 2011; Shulman et al., 2013). HIIT is a form of physical exercise that is characterized by brief, intermittent bursts of vigorous activity, interspersed by periods of rest or low-intensity exercise (Gibala et al., 2012). In our DfPD program, the dance classes are structured with a myriad of factors in mind such as training intensity, speed of rhythm, symptom-specific concerns related to

balance, cognition, motor skill, depression and physical confidence, as well as activity duration and movement patterns. The professionally trained teachers incorporate movement from modern, ballet, tap, folk and social dancing, and choreographic repertory to engage participants' minds and bodies within weekly adapting class structures. With this diverse class structure, the DfPD program can be described as being similar to HIIT dance training, as the classes incorporate both seated dance which provide low-intensity exercise with interspersed upbeat, fast-moving dance styles that provide bursts of vigorous activity. HIIT has been shown to be infinitely variable with the specific physiological adaptations induced by this form of exercise, for instance aerobic capacity (measured by peak VO^2) and movement initiation time all improved following HIIT intervention (Gibala et al., 2012). An accumulation of recent research shows that long duration and high intensity training, such as HIIT, may induce neuroplasticity and have neuroprotective effects in PD by increasing serum levels of brain-derived neurotrophic factor (BDNF) in both animal models of PD (Bergen et al., 2002) and PwPD (Sabaghi et al., 2019). BDNF is a growth protein that has been shown to be protective against the neurodegeneration observed in PD symptoms (O'Callaghan et al., 2020). Training in dance can thus lead to increases in BDNF levels which ultimately repair and provide further protection to areas of the brain that are damaged by PD, such as the basal ganglia, i.e., substantia nigra, areas responsible for planning and control of motor movement. This reparative and protective neural restoration may be evidenced by the hindrance of motor and non-motor symptoms displayed in our results. A review of studies that incorporated music and dance indicated the beneficial aspects of using this tool as a form of rehabilitation for people with PD as it improves cadence, speed, gait, balance, and stability while stimulating improvements in both the motor and cognitive symptoms in PD (McNeely et al., 2015; Pereira et al., 2019). The neuroprotective effects of dance are a potential explanation for these results, other underlying neural mechanisms suggest

that regular participation in dance facilitates neural activation of PD impaired sensory-motor areas thus influencing the motor control and improving motor symptoms in PwPD (dos Santos Delabary et al., 2020).

Our study is the first to also examine changes in UPDRS parts I, II and IV over three years. Our results clearly show that the non-motor aspects of daily living (UPDRS part I), motor experiences of daily living (UPDRS part II) and motor complications (UPDRS part IV) show no significant impairment after three years of training once a week. Again, these results markedly differ from those of Jankovic and Kapadia's (2001), which showed that annual impairment progressed in PwPD who were not participating in weekly training, also closely matching the results we showed here in our PD-Reference group.

Research on other nonpharmacological exercise programs (Lauzé et al., 2016; Cheon et al., 2013; Yang et al., 2014) designed to re-duce the risk of neurodegeneration in PD have shown motor function improvements; however, these alternate programs seem less efficient at improving clinical symptoms and psychosocial aspects of PD, with only 50% or less of results reporting positive effects (Lauzé et al., 2016). In addition, the impact of physical activity appears to be weaker for both cognitive function and depression in PD (Yang et al., 2014). Other forms of dance, such as Argentine tango (McKee & Hackney, 2010), Irish dancing (Shanahan et al., 2017) and PD structured dance classes (Rocha et al., 2017), have shown comparable findings to research on DfPD classes, where both motor and non-motor aspects of PD symptoms improve after participating in dance classes.

Dance intervention studies on PwPD have shown that continuous participation in scheduled dance classes improves balance in PwPD as shown by changes of 3–4 points on the Berg Balance score (Lim et al., 2005). A large meta-analysis study conducted on the general population by

Asmundson et al., (2013) indicated that exercise programs which last for 16-weeks or more produced the greatest anxiolytic effects, thus duration of exercise not only provides motor improvements but it also provides a protective effect against the development of anxiety in healthy older populations—a non-motor symptom that is seen in many PwPD (Asmundson et al., 2013). In addition to testing exercise and dance's effects on affect, self-efficacy, gait and attentional dual tasks in seven PwPD, we designed a matched-intensity exercise control task (Fontanesi & DeSouza, 2021) and performed the test a few days before or after dance class in the same subject and measured heart rate and electrodermal activity. Heart rate was the same for both dance and matched-intensity exercise, but the dual task showed benefits for the dance over matched-intensity exercise suggesting dance trains additional aspects than just movement sequences.

The limitations of this study are that it is a small-scale preliminary report that was initially conducted to evaluate feasibility, duration and improve our future study design prior to establishing a full-scale research study with the aim of a future RCT design, and thus, the results presented here are of a pilot project, where the interpretations of the results should be approached with caution. The other limitation to our study, which can be found in all pilot studies, those that are not properly randomized and controlled, there is the issue of selection bias. Following this pilot study, the goal is to design a solid randomized control trial which will eliminate the issue of any selection bias and the interpretations of the results will thus be warranted.

4.6. CONCLUSIONS

Our results indicate positive benefits of weekly training for stopping disease progression of motor and non-motor symptoms of Parkinson's disease. Previous longitudinal studies [97,98] suggest an annual decline in motor function whereas our cohort shows that the annual motor

impairment is drastically reduced. These findings strongly suggest the benefits of dance in people with PD as a supplement to a normal treatment regimen.

4.7. ACKNOWLEDGMENTS

We are indebted to R. Bar, S. Robichaud, R. Barnstaple, D. Rabinovich, R. Cohan, P. Dhami, S. McGuire, C. Leger, S. Leung and G. Levkov for invaluable assistance. All of the lab (http://www.joeLAB.com) members for their dedication since study inception in 2013. We are also thankful for the continued collaborations with Canada's National Ballet School (Dr. R. Bar) and Dance with Parkinson's Canada (S. Robichaud) and Trinity St. Paul's Church in Toronto, ON.

4.8 LONGITUDINAL rsEEG AND FUTURE DIRECTIONS

Originally an additional goal for this project was to analyze rsEEG over time in our 16 PD dance group to evaluate any potential changes in alpha rhythm over the 3-years of participation in the DwPD program in order to add to the findings that were seen in Chapter 2 (single dance class effects).

After careful observation of each collected raw EEG time point (totaling 6 time point sessions over the 3-years), the overall PD dancer group size was n=3. In order to make meaningful statistical comparisons from time point 1 to time point 6 in rsEEG alpha rhythm changes one should ultimately have the same individuals in each time point to successfully compare the means from time point 1 to time point 6. Reasons as to why the sample size decreased over time are things such as too much noise throughout the 6-minute collected data set, too many data segments were removed due to noise, artifacts, muscle movement, connectivity issues which contaminates the data, removal of too many channels (two or more channels), connection from EEG headset was

lost during the 6-minute recording, more than two electrodes had no connection throughout the recording leading to noise, either EO (3-minute condition) or EC (3 minute condition) was not recorded, inappropriate start of recording when reference electrodes had no connection or trying to place/re-arrange headset at some point throughout recording due to loss of connectivity or participant movement (sneeze or itch). All of these reasons for removal or omitting of entire data sets would lead to the raw cleaned data not being suitable for further analysis and would impact the interpretation of the final results. Being that our sample size is so small and has decreased significantly from our initial size of n=16, and since this small sample size was not what was originally planned for analyses purposes at the start of this experiment meant for comparisons, any statistical analyses was avoided at this point in time and instead rsEEG pre-processing was conducted over the 6 sessions for this small sample size and head maps were generated for the purposes of visual inspection. Visually inspecting the head maps, and focusing on the EC condition only, one could see that there is a potential of a gradual increase in alpha peak power (μV^2) over time. This could imply that with continued dance participation, BG generated alpha levels are being restored and so much so as to the possibility of the frequency being similar to a healthy, non-PD brain. Through research we know that BG rhythm in PD is unsynchronized which could be a result of dopamine depletion, it is possible that dance training helps rebuild and restore this rhythm that may then be explained in the stagnant motor symptom progression. These are just speculations and future research needs to be completed in order to draw any sensible conclusions.

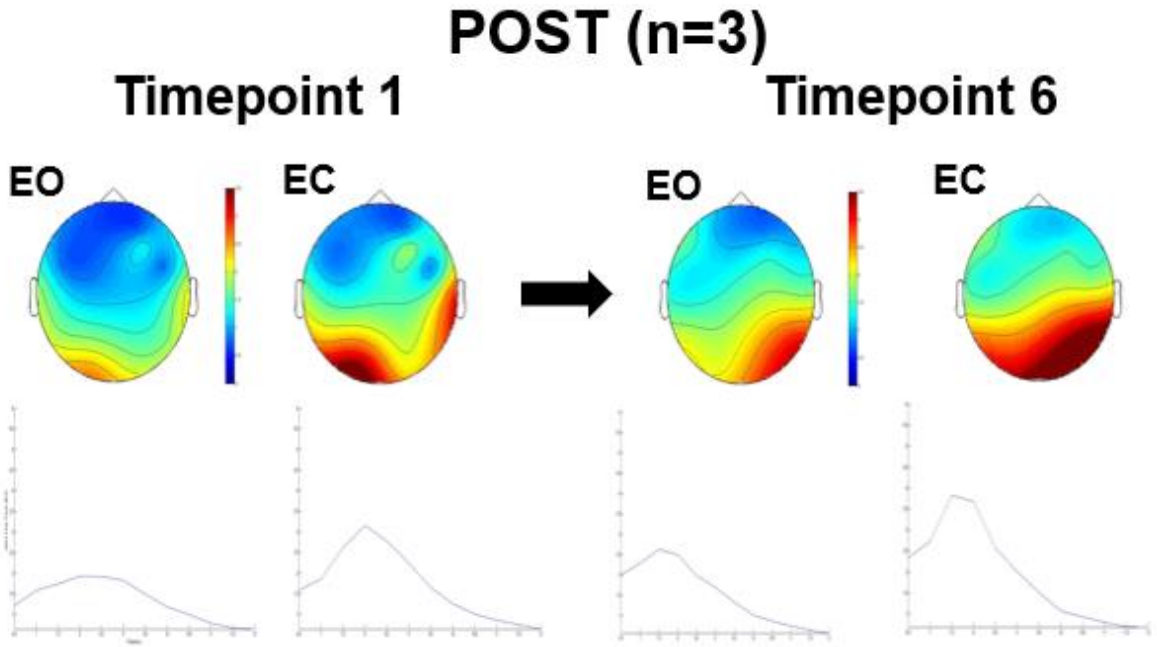


Figure 4.8. Visual display of alpha peak power (μV^2) head maps for PD-Dancers (n=3) at Timepoint 1 and Timepoint 6 (just over 3-years of dance participation).

CHAPTER FIVE

GENERAL DISCUSSION

5.1 SUMMARY OF MAJOR FINDINGS

This dissertation presents evidence on the beneficial and positive effects dance has on the brain, QoL, behavior (observable and measurable motor and non-motor behavior) and affect (expression of positive and negative mood) on PwPD after short-term single dance class (Chapter 2 and Chapter 3) and longer term of over 12-weeks of dance participation (Chapter 4) involvement in dance training. The results of my three dissertation research projects provide a better understanding of the relationship between dance and its impacts on PD symptomology and disease progression. The results provide strong support of dance as a potential exercise regime that should be considered in the treatment of PD. We will now take a look at these research results and present each of them in relation and as an explanation of the influence that participation in dance had on the PD BG brain circuitry. I will discuss and go through each BG-thalamo-cortical loop (represented from Figure 1.2) and present each loop with respect to the findings from Chapters 2-4, I will begin by describing the limbic loop first.

Mood disorders such as anxiety and depression arise throughout the course of PD and also present as side effects of current PD treatments. In Chapter 2, positive affect did not change from before to after the dance class however negative affect decreased in our PwPD dancers. These results could be explained by potential changes within the damaged and dopamine depleted limbic system. One possible explanation for our findings is that there could be some functional reorganization within this limbic loop after dance training that may have a stronger influence and impact on negative feelings or affect than it would on positive feelings or affect. We know that the limbic loop structures such as the amygdala, ventral striatum (including the NAcc) and anterior cingulate cortex have strong influence on negative thoughts and emotional processing associated with depressed mood and state, it could be that dance exercise changes

something in these key structures which in turn decreases any negative mood or thoughts that are linked to depression – which is shown in our Chapter 2 findings of only the negative affect decreasing post dance class participation. In fact, a study by Wang et al., (2013) showed functional regional cerebral blood flow (rCBF) increases in limbic areas such as the amygdala, hippocampus, ventral striatum, NAcc, septum and insula (Wang et al., 2013) indicating functional reorganization in limbic circuits as a function of long-term aerobic exercise. Our results from Chapter 2 showing changes of positive and negative affect following dance class participation along with the existing literature in human PD subjects document the important interaction that exists between the BG and the limbic system, and most importantly the notion that parts of the limbic system, such as the striatum and NAcc may be areas for the anxiolytic and antidepressant effects seen following exercise (Wang et al., 2013; Wegner et al., 2014; Greenwood et al., 2012). Thus, it is important to optimize levels of dopamine because dopamine levels modulate motivation and reward behavior, that is dopamine deficiencies have been related to depression whereas excess dopamine is related to mania, and exercise may also provide some sort of dopamine modulation (Petzinger et al., 2015).

Additionally, the BG's prefrontal loop plays a role in cognitive and executive functions. Our longitudinal results from Chapter 3 using the UPDRS-Part I assessing cognitive impairment including altered levels of memory loss, deficits in attention and orientation, cognitive slowing and impaired reasoning and our PD-Dancers showed no progression of disease on tests of these non-motor aspects of daily living. A systematic review of randomized clinical trials by da Silva et al., (2018) aimed to examine the effects of physical exercise on cognitive impairment in PwPD and their results showed that exercise promotes positive and significant effects in global cognitive function, processing speed, sustained attention and mental flexibility (Hobson &

Meara, 2004). Longer dance interventions have been shown to improve cognitive abilities that short-term dance interventions cannot, such as executive function, visual spatial memory, response time and fluid intelligence (Hashimoto et al., 2015; McKee & Hackney, 2013). It could be that our PD dancers who trained over 3-years strengthened their memory and cognitive functions by continuously learning new movements and adding to previous dance choreography at the weekly dance sessions. This ongoing training may ultimately either strengthen the PD damaged prefrontal loop with the BG or provide some sort of neuroprotective features that help maintain cognitive function instead of further debilitating it with the progression of PD and what would be normally seen in PwPD with no dance exercise routines in their lives.

Damage to the BG circuits that are associated with motor areas of the cortex, as seen in PD body movement loop (Figure 1.2), leads to motor symptoms of resting tremor, rigidity, bradykinesia, freezing of gait and dystonia. Our results from Chapters 2 through Chapter 3 indicate improvements of balance and gait, using the BBS and TUG in Chapter 2, following 12-weeks of dance training. In Chapter 3, improvements on PD motor symptoms were shown in a reduction of scores of the UPDRS Part III after a single dance class. Finally, and most dramatic out of all these Chapter results, is that of Chapter 4, where the progression of motor symptoms did not worsen over a 3-year period of dance training using the UPDRS Part III measure, shown in a consistency of motor UPDRS Part III scores over time in our PD-Dancers whereas our PD-Reference group displayed the regular course of motor deterioration typically seen in PwPD and as shown in Jankovic and Kapadia (2001) and the Parkinson Study Group.

An explanation for these behavioral improvements seen the PwPD motor function is the ability of the brain to respond to exercise through adaptive neuroplastic mechanisms which result in long-lasting alterations in neuronal circuity (structure and function), precisely at the level of

the synapse (Petzinger et al., 2011). In the healthy brain, these structural and neuronal changes arise from learning and encoding of new behaviors, they have also been evoked in the injured brain during the repair processes following or during exercise or rehabilitation training to help relearn impaired or lost behaviors (Petzinger et al., 2011). What could be happening in the brain of these PD-Dancers that is different from PD non-dancers, is some sort of exercise-induced neuroprotection.

Some studies have indicated an elevation of the presence of BDNF (Cohen et al., 2003; Tillerson et al., 2003), the most widely distributed neurotrophic factor in the adult mammalian brain, which provides protection from toxins by activating downstream signalling cascades including second messenger systems and protein kinases that may enhance neuronal survival and function within the BG circuitry and thus increase dopaminergic neurotransmission (Neeper et al., 1996). Along with dopamine neurotransmission changes, animal studies have supported the suggestion that exercise may induce alterations in glutamate and glutamatergic receptor families, such as the *N*-methyl-D-aspartate (NMDA) or α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor subtypes (Dietrich et al., 2005), glutamate receptor expression is altered in PD (Petzinger et al., 2011) and these receptors are critical components of neuroplasticity which bring normal synaptic function and encode information, including long-term potentiation (LTP) and long-term depression (LTD) within the healthy brain (Kreitzer & Malenka, 2008). In PD and toxin-induced PD studies, changes in glutamatergic neurotransmission have been shown as changes in the synaptic connections of medium spiny neurons, cells found in the caudate and putamen providing the majority of output connections from the striatum, by a loss of glutamatergic synapses and loss of synaptic plasticity (such as LTD) (Petzinger et al., 2011). This loss, as seen in PD, has been attributed to a hyperexcitability

state within the striatal medium spiny neurons and loss of synaptic connections and are thought to be responsible for mediating motor deficits (Calabresi et al., 1996). It could be that exercise, such as dance, may lead to a general reduction in glutamatergic hyperexcitability and diminished synaptic strength (seen in LTD) at the level of the medium spiny neuron thus restoring synaptic integrity within the BG and ultimately restoring behavioral motor function.

rsEEG alpha results revealed greater alpha power in PD than HC, alpha frequency was highest in HC than PD, and overall anterior (frontal) alpha power was highest after a single dance class and in EC condition only (Chapter 3). In Chapter 4, being that our sample size was significantly reduced to n=3, I was only able to construct a visual inspection and speculation of the results and their interpretations. Thus, as described below in the limitations section, these results are to be interpreted with caution and speculation. Alpha peak power (μV^2) appears to be gradually increasing with ongoing dance training in our 3 PD-Dancers. Following the Pacemaker hypothesis which states that the thalamus is the origin of alpha rhythms (further described in Chapter 3), it is obvious that some dysfunction should be initially evident in our PD-Dancers. This was evident in the results of Chapter 3, where alpha frequency was greater in HC than PD group. We saw an increase in alpha peak power after the dance class and visually gradually increasing over dance training for 3-years. Studies on PD DBS of the STN suggest that high frequency DBS suppresses or over-rides pathological oscillatory activity which behaves as a noisy and disruptive signal in the brain (Eusebio et al., 2011; Abbasi et al., 2018) and alleviates PD motor symptoms while simultaneously suppressing alpha and beta activity across widespread cortical areas including the sensorimotor cortex and BG (Barone & Rossiter, 2021). These studies indicate a causal role between alpha and beta suppression in order to initiate motor movement (Barone & Rossiter, 2021). Also, an increase of beta amplitude above baseline levels

is observed following movement cessation and serves as an indicator of movement outcome and preserves the existing motor states from internal and external sources of noise (Barone & Rossiter, 2021, Baker, 2007). A reduced cortical alpha rhythm, as seen in research and hypothesized from the Pacemaker hypothesis could be due to the inhibitory drive originating from the BG via the thalamus. It may be that dance increases this global cortical alpha power by participating in multisensory training and conversely creating an excitatory drive within the BG. In fact, when using levodopa treatments to help modulate the levels of dopamine, a suppression of beta power was recorded in the STN (Little et al., 2013) in contrast an increase in beta power was recorded on the motor cortex (Cao et al., 2020). A similar response may be occurring in our results except for in alpha power and instead of levodopa as the treatment source it is multisensory training. It could be that multisensory training, in the form of dance, is behaving as an external BG neuromodulator, taking over the role of the depleted dopamine in the PD brain and thus normalizing – or modulating- PD symptoms and symptom progression ultimately restoring function and improving QoL. In fact, a study investigated the effects of levodopa administration on rsEEG changes and found that both alpha and beta power increased on centro-parietal regions as a function of L-dopa administration indicating that these changes arise as a function of dopaminergic mechanisms (Melgaru et al., 2014). Thus, dance could also be acting as an external dopaminergic mechanism leading to the global increases seen in Chapter 3 and potentially Chapter 4 alpha peak power rsEEG results in our PD-Dancers.

5.2 LIMITATIONS

In PD, altered synchronization along the beta frequency band within the STN contributes to the hyperexcitability of striatal medium spiny neurons, as discussed above in the general

discussion section, this hyperexcitability facilitates motor symptoms associated with PD (Israili & Israili, 2018). It could be that dance training synchronizes beta oscillations through the use of a combination of music and coupled body movements, restoring the rhythm of the BG circuitry in a way that then improves PD motor deficits. Scientifically it has been proposed that the use of music as an auditory cue permits the bypassing of the dysfunctional BG, by accessing the supplementary motor area through the thalamus (Nieuwboer et al., 1997) or the pre-motor cortex via the cerebellum (Chuma et al., 2006). This is an area that is of limitation in my current study as I focused solely on a single frequency band, being the alpha band, and thus cannot generalize to this being a possible explanation of my rsEEG results seen in Chapters 3 and 4 (for a small sample size of n=3).

This leads to another limitation of my research, specifically in Chapter 4 when observing rsEEG changes over time. My sample size was too small to interpret and to be able to run any statistical analyses on. Thus, the results presented there are of only visual interpretation and act as a baseline for continued rsEEG data collection over time to encompass a larger sample size which would then provide a better framework and interpretation of our rsEEG findings. It would also be of importance to have a non-dance PD group and a healthy control group that are matched on the same characteristics (age-, gender-, disease severity, and disease duration) in order to conduct between group statistical comparisons and draw conclusions as differences between groups that may arise as a function of dance.

Chapter 4 was also a non-controlled study, it did not incorporate a true control, PD non-dance group. Thus, the comparisons made to our MJFF PD-Reference group and to that of other studies in this Chapter which behaved as our control studies (Jankovic and Kapadia in 2001 and the Parkinson Study Group in 2004) should be interpreted with caution. However, being that this

dissertation research includes a clinical group, it is of unethical reasoning and basis to ask participants not to participate in dance in our Canada's National Ballet School and Trinity St. Paul's Church DwPD groups.

We have indicated that L-dopa replacements influence alpha and beta power by increasing it when measured cortically. One downfall is that our PD-Dancers were not removed from their prescribed L-dopa replacements, as this is ethically unsound to do in clinical research. Thus, all alpha changes results should be interpreted with this in mind and with caution, as it is difficult to extract whether the changes seen in increasing alpha power and frequency are solely due to dance or solely due to L-dopa or both. Future studies could control or document for any drug induced effects by the time of dosage administration, as we know that L-dopa has a short plasma half-life of 50 minutes without carbidopa and 90-minutes with carbidopa (Dolhun & Richard, 2015).

5.3 FUTURE DIRECTIONS

It is apparent that dance related exercise training within PD provides benefits in symptom relief and management of these debilitating motor symptoms which negatively impact QoL. Thus, dance training, or multisensory training as I like to refer to it, should be implemented as part of a routine treatment for PD. To date, there are many animal models of PD that reveal the underlying neural and molecular mechanisms that arise from regular exercise alone, it would be important to consider large, controlled double-blind clinical human trials, as well as animal models, while studying the effects of dance as the form of exercise within the brain.

Additionally, it is of importance to continue to address multiple oscillatory frequency changes (and not solely alpha rhythm) that arise over time in various frequency bands within PD-Dancers as our group did in Levkov (2015). Linking these frequency changes to motor and non-

motor symptom changes will help to understand what mechanisms are occurring in the brain and may shed light on it is the neuroprotective, neuroplastic and/or neurotrophic factors that are taking place. I believe that our lab is continuing to explore this aspect using our rsEEG paradigm but over a longer period of time and with a greater sample size.

5.4 CONCLUSION

Dance is a multifaceted form of exercise which provides several dimensions of exercise training (e.g., aerobic, flexibility, balance) at the same time providing planned, structured, and repetitive movements to music whilst also encouraging socialization and enjoyment. Dance incorporates all of our senses by providing a multisensory engaging and stimulating environment. As we have seen, Parkinson's is a brain wide, multisystem neurodegenerative disease that essentially stems from deep brain BG structures to ultimately encompasses whole brain structures seen in the different motor and non-motor loops. It could be that this particular, multisensory form of exercise provides a dance-dependent neuroplasticity which possibly modifies PD progression by potentially restoring BG homeostasis and synaptic integrity within BG structures that then impact wide-spread PD brain areas. Basically, our human sensory organs (e.g.: eyes, skin, musculoskeletal, ears, vestibular, nose and ears) when stimulated and challenged by our environment, through learning and exploring different kinds of movement, cause specific changes that tell the brain when to become plastic in response to this stimulation. Our stimulated sensory systems explore and learn new ways to move, and in this process develop and reorganize the nervous system and the brain, and not necessarily fix them. When these stimulated sensory and motor events occur simultaneously and in repetition in the brain, they become linked, because neurons that fire together wire together, and the brains pathways for these new changes emerge. Being that dance offers multisensory stimulation in its environment

could be the importance of why this type of exercise outweighs any other type of exercise in its benefits to PwPD and their diverse symptoms, and thus dance should be recognized as a dominant more powerful form of therapy to help this population in impeding their disease progression. Refer to Figure 5.2, on next page, as a visual depiction of how dance is a whole brain exercise.

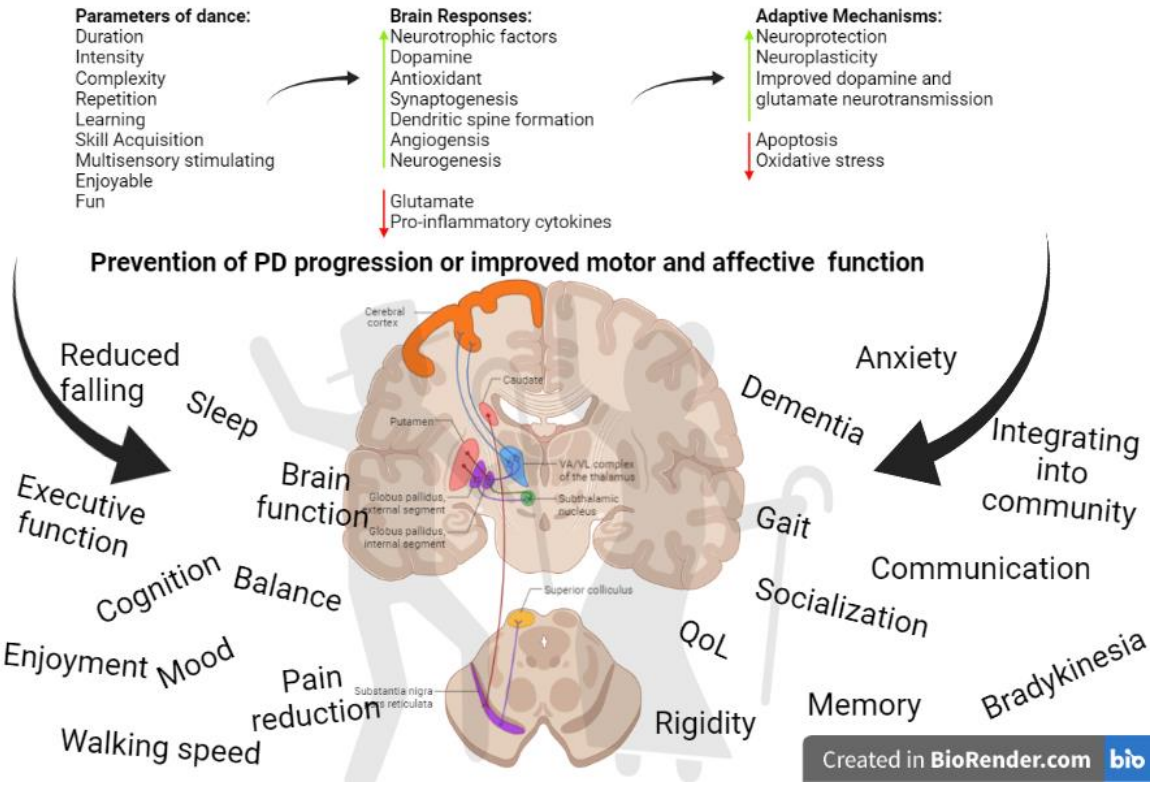


Figure 5.2. Potential mechanisms of dance on the brain in PwPD. Summary of the neuroprotective, neuroplastic and neurotrophic impacts of dance training on BG brain circuitry.

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Appendix A

The effects of motor learning and rehearsal: an fMRI study comparing people with Parkinson's disease, classical ballet dancers, and age-matched controls

Consent Form

We are a team of researchers at York University, comprising of Dr. Joseph DeSouza, Rachel Bar, Karolina Bearss and Rebecca Spiegel. We can be contacted at dancestudy.yorku@gmail.com

We are planning to study the effects of rehearsal on the brain, and to do so we will need to collect functional Magnetic Resonance Imaging (MRI) scans from participants' brains, electroencephalographic (EEG) brain signals, attention, working memory, and motor test results, and lastly some questionnaire responses, on three different dates, over three months.

We are therefore asking if you would agree to participate in our research by undergoing fMRI scans, and EEG tests, in addition to participating in attention, working memory, and motor tests, and questionnaires on three different dates over the next three months. As well, there will be one initial 45-minute workshop, which you will be required to participate in before the study begins.

Each MRI scan should take about ten minutes to complete and will occur at the Sherman Health Science Research Centre at York University's Keele Campus. The EEG test should take about thirty minutes to complete and will occur either at the National Ballet School or in a testing room at the Sherman Health Science Research Centre. The attention and working memory tests should take about fifteen minutes to complete, and the motor tasks and questionnaires should take about thirty minutes to complete. Both will take place at either at the National Ballet School or at York University's Keele Campus. For testing occurring at York University, you will be compensated for travel expenses to and from the campus.

You do not have to participate at all, or, even if you agree now, you can terminate your participation at any time without prejudice. Your name will not be attached to the research at all and we will ensure that your participation remains confidential. Refusal to participate or to answer any particular questions, or decision to withdraw from the study, will not affect your relationship with the researchers, York University, or any other group associated with this project. If you withdraw from the study, all associated data collected will be immediately destroyed wherever possible.

We can tell you that the results of your scans and tests may be included in a research publication; however, your scans and results would be anonymous and nobody could connect your scans or results with you as an individual.

A benefit you may experience by participating in this study is greater knowledge about the benefits observed from dance, as well as expanding your knowledge about magnetic resonance imaging (MRI) technology and EEG. Also, you will receive a printed anatomical scan of your brain.

What Is Involved in the Study?

MRI: Your participation will involve measuring the anatomy and activity of your brain using magnetic resonance imaging (MRI). MRI scanners image your brain using radio waves and very strong magnetic fields. You will be asked to fill out a safety screening form to assess whether it

is safe for you to enter the MR room. It is important that you provide us with an accurate and up-to-date medical history, and when unsure to ask clarifying questions so that we can proceed safely. You will then be asked to remove any metallic objects you may be carrying (for example, wallets, watches, earrings or piercings) and possibly to change clothing into a gown that we will provide (if deemed necessary because of large zippers etc.). You will be required to lie completely still on the patient bed that will slide into the bore of the MRI scanner. You will be able to communicate with us at all times via a built-in intercom. You will be holding an emergency bulb that you can squeeze at any time to let us know you want to come out of the MRI scanner. The MRI scans will only be administered by qualified personnel.

This is Not a Clinical Evaluation

The images of your brain collected in this study are not intended to reveal any disease state, in part because this MRI protocol is not designed for clinical diagnosis. Thus, your brain images will not be routinely examined by a clinical radiologist. The personnel at the Neuroimaging Laboratory are not qualified to medically evaluate your images. However, if in the course of collecting images of your brain we have any concerns, we may show your scans to a clinical radiologist, who may suggest that you obtain further diagnostic tests.
At the investigator's discretion, you may view your brain images and receive digital copies of them. However, you should be aware that brain structures within the normal population are highly variable, and that it is difficult to draw any conclusions from your images; you should be aware of the potential distress or discomfort that may occur by viewing your own images. Do not rely on this research MRI to detect or screen for brain abnormalities.

While in the MRI scanner, you will be asked to do tasks such as listen to music, visualize yourself dancing to the music, to view visual stimuli, and to wiggle your toes.

EEG: Your participation will involve measuring brain waves recorded while you participate in a variety of different activities. EEG involves recording naturally occurring electric and magnetic fields generated by firing neurons from the surface of your scalp. These will be recorded using small electrodes, which are part of a portable EEG cap, namely the EMOTIV 14-channel head cap. A researcher will place the EEG cap on your scalp. Your hair and scalp may get slightly wet due to the saline solution located on the 14 electrodes, however saline solution is completely non-toxic, and will dry shortly after the EEG cap is removed. During the EEG session, you will be asked to sit quietly and let your mind wander while we measure your resting state brain waves.

Attention and Working Memory: You will be asked to participate in two game-like simulations on a portable laptop. During these tasks, you will be asked to perform simple mathematical operations in your head, to remember letters that were previously presented, and to view faces and words that depict various emotions. We will be looking at the rate with which you respond during these two tasks, as well as the number of errors you make, which will indicate the strength of your attention and working memory capacities.

Motor Tasks and Questionnaires: You will be asked to perform several motor movements to test skills such as balance, gait, and transfers. Questionnaires will be administered in which you will be asked to indicate your opinion regarding various aspects of your own life.

De-identified data will be kept indefinitely.

What Are the Risks of the Study?

Metal: The MRI scanner produces a constant strong magnetic field, which may cause any metal implants and/or clips within your body to shift position. The magnetic field may also cause any implanted medical devices to malfunction. Thus, if you have any implanted metal, clips or devices, it is hazardous to your health to participate in this study. Please provide us with as much information as you can, for example if you had surgery in the past, so that we may decide whether it is safe for you to be a subject. Metallic objects brought into the MRI environment can become hazardous projectiles. Metal earrings, body piercings, and necklaces must be removed prior to the study.

Pregnancy: Exposure to MRI scanning might be harmful to a pregnant female or an unborn child. Although there are no established guidelines at this time about MR and pregnancy, you should be informed that there is a possibility of a yet undiscovered pregnancy related risk. If you know or suspect you may be pregnant or if you do not want to expose yourself to this risk, we recommend that you do not participate in this study.

Inner ear damage: MRI scanning produces loud noises that can cause damage to the inner ear if appropriate sound protection is not used. Earplugs and/or headphones will be provided to protect your ears. The earplugs will reduce but not eliminate the MRI noise.

Claustrophobia: When you are inside the MRI scanner, the MRI scanner surrounds your body and your head will also be positioned inside a close-fitting scanning coil. If you feel anxious in confined spaces you may not want to participate. If you decide to participate and begin to feel claustrophobic later, you will be able to tell us via the intercom and we will discontinue the study immediately.

Burns: In rare cases, contact with the MRI transmitting and receiving coil, conductive materials such as wires or other metallic objects, or skin-to-skin contact that forms conductive loops may result in excessive heating and burns during the experiment. The operators of the MRI scanner will take steps, such as using foam pads when necessary, to minimize this risk. Tattoos with metallic inks can also potentially cause burns. Any heating or burning sensations during a scan in progress should be reported to the operators immediately and we will discontinue the scan. Besides the risks listed above, there are no other known risks from the magnetic field or radio waves at this time. Although functional MRI scanning has been used for more than 15 years, long-term effects are unknown. If new findings about the risks of the MRI technique become available within a year of your participation, we will let you know about them.

Tiredness: You may find participating in all of these tasks in one day tiring.

What about Confidentiality?

All information obtained during the study will be held in strict confidence to the fullest extent possible by law. In no case will your personal information be shared with any other individuals or groups without your expressed written consent. Your brain images will be stored on secured computer servers and will be archived indefinitely. The experimental data acquired in this study may (in an anonymized form, that cannot be connected to you), be used for teaching purposes, be presented at meetings, published, shared with other scientific researchers or used in future studies. Your name or other identifying information will not be used in any publication or teaching materials without your specific permission.

If you have questions about the research in general or about your role in the study, please feel free to contact principal investigator Dr. Joseph DeSouza either by telephone (416 736 2100 Ext.

22946) or email (desouza@yorku.ca). This research has been reviewed by the Human Participants Review Committee, York University's Ethics Review Board and conforms to the standards of the Canadian Tri-council Research ethics guidelines. If you have any questions about this process, or about your rights as a participant in the study, please contact the Sr. Manager & Policy Advisor for the Office of Research Ethics, 5th Floor, York Research Tower, York University (telephone 416-736-5914 or e-mail ore@yorku.ca).

_____	_____
Participant signature	Date
_____	_____
Researcher Signature	Date

Appendix B

Table 1: Exercises featured in the dance class at NBS

Exercise	Description	Purpose
Danced name introduction	Stating your name with a corresponding dance movement. The rest of the class first watches before repeated the participants name and movement. Standing or seated.	Feeling welcomed and welcoming everyone in the class. Practicing skills of choreographing on the spot.
Tendus	Pressing the feet along the floor until the leg is fully extended. Arms follow a similar extension motion. Seated.	Warming up the feet and lower leg, while working on strengthening the core.
Shuffle dance	A series of shuffles, stamps, and ankle inversions. Seated.	Facilitating flexibility and mobility in the ankles and knees.
Magic dance	Dancing with an imaginary ball and scarf, while exploring a range of motion. Seated.	An opportunity for vivid imagery and creative interpretation.
Rainfall cannon	Simulating the sounds of an approaching rainstorm using various body parts as percussion instruments. Seated.	Practicing movement initiation by waiting to execute a movement in proper sequence
Winning the poker game	Rising slowing from a chair while moving in a celebratory manner.	Practicing rising from a seated position in a safe manner.
Sculptor and painter mirrored pairs	A paired improvisation dance, done face to face. One partner would lead while the other mirrored their painting motion. This dance finished with a series of intertwined poses. Seated and standing aspects.	Mirroring a partner in a detailed fashion, and practicing creative movement initiation by improvising and developing unique poses.
Plies in parallel and second position	Holding on to the back of a chair, plies (bending of the knees) and rises were done in parallel (feet together) and apart. Standing.	Developing strength and balance while standing and increasing range of motion in the legs.
Lunging side to side	While holding onto the back of the chair, transferring weigh from side to side with legs in second position and “brandishing a fist” at a neighbouring participant. Standing.	Finding a core center for balance by lunging off balance and returning to a central position.
Waltz	Waltz step performed first on the spot and the travelling. Standing.	Safely dancing in the center, and physically embodying the triplet rhythm of a waltz.

Shy to confident shuffle dance	A standing variation of the seated shuffle dance, where the movements are done first in a demur and small manner, but gradually increase in confidence until they are gregariously expressed.	A fun way of practicing moving with confidence and with clear intention.
The Showdown Hoedown	Approximately a 2 minute choreography done facing a partner, first dancing as advisories in the “showdown” and then together as companions in the “hoedown.” Standing.	Challenging participants to recall a lengthy piece of choreography with multiple sections and changes of direction

MDS-UPDRS

The *Movement* Disorder Society (MDS)-sponsored new version of the UPDRS is founded on the critique that was formulated by the Task Force for Rating Scales in Parkinson's disease (*Mov Disord* 2003;18:738-750). Thereafter, the MDS recruited a Chairperson to organize a program to provide the Movement Disorder community with a new version of the UPDRS that would maintain the overall format of the original UPDRS, but address issues identified in the critique as weaknesses and ambiguities. The Chairperson identified subcommittees with chairs and members. Each part was written by the appropriate subcommittee members and then reviewed and ratified by the entire group. These members are listed below.

The MDS-UPDRS has four parts: Part I (non-motor experiences of daily living), Part II (motor experiences of daily living, Part III (motor examination) and Part IV (motor complications). 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. Part II is designed to be a self-administered questionnaire like Part IB, but can be reviewed by the investigator to ensure completeness and clarity. Of note, the official versions of Part IA, Part IB and Part II of the MDS-UPDRS do not have separate on or off ratings. However, for individual programs or protocols the same questions can be used separately for on and off. Part III has instructions for the rater to give or demonstrate to the patient; it is completed by the rater. 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.

The authors of this new version are: Chairperson: Christopher G. Goetz

Part I: Werner Poewe (chair), Bruno Dubois, Anette Schrag
Part II: Matthew B. Stern (chair), Anthony E. Lang,
Peter A. LeWitt Part III: Stanley Fahn (chair), Joseph
Jankovic, C. Warren Olanow
Part IV: Pablo Martinez-Martin (chair), Andrew Lees, Olivier Rascol, Bob van Hilten
Development Standards: Glenn T. Stebbins (chair), Robert Holloway, David Nyenhuis
Appendices: Cristina Sampaio (chair), Richard Dodel, Jaime Kulisevsky
Statistical Testing: Barbara Tilley (chair), Sue Leurgans, Jean Teresi,
Consultant: Stephanie Shaftman, Nancy LaPelle Contact person: Christopher G. Goetz, MD
Rush University Medical Center 1725 W. Harrison Street, Suite 755 Chicago, IL USA 60612
Telephone 312-942-8016 Email: cgoetz@rush.edu July 1, 2008

Overview: This portion of the scale assesses the non-motor impact of Parkinson's disease (PD) on patients' experiences of daily living. There are 13 questions. Part 1A is administered by the rater (six questions) and focuses on complex behaviors. Part 1B is a component of the self-administered Patient Questionnaire that covers seven questions on non-motor experiences of daily living.

Part 1A:

In administering Part IA, the examiner should use the following guidelines:

1. Mark at the top of the form the primary data source as patient, caregiver, or patient and caregiver in equal proportion.
2. The response to each item should refer to a period encompassing the prior week including the day on which the information is collected.
3. All items must have an integer rating (no half points, no missing scores). In the event that an item does not apply or cannot be rated (e.g., amputee who cannot walk), the item is marked UR for Unable to Rate.
4. The answers should reflect the usual level of function and words such as "usually", "generally", "most of the time" can be used with patients.
5. Each question has a text for you to read (Instructions to patients/caregiver). After that statement, you can elaborate and probe based on the target symptoms outlined in the Instructions to examiner. You should NOT READ the RATING OPTIONS to the patient/caregiver, because these are written in medical terminology. From the interview and probing, you will use your medical judgment to arrive at the best response.
6. Patients may have co-morbidities and other medical conditions that can affect their function. You and the patient must rate the problem as it exists and do not attempt to separate elements due to Parkinson's disease from other conditions.

EXAMPLE OF NAVIGATING THROUGH THE RESPONSE OPTIONS FOR PART 1A

Suggested strategies for obtaining the most accurate answer:

After reading the instructions to the patient, you will need to probe the entire domain under discussion to determine Normal vs. problematic: If your questions do not identify any problem in this domain, record 0 and move on to the next question.

If your questions identify a problem in this domain, you should work next with a reference anchor at the mid-range (option 2 or Mild) to find out if the patient functions at this level, better or worse. You will not be reading the choices of responses to the patient as the responses use clinical terminology. You will be asking enough probing questions to determine the response that should be coded.

Work up and down the options with the patient to identify the most accurate response, giving a final check by excluding the options above and below the selected response.

Is this item normal for you? ‘Yes’. Mark (0) Normal.

‘No, I have problems.’

Consider mild (2) as a reference point ‘Yes, slight is closest’. Confirm and mark (1) Slight.

If mild is closer thanand then slight.compare with slight (1).

Consider moderate (3) to see if this ‘No, moderate is too severe’. Confirm and mark (2) Mild. answer fits better.

If moderate is closer thanConsider severe mild. (4) to see if this ‘No, severe is too severe’.

Confirm and mark (3) Moderate. answer fits better.

‘Yes, severe is closest.’ Confirm and mark (4) Severe.

_____ Patient Name or Subject ID	_____ Site ID	_____ - _____ - __ (mm-dd-yyyy) Assessment Date	_____ Investigator’s Initials

MDS UPDRS

Part I: Non-Motor Aspects of Experiences of Daily Living (nM-EDL)

Part 1A: Complex behaviors: [completed by rater]

Primary source of information:

☐ Patient ☐ Caregiver ☐ Patient and Caregiver in Equal Proportion

To be read to the patient: I am going to ask you six questions about behaviors that you may or may not experience. Some questions concern common problems and some concern uncommon ones. If you have a problem in one of the areas, please choose the best response that describes how you have felt MOST OF THE TIME during the PAST WEEK. If you are not bothered by a problem, you can simply respond NO. I am trying to be thorough, so I may ask questions that have nothing to do with you.

1.1 COGNITIVE IMPAIRMENT	**SCORE**
Instructions to examiner: Consider all types of altered level of cognitive function including cognitive slowing, impaired reasoning, memory loss, deficits in attention and orientation. Rate their impact on activities of daily living as perceived by the patient and/or caregiver. *Instructions to patients [and caregiver]: Over the past week have you had problems remembering things, following conversations, paying attention, thinking clearly, or finding your way around the house or in town? [If yes, examiner asks patient or caregiver to elaborate and probes for information]* 0: Normal: No cognitive impairment. 1: Slight: Impairment appreciated by patient or caregiver with no concrete interference with the patient's ability to carry out normal activities and social interactions. 2: Mild: Clinically evident cognitive dysfunction, but only minimal interference with the patient's ability to carry out normal activities and social interactions. 3: Moderate: Cognitive deficits interfere with but do not preclude the patient's ability to carry out normal activities and social interactions.	☐

4: Severe: Cognitive dysfunction precludes the patient's ability to carry out normal activities and social interactions.	

	SCORE
1.2 HALLUCINATIONS AND PSYCHOSIS Instructions to examiner: Consider both illusions (misinterpretations of real stimuli) and hallucinations (spontaneous false sensations). Consider all major sensory domains (visual, auditory, tactile, olfactory and gustatory). Determine presence of unformed (for example sense of presence or fleeting false impressions) as well as formed (fully developed and detailed) sensations. Rate the patients insight into hallucinations and identify delusions and psychotic thinking. *Instructions to patients [and caregiver]: Over the past week have you seen, heard, smelled or felt things that were not really there?* [If yes, examiner asks patient or caregiver to elaborate and probes for information] 0: Normal: No hallucinations or psychotic behaviour. 1: Slight: Illusions or non-formed hallucinations, but patient recognizes them without loss of insight. 2: Mild: Formed hallucinations independent of environmental stimuli. No loss of insight. 3: Moderate: Formed hallucinations with loss of insight. 4: Severe: Patient has delusions or paranoia.	☐

1.3 DEPRESSED MOOD

Instructions to examiner: Consider low mood, sadness, hopelessness, feelings of emptiness or loss of enjoyment. Determine their presence and duration over the past week and rate their interference with the patient's ability to carry out daily routines and engage in social interactions.

Instruction to the patient (and caregiver): Over the past week have you felt low, sad, hopeless or unable to enjoy things? If yes, was this feeling for longer than one day at a time? Did it make it difficult for you carry out your usual activities or to be with people? If yes, examiner asks patient or caregiver to elaborate and probes for information]

0: Normal: No depressed mood.

1: Slight: Episodes of depressed mood that are not sustained for more than one day at a time. No interference with patient's ability to carry out normal activities and social interactions.

2: Mild: Depressed mood that is sustained over days, but without interference with normal activities and social interactions.

3: Moderate: Depressed mood that interferes with, but does not preclude, the patient's ability to carry out normal activities and social interactions.

4: Severe: Depressed mood precludes patient's ability to carry out normal activities and social interactions.

1.4 ANXIOUS MOOD	SCORE
Instructions to examiner: Determine nervous, tense, worried or anxious feelings (including panic attacks) over the past week and rate their duration and interference with the patient's ability to carry out daily routines and engage in social interactions. *Instructions to patients [and caregiver]: Over the past week have you felt nervous, worried or tense? If yes, was this feeling for longer than one day at a time? Did it make it difficult for you to follow your usual activities or to be with other people*? [If yes, examiner asks patient or caregiver to elaborate and probes for information.] 0: Normal: No anxious feelings. 1: Slight: Anxious feelings present but not sustained for more than one day at a time. No interference with patient's ability to carry out normal activities and social interactions. 2: Mild: Anxious feelings are sustained over more than one day at a time, but without interference with patient's ability to carry out normal activities and social interactions. 3: Moderate: Anxious feelings interfere with, but do not preclude, the patient's ability to carry out normal activities and social interactions. 4: Severe: Anxious feelings preclude patient's ability to carry out normal activities and social interactions.	☐

1.5 APATHY

Instructions to examiner: Consider level of spontaneous activity, assertiveness, motivation and initiative and rate the impact of reduced levels on performance of daily routines and social interactions. Here the examiner should attempt to distinguish between apathy and similar symptoms that are best explained by depression.

Instructions to patients (and caregiver): Over the past week, have you felt indifferent to doing activities or being with people? If yes, examiner asks patient or caregiver to elaborate and probes for information.]

0: Normal: No apathy.

1: Slight: Apathy appreciated by patient and/or caregiver, but no interference with daily activities and social interactions.

2: Mild: Apathy interferes with isolated activities and social interactions.

3: Moderate: Apathy interferes with most activities and social interactions.

4: Severe: Passive and withdrawn, complete loss of initiative.

SCORE

1.6 FEATURES OF DOPAMINE DYSREGULATION SYNDROME

Instructions to examiner: Consider involvement in a variety of activities including atypical or excessive gambling (e.g. casinos or lottery tickets), atypical or excessive sexual drive or interests (e.g., unusual interest in pornography, masturbation, sexual demands on partner), other repetitive activities (e.g. hobbies, dismantling objects, sorting or organizing), or taking extra non-prescribed medication for non-physical reasons (i.e., addictive behavior). Rate the impact of such abnormal activities/behaviors on the patient's personal life and on his family and social relations (including need to borrow money or other financial difficulties like withdrawal of credit cards, major family conflicts, lost time from work, or missed meals or sleep because of the activity).

Instructions to patients [and caregiver]: Over the past week, have you had unusually strong urges that are hard to control? Do you feel driven to do or think about something and find it hard to stop? [Give patient examples such as gambling, cleaning, using the computer, taking extra medicine, obsessing about food or sex, all depending on the patients.

0: Normal: No problems present.

1: Slight: Problems are present but usually do not cause any difficulties for the patient or family/caregiver.

2: Mild: Problems are present and usually cause a few difficulties in the patient's personal and family life.

3: Moderate: Problems are present and usually cause a lot of difficulties in the patient's personal and family life.

4: Severe: Problems are present and preclude the patient's ability to carry out normal activities or social interactions or to maintain previous standards in personal and family life.

Patient Questionnaire:

Instructions:

This questionnaire will ask you about your experiences of daily living.

There are 20 questions. We are trying to be thorough, and some of these questions may therefore not apply to you now or ever. If you do not have the problem, simply mark 0 for NO.

Please read each one carefully and read all answers before selecting the one that best applies to you.

We are interested in your average or usual function over the past week including today. Some patients can do things better at one time of the day than at others. However, only one answer is allowed for each question, so please mark the answer that best describes what you can do most of the time.

You may have other medical conditions besides Parkinson's disease. Do not worry about separating Parkinson's disease from other conditions. Just answer the question with your best response.

Use only 0, 1, 2, 3, 4 for answers, nothing else. Do not leave any blanks.

Your doctor or nurse can review the questions with you, but this questionnaire is for patients to complete, either alone or with their caregivers.

Who is filling out this questionnaire (check the best answer):

☐ Patient ☐ Caregiver ☐ Patient and Caregiver in Equal Proportion

Part I: Non-Motor Aspects of Experiences of Daily Living (nM-EDL)		
		SCORE
1.7 SLEEP PROBLEMS	ıave you had trouble going to sleep at night or staying sleep Consider how rested you felt after waking up in the ıorning. Over through the nnight?	
0: Normal:	No problems.	
1: Slight:	Sleep problems are present but usually do not cause trouble getting a full night of sleep.	
2: Mild:	Sleep problems usually cause some difficulties getting a full night of sleep.	
3: Moderate:	Sleep problems cause a lot of difficulties getting a full night of sleep, but I still usually sleep for more than half the night.	☐
4: Severe:	I usually do not sleep for most of the night.	
1.8 DAYTIME SLEEPINESS		
	Over the past week, have you had trouble staying awake during the daytime?	
0: Normal:	No daytime sleepiness.	
1: Slight:	Daytime sleepiness occurs but I can resist and I stay awake.	

2: Mild:	Sometimes I fall asleep when alone and relaxing. For example, while reading or watching TV.	
3: Moderate:	I sometimes fall asleep when I should not. For example, while eating or talking with other people.	☐
4: Severe:	I often fall asleep when I should not. For example, while eating or talking with other people.	

SENSATIONS		**SCORE**
1.9 PAIN AN / **OTHER S**	ek, have you had uncomfortable feelings in your body like pain, aches	
Over tingling or cramps?		
0: Normal:		
1: Slight:	No uncomfortable feelings.	
2: Mild:	I have these feelings. However, I can do things and be with other people without difficulty.	
3: Moderate:	These feelings cause some problems when I do things or am with other people.	
	These feelings cause a lot of problems, but they do not stop me from doing things or being with other people.	
4: Severe:	These feelings stop me from doing things or being with other people.	☐

1.10 URINARY PROBLEMS

Over the past week, have you had trouble with urine control? For example, an urgent need to urinate, a need to urinate too often, or urine accidents?

0: Normal:	No urine control problems.	
1: Slight:	I need to urinate often or urgently. However, these problems do not cause difficulties with my daily activities.	
2: Mild:	Urine problems cause some difficulties with my daily activities. However, I do not have urine accidents.	
3: Moderate:	Urine problems cause a lot of difficulties with my daily activities, including urine accidents.	☐
4: Severe:	I cannot control my urine and use a protective garment or have a bladder tube.	

1.11	CONSTIPATION PROBLEMS	SCORE
	Over the past week have you had constipation troubles that cause you difficulty moving your bowels?	
0: Normal:	No constipation.	
1: Slight:	I have been constipated. I use extra effort to move my bowels. However, this problem does not disturb my activities or my being comfortable.	
2: Mild:	Constipation causes me to have some troubles doing things or being comfortable.	
3: Moderate:	Constipation causes me to have a lot of trouble doing things or being comfortable. However, it does not stop me from doing anything.	
4: Severe:	I usually need physical help from someone else to empty my bowels.	

1.12 LIGHT HEADEDNESS ON STANDING

Over the past week, have you felt faint, dizzy or foggy when you stand up after sitting or lying down?

0: Normal:	No dizzy or foggy feelings.
1: Slight:	Dizzy or foggy feelings occur. However, they do not cause me troubles doing things.
2: Mild:	Dizzy or foggy feelings cause me to hold on to something, but I do not need to sit or lie back down.
3: Moderate:	Dizzy or foggy feelings cause me to sit or lie down to avoid fainting or falling.
4: Severe:	Dizzy or foggy feelings cause me to fall or faint.

		SCORE
1.13 FATIGUE	Over the past week, have you usually felt fatigued? This feeling is not part of being sleepy or sad	
0: Normal:	No fatigue.	
1: Slight:	Fatigue occurs. However it does not cause me troubles doing things or being with people.	
2: Mild:	Fatigue causes me some troubles doing things or being with people.	
3: Moderate:		
4: Severe:	Fatigue causes me a lot of troubles doing things or being with people. However, it does not stop me from doing anything.	
	Fatigue stops me from doing things or being with people.	

Part II: Motor Aspects of Experiences of Daily Living (M-DL)

2.1 SPEECH		
Over the past week, have you had problems with your speech?		
0: Normal:	Not at all (no problems).	
1: Slight:	My speech is soft, slurred or uneven, but it does not cause others to ask me to repeat myself.	
2: Mild:	My speech causes people to ask me to occasionally repeat myself, but not everyday.	
3: Moderate:		

	My speech is unclear enough that others ask me to repeat myself every day even though most of my speech is understood.	
4: Severe:	Most or all of my speech cannot be understood.	

		SCORE
2.2 SALIVA & DROOLING	Over the past week, have you usually had too much saliva during when you are awake or when you sleep?	
0: Normal:	Not at all (no problems).	
1: Slight:	I have too much saliva, but do not drool.	
2: Mild:	I have some drooling during sleep, but none when I am awake.	
3: Moderate:	I have some drooling when I am awake, but I usually do not need tissues or a handkerchief.	
4: Severe:	I have so much drooling that I regularly need to use tissues or a handkerchief to protect my clothes.	☐

2.3 CHEWING AND SWALLOWING

Over the past week, have you usually had problems swallowing pills or eating meals? Do you need your pills cut or crushed or your meals to be made soft, chopped or blended to avoid choking?

0: Normal:	No problems.
1: Slight:	I am aware of slowness in my chewing or increased effort at swallowing, but I do not choke or need to have my food specially prepared.
2: Mild:	I need to have my pills cut or my food specially prepared because of chewing or swallowing problems, but I have not choked over the past week.
3: Moderate.	I choked at least once in the past week.
4: Severe:	Because of chewing and swallowing problems, I need a feeding tube.

		SCORE
2.4 EATING TASKS	Over the past week, have you usually had troubles handling your food and using eating utensils? For example, do you have trouble handling finger foods or using forks, knifes, spoons, chopsticks?	
0: Normal:	Not at all (No problems).	
1: Slight:	I am slow, but I do not need any help handling my food and have not had food spills while eating.	
2: Mild:	I am slow with my eating and have occasional food spills. I may need help with a few tasks such as cutting meat.	☐
3: Moderate:	I need help with many eating tasks but can manage some alone.	
4: Severe:	I need help for most or all eating tasks.	
2.5 DRESSING	Over the past week, have you usually had problems dressing? For example, are you slow or do you need help with buttoning, using zippers, putting on or taking off your clothes or jewelry?	
0: Normal:	Not at all (no problems).	
1: Slight:	I am slow but I do not need help.	
2: Mild:	I am slow and need help for a few dressing tasks (buttons, bracelets).	☐
3: Moderate:	I need help for many dressing tasks.	

4: Severe:	I need help for most or all dressing tasks.	

		SCORE
2.6 HYGIENE		
	Over the past week, have you usually been slow or do you need help with washing, bathing, shaving, brushing teeth, combing your hair or with other personal hygiene?	
0: Normal:	Not at all (no problems).	
1: Slight:	I am slow but I do not need any help.	
2: Mild:	I need someone else to help me with some hygiene tasks.	
3: Moderate:	I need help for many hygiene tasks.	
4: Severe:	I need help for most or all of my hygiene tasks.	
2.7 HANDWRITING		
	Over the past week, have people usually had trouble reading your handwriting?	
0: Normal:	Not at all (no problems).	

1: Slight: 2: Mild: My writing is slow, clumsy or uneven, but all words are clear. Some words are unclear and difficult to read. 3: Moderate: Many words are unclear and difficult to read. Most or all words cannot be read. 4: Severe:	☐
2.8 DOING HOBBIES AND OTHER ACTIVITIES Over the past week, have you usually had trouble doing your hobbies or other things that you like to do? 0: Normal: Not at all (no problems). 1: Slight: 2: Mild: I am a bit slow but do these activities easily. I have some difficulty doing these activities. 3: Moderate: I have major problems doing these activities, but still do most. 4: Severe: I am unable to do most or all of these activities.	☐

		SCORE
2.9 TURNING IN BED	Over the past week, do you usually have trouble turning over in bed?	
0: Normal:	Not at all (no problems).	
1: Slight:	I have a bit of trouble turning, but I do not need any help.	
2: Mild	I have a lot of trouble turning and need occasional help from someone else.	
3: Moderate:	To turn over I often need help from someone else.	
4: Severe:	I am unable to turn over without help from someone else.	☐
2.10 TREMOR	Over the past week, have you usually had shaking or tremor?	
0: Normal:	Not at all. I have no shaking or tremor.	
1: Slight:	Shaking or tremor occurs but does not cause problems with any activities.	☐
2: Mild:	Shaking or tremor causes problems with only a few activities.	
3: Moderate:	Shaking or tremor causes problems with many of my daily activities.	
4: Severe:	Shaking or tremor causes problems with most or all activities.	

2.11 GETTING OUT OF BED, A CAR, OR A DEEP CHAIR	Over the past week, have you usually had trouble getting out of bed, a car seat, or a deep chair?	
0: Normal:	Not at all (no problems).	
1: Slight:	I am slow or awkward, but I usually can do it on my first try.	
2: Mild:	I need more than one try to get up or need occasional help.	
3: Moderate:	I sometimes need help to get up, but most times I can still do it on my own.	
4: Severe:	I need help most or all of the time.	

		SCORE
2.12 WALKING AND BALANCE		
0: Normal:	Over the past week, have you usually had problems with balance and walking?	
1: Slight:	Not at all (no problems).	
2: Mild:	I am slightly slow or may drag a leg. I never use a walking aid.	
3: Moderate:	I occasionally use a walking aid, but I do not need any help from another person.	
4: Severe:		

	I usually use a walking aid (cane, walker) to walk safely without falling. However, I do not usually need the support of another person. I usually use the support of another persons to walk safely without falling.	☐
2.13 FREEZING Over the past week, on your usual day when walking, do you suddenly stop or freeze as if your feet are stuck to the floor.		
0: Normal:	Not at all (no problems).	
1: Slight:	I briefly freeze but I can easily start walking again. I do not need help from someone else or a walking aid (cane or walker) because of freezing.	
2: Mild:	I freeze and have trouble starting to walk again, but I do not need someone's help or a walking aid (cane or walker) because of freezing.	☐

3: Moderate:	When I freeze I have a lot of trouble starting to walk again and, because of freezing, I sometimes need to use a walking aid or need someone else's help.	
4: Severe:	Because of freezing, most or all of the time, I need to use a walking aid or someone's help.	

This completes the questionnaire. We may have asked about problems you do not even have, and may have mentioned problems that you may never develop at all. Not all patients develop all these problems, but because they can occur, it is important to ask all the questions to every patient. Thank you for your time and attention in completing this questionnaire.

Part III: Motor Examination

Overview: This portion of the scale assesses the motor signs of PD. In administering Part III of the MDS-UPDRS the examiner should comply with the following guidelines:

At the top of the form, mark whether the patient is on medication for treating the symptoms of Parkinson's disease and, if on levodopa, the time since the last dose.

Also, if the patient is receiving medication for treating the symptoms of Parkinson's Disease, mark the patient's clinical state using the following definitions:

ON is the typical functional state when patients are receiving medication and have a good response.

OFF is the typical functional state when patients have a poor response in spite of taking medications.

The investigator should "rate what you see". Admittedly, concurrent medical problems such as stroke, paralysis, arthritis, contracture, and orthopedic problems such as hip or knee replacement and scoliosis may interfere with individual items in the motor examination. In situations where it is absolutely impossible to test (e.g., amputations, plegia, limb in a cast), use the notation "**UR**" for Unable to Rate. Otherwise, rate the performance of each task as the patient performs in the context of co-morbidities.

All items must have an integer rating (no half points, no missing ratings).

Specific instructions are provided for the testing of each item. These should be followed in all instances. The investigator demonstrates while describing tasks the patient is to perform and rates function immediately thereafter. For Global Spontaneous Movement and Rest Tremor items (3.14 and 3.17), these items have been placed purposefully at the end of the scale because clinical information pertinent to the score will be obtained throughout the entire examination.

At the end of the rating, indicate if dyskinesia (chorea or dystonia) was present at the time of the examination, and if so, whether these movements interfered with the motor examination.

3a Is the patient on medication for treating the symptoms of Parkinson's Disease? ☐ No ☐ Yes

3b If the patient is receiving medication for treating the symptoms of Parkinson's Disease, mark the patient's clinical state using the following definitions:

☐ ON: On is the typical functional state when patients are receiving medication and have a good response.

☐ OFF: Off is the typical functional state when patients have a poor response in spite of taking medications.

3c Is the patient on Levodopa ? ☐ No ☐ Yes

3.C1 If yes, minutes since last levodopa dose: _____

	SCORE
3.1 SPEECH Instructions to examiner: Listen to the patient's free-flowing speech and engage in conversation if necessary. Suggested topics: ask about the patient's work, hobbies, exercise, or how he got to the doctor's office. Evaluate volume, modulation (prosody) and clarity, including slurring, palilalia (repetition of syllables) and tachyphemia (rapid speech, running syllables together). 0: Normal: No speech problems. 1: Slight: Loss of modulation, diction or volume, but still all words easy to understand. 2: Mild: Loss of modulation, diction, or volume, with a few words unclear, but the overall sentences easy to follow. 3: Moderate: Speech is difficult to understand to the point that some, but not most, sentences are poorly understood. 4: Severe: Most speech is difficult to understand or unintelligible.	☐

3.2 FACIAL EXPRESSION

Instructions to examiner: Observe the patient sitting at rest for 10 seconds, without talking and also while talking. Observe eye-blink frequency, masked facies or loss of facial expression, spontaneous smiling and parting of lips.

0: Normal: Normal facial expression.

1: Slight: Minimal masked facies manifested only by decreased frequency of blinking.

2: Mild: In addition to decreased eye-blink frequency, Masked facies present in the lower face as well, namely fewer movements around the mouth, such as less spontaneous smiling, but lips not parted.

3: Moderate: Masked facies with lips parted some of the time when the mouth is at rest.

4: Severe: Masked facies with lips parted most of the time when the mouth is at rest.

SCORE

3.3 RIGIDITY

Instructions to examiner: Rigidity is judged on slow passive movement of major joints with the patient in a relaxed position and the examiner manipulating the limbs and neck. First, test without an activation maneuver. Test and rate neck and each limb separately. For arms, test the wrist and elbow joints simultaneously. For legs, test the hip and knee joints simultaneously. If no rigidity is detected, use an activation maneuver such as tapping fingers, fist opening/closing, or heel tapping in a limb not being tested. Explain to the patient to go as limp as possible as you test for rigidity.

0: Normal: No rigidity.

1: Slight: Rigidity only detected with activation maneuver.

2: Mild: Rigidity detected without the activation maneuver, but full range of motion is easily achieved.

3: Moderate: Rigidity detected without the activation maneuver; full range of motion is achieved with effort.

4: Severe: Rigidity detected without the activation maneuver and full range of motion not achieved.

Neck

RUE

LUE

RLE

LLE

3.4 FINGER TAPPING

Instructions to examiner: Each hand is tested separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to tap the index finger on the thumb 10 times as quickly AND as big as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude.

0: Normal: No problems.

1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the tapping movement; b) slight slowing; c) the amplitude decrements

	near the end of the 10 taps.	R L
2: Mild:	Any of the following: a) 3 to 5 interruptions during tapping; b) mild slowing; c) the amplitude decrements midway in the 10-tap sequence.	
3: Moderate:	Any of the following: a) more than 5 interruptions during tapping or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st tap.	
4: Severe:	Cannot or can only barely perform the task because of slowing, interruptions or decrements.	

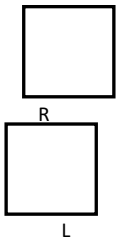
3.5 HAND MOVEMENTS	**SCORE**
Instructions to examiner: Test each hand separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to make a tight fist with the arm bent at the elbow so that the palm faces the examiner. Have the patient open the hand 10 times as fully AND as quickly as possible. If the patient fails to make a tight fist or to open the hand fully, remind him/ her to do so. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude.	
0: Normal: No problem.	R L
1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) the amplitude decrements near the end of the task.	
2: Mild: Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowing; c) the amplitude decrements midway in the task.	
3: Moderate: Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st open-and-close sequence.	
4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.	

3.6 PRONATION-SUPINATION MOVEMENTS OF HANDS

Instructions to examiner: Test each hand separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to extend the arm out in front of his/her body with the palms down; then to turn the palm up and down alternately 10 times as fast and as fully as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude.

0: Normal: No problems.

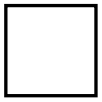
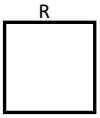
1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) the amplitude decrements near the end of the sequence.



2: Mild: Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowing;
c) the amplitude decrements midway in the sequence.

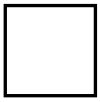
3: Moderate: Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing c) the amplitude decrements starting after the 1st supination-pronation sequence.

4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.

		SCORE
3.TOE TAPPING Instructions to examine Test each foot patient is bei then tap the toes 10 amplitude, hesitation	r: Have the patient sit in a straight-backed chair with arms, both feet on the floor. ately. Demonstrate the task, but do not continue to perform the task while the d. Instruct the patient to place the heel on the ground in a comfortable position and times as big and as fast as possible. Rate each side eparately, evaluating speed, s, halts and decrementing amplitude.	
0: Normal:	No problem.	 R  L
1: Slight:	Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the tapping movement; b) slight slowing; c) amplitude decrements near the end of the ten taps.	
2: Mild:	Any of the following: a) 3 to 5 interruptions during the tapping movements; b) mild slowing; c) amplitude decrements midway in the task.	
3: Moderate:	Any of the following: a) more than 5 interruptions during the tapping movements or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) amplitude decrements after the first tap.	
4: Severe:	Cannot or can only barely perform the task because of slowing, interruptions or decrements.	

3.8 LEG AGILITY

Instructions to examiner: Have the patient sit in a straight-backed chair with arms. The patient should have both feet comfortably on the floor. Test each leg separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to place the foot on the ground in a comfortable position and then raise and stomp the foot on the ground 10 times as high and as fast as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude.

0: Normal:	No problems.	
1: Slight:	Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) amplitude decrements near the end of the task.	

2: Mild:	Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowness; c) amplitude decrements midway in the task.	R L
3: Moderate:	Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing in speed; c) amplitude decrements after the first tap.	
4: Severe:	Cannot or can only barely perform the task because of slowing, interruptions or decrements.	

		SCORE
3.9 ARISING FROM CHAIR Instructions to examiner: floor and sitting back in t across the chest and the u to two more times. If arms folded across th ch to push off using his/her If still not successful, ass 3.13	Have the patient sit in a straight-backed chair with arms, with both feet on the he chair (if the patient is not too short). Ask the patient to cross his/her arms n to stand up. If the patient is not successful, repeat this attempt a maximum still unsuccessful, allow the patient to move forward in the chair to arise with est. Allow only one attempt in this situation. If unsuccessful, allow the patient hands on the arms of the chair. Allow a maximum of three trials of pushing off. ist the patient to arise. After the patient stands up, observe the posture for item	
0: Normal:	No problems. Able to arise quickly without hesitation.	
1: Slight:	Arising is slower than normal; or may need more than one attempt; or may need to move forward in the chair to arise. No need to use the arms of the chair. Pushes self up from arms of chair without difficulty.	
2: Mild:	Needs to push off, but tends to fall back; or may have to try more than one time using arms of chair, but can get up without help.	
3: Moderate:	Unable to arise without help.	
4: Severe:		

3.10 GAIT

Instructions to examiner: Testing gait is best performed by having the patient walking away from and t~~owards the examiner so~~ that both right and left sides of the body can be easily observed simultaneously. The patient should walk at least 10 meters (30 feet), then turn around and return to the examiner. This item measures multiple behaviors: stride amplitude, stride speed, height of foot lift, heel strike during walking, turning, and arm swing, but not freezing. Assess also for "freezing of gait" (next item 3.11) while patient is walking. Observe posture for item 3.13

0: Normal: No problems.

1: Slight: Independent walking with minor gait impairment.

2: Mild: Independent walking but with substantial gait impairment.

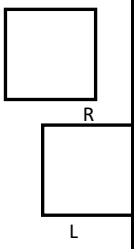
3: Moderate: Requires an assistance device for safe walking (walking stick, walker) but not a person.

4: Severe: Cannot walk at all or only with another person's assistance.

	SCORE
3.11 FREEZIN OF GAIT Instructions to examiner: episodes. Observe for st the end of the task. assessment. 0: Normal: 1: Slight: 2: Mild: 3: Moderate: 4: Severe:	While assessing gait, also assess for the presence of any gait freezing hesitation and stuttering movements especially when turning and ıching To the extent that safety permits, patients may NOT use sensory :ks during the No freezing. Freezes on starting, turning or walking through doorway with a single halt during any of these events, but then continues smoothly without freezing during straight walking. Freezes on starting, turning or walking through doorway with more than one halt during any of these activities, but continues smoothly without freezing during straight walking. Freezes once during straight walking. Freezes multiple times during straight walking.	
3.12 POSTURAL STABILITY Instructions to examiner: The test examines the response to sudden body displacement produced by a quick, forceful pull on the shoulders while the patient is standing erect with eyes open and feet comfortably apart and parallel to each other. Test retropulsion. Stand behind the patient and instruct the patient on what is about to happen. Explain that s/he is allowed to take a step backwards to avoid falling. There should be a solid wall behind the examiner, at least 1-2 meters away to allow for the observation of the number of retropulsive steps. The first pull is an instructional demonstration and is purposely milder and not rated. The second time the shoulders are pulled briskly and forcefully towards the examiner with enough force to displace the center of gravity so that patient MUST take a step backwards. The examiner needs to be ready to catch the patient, but must stand sufficiently back so as to allow enough room for the patient to take several steps to recover independently. Do not allow the patient to flex the body abnormally forward in anticipation of the pull. Observe for the number of steps backwards or falling. Up to and including two steps for recovery is considered normal, so abnormal ratings begin with three steps. If the patient fails to understand the test, the examiner can repeat the test so that the rating is based on an assessment that the	

examiner feels reflects the patient's limitations rather than misunderstanding or lack of preparedness. Observe standing posture for item 3.13 0: Normal: No problems: Recovers with one or two steps. 1: Slight: 3-5 steps, but subject recovers unaided. 2: Mild: More than 5 steps, but subject recovers unaided. 3: Moderate: Stands safely, but with absence of postural response; falls if not caught by examiner. 4: Severe: Very unstable, tends to lose balance spontaneously or with just a gentle pull on the shoulders.	☐

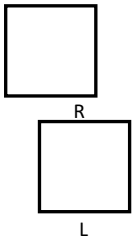
	SCORE
3.13 **POSTURE** Instructions examine dur walking, and wl to stand straight an in th three observa r: Posture is assessed with the patient standing erect after arising from a chair, being tested for postural reflexes. If you notice poor posture, tell the patient d see if the posture improves (see option 2 below). Rate the worst posture seen tion points. Observe for flexion and side-to-side leaning. 0: Normal: No problems. 1: Slight: Not quite erect, but posture could be normal for older person. 2: Mild: Definite flexion, scoliosis or leaning to one side, but patient can correct posture to normal posture when asked to do so. 3: Moderate: Stooped posture, scoliosis or leaning to one side that cannot be corrected volitionally to a normal posture by the patient. 4: Severe: Flexion, scoliosis or leaning with extreme abnormality of posture.	
3.14 GLOBAL SPONTANEITY OF MOVEMENT (BODY BRADYKINESIA) Instructions to examiner: This global rating combines all observations on slowness, hesitancy, and small amplitude and poverty of movement in general, including a reduction of gesturing and of crossing the legs. This assessment is based on the examiner's global impression after observing for spontaneous gestures while sitting, and the nature of arising and walking. 0: Normal: No problems. 1: Slight: Slight global slowness and poverty of spontaneous movements. 2: Mild: Mild global slowness and poverty of spontaneous movements. 3: Moderate: Moderate global slowness and poverty of spontaneous movements.	

4: Severe:	Severe global slowness and poverty of spontaneous movements.	
3.15 POSTURAL TRE Instructions to examine to be included in this ra patient to stretch the ar the fingers comfortably seconds. 0: Normal: 1: Slight: 2: Mild: 3: Moderate: 4: Severe:	**MOR OF THE HANDS** r: All tremor, including re-emergent rest tremor, that is present in this posture is ting. Rate each hand separately. Rate the highest amplitude seen. Instruct the ms out in front of the body with palms down. The wrist should be straight and separated so that they do not touch each other. Observe this posture for 10 No tremor. Tremor is present but less than 1 cm in amplitude. Tremor is at least 1 but less than 3 cm in amplitude. Tremor is at least 3 but less than 10 cm in amplitude. Tremor is at least 10 cm in amplitude.	

SCORE

3.16KINETIC TREMOR OF THE HANDS

: This is tested by the finger-to-nose maneuver. With the arm
ing from the n, have the patient perform at least three finger-to-
maneuvers with each hand le to touch the examiner's finger. The
r-to-nose maneuver should be
not to hide any tremor that could occur with very fast arm
movements. Repeat each hand separately. The tremor can be
present throughout the movement
either target (nose or finger). Rate the highest amplitude seen.



<u>Instructions to examiner</u>

outstretched positio
reaching as far as possib performed slowly enough with the other hand, ratin or as the tremor reache

0: Normal: No tremor.

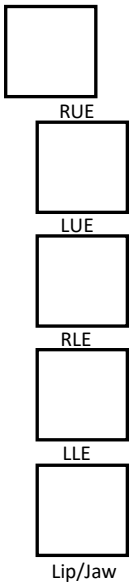
1: Slight: Tremor is present but less than 1 cm in amplitude.

2: Mild: Tremor is at least 1 but less than 3 cm in amplitude.

3: Moderate: Tremor is at least 3 but less than 10 cm in amplitude.

4: Severe: Tremor is at least 10 cm in amplitude.

3.17 REST TREMOR



AMPLITUDE

Instructions to examiner

examination to: This and the next item have been placed purposefully at the end allow the the exam, of the rater to gather observations on rest tremor that may including whe appear at any time during n quietly sitting, during walking and moving but others during activities when some body parts are are a Rate only the: rest. Score the maximum amplitude that is seen at any time as amplitude As part of he final score. and not the persistence or the intermittency of the this rating, th chair remor. e patient should sit quietly in a chair with the hands placed (not in the lap) an n the arms of the directives. Rest the feet comfortably supported on the floor for 10 seconds tremor maximum with no other is assessed separately for all four limbs and also amplitude tha for the lip/jaw. Rate only the t is seen at any time as the final rating.

Extremity ratings

0: Normal: No tremor.

1: Slight.: ≤ 1 cm in maximal amplitude.

2: Mild: > 1 cm but < 3 cm in maximal amplitude.

3: Moderate: 3 - 10 cm in maximal amplitude.

4: Severe: > 10 cm in maximal amplitude.

Lip/Jaw ratings

0: Normal: No tremor.

1: Slight: ≤ 1 cm in maximal amplitude.

2: Mild: > 1 cm but ≤ 2 cm in maximal amplitude.

3: Moderate: > 2 cm but ≤ 3 cm in maximal amplitude.

4: Severe: > 3 cm in maximal amplitude.

	SCORE
3.18 CONSTANCY OF REST TREMOR Instructions to examiner: This item receives one rating for all rest tremor and focuses on the constancy of rest tremor during the examination period when different body parts are variously at rest. It is rated purposefully at the end of the examination so that several minutes of information can be coalesced into the rating. 0: Normal: No tremor. 1: Slight: Tremor at rest is present ≤ 25% of the entire examination period. 2: Mild: Tremor at rest is present 26-50% of the entire examination period. 3: Moderate: Tremor at rest is present 51-75% of the entire examination period. 4: Severe: Tremor at rest is present > 75% of the entire examination period.	☐

DYSKINESIA IMPACT ON PART III RATINGS

A. Were dyskinesias (chorea or dystonia) present during examination? ☐ No ☐ Yes

B. If yes, did these movements interfere with your ratings? ☐ No ☐ Yes

HOEHN AND YAHR STAGE

0: Asymptomatic.

1: Unilateral involvement only.

2: Bilateral involvement without impairment of balance.

3: Mile to moderate involvement; some postural instability but physically independent; needs assistance to recover from pull test.

4: Severe disability; still able to walk or stand unassisted.

5: Wheelchair bound or bedridden unless aided.

4.2 FUNCTIONAL IMPACT OF DYSKINESIAS	SCORE
Instructions to examiner: Determine the degree to which dyskinesias impact on the patient's daily function in terms of activities and social interactions. Use the patient's and caregiver's response to your question and your own observations during the office visit to arrive at the best answer. *Instructions to patient [and caregiver]: Over the past week, did you usually have trouble doing things or being with people when these jerking movements occurred? Did they stop you from doing things or from being with people?* 0: Normal: No dyskinesias or no impact by dyskinesias on activities or social interactions. 1: Slight: Dyskinesias impact on a few activities, but the patient usually performs all activities and participates in all social interactions during dyskinetic periods. 2: Mild: Dyskinesias impact on many activities, but the patient usually performs all activities and participates in all social interactions during dyskinetic periods. 3: Moderate: Dyskinesias impact on activities to the point that the patient usually does not perform some activities or does not usually participate in some social activities during dyskinetic episodes. 4: Severe: Dyskinesias impact on function to the point that the patient usually does not perform most activities or participate in most social interactions during dyskinetic episodes.	☐
B . MOTOR FLUCTUATIONS	
4.3 TIME SPENT IN THE OFF STATE Instructions to examiner: Use the number of waking hours derived from 4.1 and determine the hours spent in the "OFF" state. Calculate the percentage. If the patient has an OFF period in the office, you can point to this state as a reference. You may also use your knowledge of the patient to describe a typical OFF period. Additionally you may use your own acting skills to enact an OFF period you have seen in the patient before or show them OFF function typical of other patients. Mark down the typical number of OFF hours, because you will need this number for completing 4.6 *Instructions to patient [and caregiver]: Some patients with Parkinson's disease have a good effect from their medications throughout their awake hours*	☐

and we call that "ON" time. Other patients take their medications but still have some hours of low time, bad time, slow time or shaking time. Doctors call these low periods "OFF" time. Over the past week, you told me before that you are generally awake hrs each day. Out of these awake hours, how many hours in total do you usually have this type of
low level or OFF function (Use this number for your calculations).

____

0: Normal:	No OFF time.
1: Slight:	≤ 25% of waking day.
2: Mild:	26 - 50% of waking day.
3: Moderate:	51 - 75% of waking day.
4: Severe:	> 75% of waking day.

1. Total Hours Awake: ____

2. Total Hours OFF: ____

3. % OFF = ((2/1)*100):

FLUCTUATIONS		SCORE
4.4 FUNCTIONA IMPACT OF	Determine the degree to which motor fluctuations impact on the patient's daily es and social interactions. This question concentrates on the difference	
Instructions to examiner: functior in terms of activiti between the ON state a patients have very mild occurs. Use the patient' the office visit to arrive at	nd the OFF state. If the patient has no OFF time, the rating must be), but if fluctuations, it is still possible to be rated 0 on this item if no impact on activities ; and caregiver's response to your question and your own observations during the best answer.	
Instructions patient [and t past week. Do the rest of the d when during good period th	*caregiver]: Think about when those low or "OFF" periods ve occurred over u usually have more problems doing things being with people than compared to you feel your medications orking? Are there some things you usually do t you have trouble with or stop doing during a low period?*	
	No fluctuations or No impact by fluctuations on performance of activities or social interactions.	
0: Normal:	Fluctuations impact on a few activities, but during OFF, the patient usually performs all activities and participates in all social interactions that typically occur during the ON state.	
1: Slight:	Fluctuations impact many activities, but during OFF, the patient still usually performs all activities and participates in all social interactions that typically occur during the ON state.	
2: Mild:	Fluctuations impact on the performance of activities during OFF to the point that the patient usually does not perform some activities or participate in some social interactions that are performed during ON periods.	
3: Moderate:	Fluctuations impact on function to the point that, during OFF, the patient usually does not perform most activities or participate in most social interactions that are performed during ON periods.	
4: Severe:		

4.5 COMPLEXITY OF MOTOR FLUCTUATIONS

Instructions to examiner: Determine the usual predictability of OFF function whether due to dose, time of day, food intake or other factors. Use the information provided by the patients and caregiver and supplement with your own observations. You will ask if the patient can count on them always coming at a special time, mostly coming at a special time (in which case you will probe further to separate slight from mild), only sometimes coming at a special time or are they totally unpredictable? Narrowing down the percentage will allow you to find the correct answer.

Instructions to patient [and caregiver]: For some patients, the low or "OFF" periods happen at certain times during day or when they do activities like eating or exercising. Over the past week, do you usually know when your low periods will occur? In other words, do your low periods always come at a certain time? Do they mostly come at a certain time? Do they only sometimes come at a certain time? Are your low periods totally unpredictable?"

0: Normal: No motor fluctuations.

1: Slight: OFF times are predictable all or almost all of the time (> 75%).

2: Mild: OFF times are predictable most of the time (51-75%).

3: Moderate: OFF times are predictable some of the time (26-50%).

4: Severe: OFF episodes are rarely predictable. (≤ 25%).

C. "OFF" DYSTONIA

4.6 PAINFUL OFF-STATE DYSTONIA

Instructions to examiner: For patients who have motor fluctuations, determine what proportion of the
OFF episodes usually includes painful dystonia? You have already determined the number of hours of "OFF" time (4.3). Of these hours, determine how many are associated with dystonia and calculate the percentage. If there is no OFF time, mark 0.

Instructions to patient [and caregiver]: In one of the questions I asked earlier, you said you generally have _____ hours of low or "OFF" time when your Parkinson's disease is under poor control. During these low or "OFF" periods, do you usually have painful cramps or spasms? Out of the total __hrs of this low time, if you add up all the time in a day when these painful cramps come, how many hours would this make?

0: Normal:	No dystonia OR NO OFF TIME.
1: Slight:	≤ 25% of time in OFF state.
2: Mild:	26-50% of time in OFF state.
3: Moderate:	51-75% of time in OFF state.
4: Severe:	> 75% of time in OFF state.

1. Total Hours Off: _____
2. Total Off Hours w/Dystonia: _____
3. % Off Dystonia = ((2/1)*100):

Summary statement to patient: READ TO PATIENT

This completes my rating of your Parkinson's disease. I know the questions and tasks have taken several minutes, but I wanted to be complete and cover all possibilities. In doing so, I may have asked about problems you do not even have, and I may have mentioned problems that you may never develop at all. Not all patients develop all these problems, but because they can occur, it is important to ask all the questions to every patient. Thank you for your time and attention in completing this scale with me.

Patient Name or Subject ID	Site ID	(mm-dd-yyyy) Assessment Date	Investigator's Initials
	___ ___ ___	___ - ___ - ___	___ ___ ___

86 MDS UPDRS Score Sheet

1.A	Source of information	☐ Patient ☐ Caregiver ☐ Patient + Caregiver	3.3b	Rigidity– RUE	
			3.3c	Rigidity– LUE	
Part I			3.3d	Rigidity– RLE	
1.1	Cognitive impairment		3.3e	Rigidity– LLE	
1.2	Hallucinations and psychosis		3.4a	Finger tapping– Right hand	
1.3	Depressed mood		3.4b	Finger tapping– Left hand	
1.4	Anxious mood		3.5a	Hand movements– Right hand	
1.5	Apathy		3.5b	Hand movements– Left hand	
1.6	Features of DDS		3.6a	Pronation- supination movements– Right hand	
1.6a	Who is filling out questionnaire	☐ Patient ☐ Caregiver ☐ Patient + Caregiver	3.6b	Pronation- supination movements– Left hand	
			3.7a	Toe tapping–Right foot	
1.7	Sleep problems		3.7b	Toe tapping– Left foot	
1.8	Daytime sleepiness		3.8a	Leg agility– Right leg	
1.9	Pain and other sensations		3.8b	Leg agility– Left leg	
1.10	Urinary problems		3.9	Arising from chair	
1.11	Constipation problems		3.10	Gait	
1.12	Light headedness on standing		3.11	Freezing of gait	
1.13	Fatigue		3.12	Postural stability	
Part II			3.13	Posture	

2.1	Speech		3.14	Global spontaneity of movement	
2.2	Saliva and drooling		3.15a	Postural tremor– Right hand	
2.3	Chewing and swallowing		3.15b	Postural tremor– Left hand	
2.4	Eating tasks		3.16a	Kinetic tremor– Right hand	
2.5	Dressing		3.16b	Kinetic tremor– Left hand	
2.6	Hygiene		3.17a	Rest tremor amplitude– RUE	
2.7	Handwriting		3.17b	Rest tremor amplitude– LUE	
2.8	Doing hobbies and other activities		3.17c	Rest tremor amplitude– RLE	
2.9	Turning in bed		3.17d	Rest tremor amplitude– LLE	
2.10	Tremor		3.17e	Rest tremor amplitude– Lip/jaw	
2.11	Getting out of bed		3.18	Constancy of rest	
2.12	Walking and balance			Were dyskinesias presen	☐ No ☐ Yes
2.13	Freezing			Did these movements interfere with ratings?	☐ No ☐ Yes
3a	Is the patient on medication?	☐ No ☐ Yes		Hoehn and Yahr Stage	
3b	Patient's clinical state	☐ Off ☐ On	**Part IV**		
3c	Is the patient on Levodopa?	☐ No ☐ Yes	4.1	Time spent with dyskinesias	
3.C1	If yes, minutes since last dose:		4.2	Functional impact of dyskinesias	
Part III			4.3	Time spent in the OFF state	
3.1	Speech		4.4	Functional impact of fluctuations	
3.2	Facial expression		4.5	Complexity of motor fluctuations	
3.3a	Rigidity– Neck		4.6	Painful OFF-state dystonia	

Appendix D

International Parkinson and
Movement Disorder Society

Certifies that

Karolina Beben

has passed the

MDS-UPDRS Training Program & Certificate Exercise

on 19 June 2015

Christopher G. Goetz, MD
Chair, MDS-UPDRS Training Program
& Certificate Exercise
Rush University Medical Center
Chicago, IL

Matthew B. Stern, MD
President
International Parkinson and Movement
Disorder Society

Rating Scale Permissions

Thank you. The information you submitted appears below.

MDS Rating Scale Permissions Request Form

Name: Joseph DeSouza
Company / Organization Name: Centre for Vision Research - York University
Address: 4700 Keele St
Dept of Psychology | Centre for Vision Research
City: Toronto
State: Ontario
Zip: M3J 1P3
Country: Canada
Telephone: 4167362100 x22946
Fax:
Email: desouza@yorku.ca

Intended use of materials: We are using the UPDRS for categorizing people with PD to correlate motor and non-motor tests with EEG, fMRI and MRI

Unified Parkinson's Disease Rating Scale (MDS-UPDRS)
No Financial Support (No charge)
Protocol number: e2013-313

Total: $0 USD

By submitting this request to MDS, you agree to the following:
I understand that all of the International Parkinson and Movement Disorder Society (MDS) Rating Scales may only be used for the purposes described above. I also understand that reproduction, translation, modification, sale, or distribution of any portion of the MDS Rating Scales is strictly prohibited and, specifically, that the MDS Rating Scales may not be incorporated into clinical trials, training or certification programs or materials, software programs, or otherwise except through use of

Appendix E

PANAS-X

This scale consists of a number of words and phrases that describe different feelings and emotions. Read each item and then mark the appropriate answer in the space next to that word. Indicate to what extent you have felt this way during the past week. Use the following scale to record your answers:

1 very slightly or not at all	2 a little	3 moderately	4 quite a bit	5 extremely
_____ cheerful	_____ sad	_____ active	_____ angry at self	
_____ disgusted	_____ calm	_____ guilty	_____ enthusiastic	
_____ attentive	_____ afraid	_____ joyful	_____ downhearted	
_____ bashful	_____ tired	_____ nervous	_____ sheepish	
_____ sluggish	_____ amazed	_____ lonely	_____ distressed	
_____ daring	_____ shaky	_____ sleepy	_____ blameworthy	
_____ surprised	_____ happy	_____ excited	_____ determined	
_____ strong	_____ timid	_____ hostile	_____ frightened	
_____ scornful	_____ alone	_____ proud	_____ astonished	
_____ relaxed	_____ alert	_____ jittery	_____ interested	
_____ irritable	_____ upset	_____ lively	_____ loathing	
_____ delighted	_____ angry	_____ ashamed	_____ confident	
_____ inspired	_____ bold	_____ at ease	_____ energetic	
_____ fearless	_____ blue	_____ scared	_____ concentrating	

PANAS-X

This scale consists of a number of words and phrases that describe different feelings and emotions. Read each item and then mark the appropriate answer in the space next to that word. Indicate to what extent you have felt this way after the class. Use the following scale to record your answers:

1 very slightly or not at all	2 a little	3 moderately	4 quite a bit	5 extremely
_____ cheerful	_____ sad	_____ active	_____ angry at self	
_____ disgusted	_____ calm	_____ guilty	_____ enthusiastic	
_____ attentive	_____ afraid	_____ joyful	_____ downhearted	
_____ bashful	_____ tired	_____ nervous	_____ sheepish	
_____ sluggish	_____ amazed	_____ lonely	_____ distressed	
_____ daring	_____ shaky	_____ sleepy	_____ blameworthy	
_____ surprised	_____ happy	_____ excited	_____ determined	
_____ strong	_____ timid	_____ hostile	_____ frightened	
_____ scornful	_____ alone	_____ proud	_____ astonished	
_____ relaxed	_____ alert	_____ jittery	_____ interested	
_____ irritable	_____ upset	_____ lively	_____ loathing	
_____ delighted	_____ angry	_____ ashamed	_____ confident	
_____ inspired	_____ bold	_____ at ease	_____ energetic	
_____ fearless	_____ blue	_____ scared	_____ concentrating	
_____ disgusted with self	_____ shy	_____ drowsy	_____ dissatisfied with self	

Appendix F

PD NMS QUESTIONNAIRE

Name: ..... Date: ..... Age: .....

Centre ID: Male ☐ Female ☐

NON-MOVEMENT PROBLEMS IN PARKINSON'S

The movement symptoms of Parkinson's are well known. However, other problems can sometimes occur as part of the condition or its treatment. It is important that the doctor knows about these, particularly if they are troublesome for you.

A range of problems is listed below. Please tick the box 'Yes' if you have experienced it **during the past month.** The doctor or nurse may ask you some questions to help decide. If you have **not** experienced the problem in the past month tick the 'No' box. You should answer 'No' even if you have had the problem in the past but not in the past month.

Have you experienced any of the following in the last month?

	Yes	No
1. Dribbling of saliva during the daytime	☐	☐
2. Loss or change in your ability to taste or smell	☐	☐
3. Difficulty swallowing food or drink or problems with choking	☐	☐
4. Vomiting or feelings of sickness (nausea)	☐	☐
5. Constipation (less than 3 bowel movements a week) or having to strain to pass a stool (faeces)	☐	☐
6. Bowel (fecal) incontinence	☐	☐
7. Feeling that your bowel emptying is incomplete after having been to the toilet	☐	☐
8. A sense of urgency to pass urine makes you rush to the toilet	☐	☐
9. Getting up regularly at night to pass urine	☐	☐
10. Unexplained pains (not due to known conditions such as arthritis)	☐	☐
11. Unexplained change in weight (not due to change in diet)	☐	☐
12. Problems remembering things that have happened recently or forgetting to do things	☐	☐
13. Loss of interest in what is happening around you or doing things	☐	☐
14. Seeing or hearing things that you know or are told are not there	☐	☐
15. Difficulty concentrating or staying focussed	☐	☐
16. Feeling sad, 'low' or 'blue'	☐	☐
17. Feeling anxious, frightened or panicky	☐	☐
18. Feeling less interested in sex or more interested in sex	☐	☐
19. Finding it difficult to have sex when you try	☐	☐
20. Feeling light headed, dizzy or weak standing from sitting or lying	☐	☐
21. Falling	☐	☐
22. Finding it difficult to stay awake during activities such as working, driving or eating	☐	☐
23. Difficulty getting to sleep at night or staying asleep at night	☐	☐
24. Intense, vivid dreams or frightening dreams	☐	☐
25. Talking or moving about in your sleep as if you are 'acting' out a dream	☐	☐
26. Unpleasant sensations in your legs at night or while resting, and a feeling that you need to move	☐	☐
27. Swelling of your legs	☐	☐
28. Excessive sweating	☐	☐
29. Double vision	☐	☐
30. Believing things are happening to you that other people say are not true	☐	☐

All the information you supply through this form will be treated with confidence and will only be used for the purpose for which it has been collected. Information supplied will be used for monitoring purposes. Your personal data will be processed and held in accordance with the Data Protection Act 1998.

Developed and validated by the International PD Non Motor Group
For information contact: susanne.tluk@uhl.nhs.uk or alison.forbes@uhl.nhs.uk

Appendix G

Mini-Mental State Examination (MMSE)

Patient's Name: _____ Date: _____

Instructions: Score one point for each correct response within each question or activity.

Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day? Month?"
5		"Where are we now? State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then the instructor asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible.
5		"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, ...) Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) 
30		TOTAL

Appendix H

Initials: _____ Date: _____

Medication Questionnaire

Please circle or answer the following questions as accurately as possible.

1. Are you taking any medications? Yes / No

   If yes, which medication(s)? Please list the medication name(s) and dosage(s).

_____

_____

_____

2. Do you take any medication(s) to be "on" for class? Yes / No

   If yes,

   a) What time do you take your medication for the 10 am class? _____
   b) What time does it become effective? _____
   c) What time does it wear off? _____

   If you participated in any of the pre- or post- class testing sessions,

   d) Did you take your medication(s) to be "on" for the test session? Yes / No
   e) What time did you take your medication for the test session? _____
   f) What time does it become effective? _____
   g) What time does it wear off? _____
   h) If you were tested before and after class, do you think your medication was equally effective before and after class? Yes / No
      If no, please explain_____
      _____

3. Has your medication or dosage recently changed? Yes / No

4. If yes above, when did the change occur? _____

5. Is there any other information you would like to share with us about medication and performance on the motor tasks?

_____

_____

_____

Date: _____

Questionnaire

Please circle or answer the following questions as accurately as possible.

1. What are the initials of your first and last name? _____

2. Age: _____

3. At what age did you learn you had Parkinson's disease? _____

4. Sex: female / male

5. With which hand do you do the following actions?

- Throw a ball R / L
- Brush your teeth R / L
- Eat soup with a spoon R / L
- Comb your hair R / L
- Cut bread with a knife R / L
- Swing a racquet or bat R / L
- Point accurately R / L
- Write your name R / L
- Hammer a nail R / L
- Is there anything you do consistently with your left hand? _____

6. How many hours of sleep do you get per night? _____

7. Extend both arms in front of your body and place the hands together so as to make a small triangle between your thumbs and the first knuckle. With both of your eyes open, look through the triangle and focus on a specific small object. Close your left eye. If the object remains in view, you are right eye dominant. If your hands appear to move off the object and move to the left, then you are left eye dominant

Eye dominance: R-eye / L-eye

Date: _____

8. Can you wink with your left eye? _____

Can you wink with your right eye? _____

9. Corrected vision? Yes / No

10. Are you taking any medications? Yes / No

If yes, which medication(s)? _____

What is/are the dosage (s)? _____

At which time(s) do you take your medication _____

11. Have you ever taken a dance class? Yes / No

12. If yes, what kind of dance class(es)? _____

At which age did you start? _____

At which age did you stop? _____

13. Have you ever participated in a dance for Parkinson's program? Yes / No

14. If yes, which program? _____

Where was it held? _____

Are you still participating in this program? Yes / No

If yes, how many time per week? _____

15. Do you participate in any physical exercise programs besides dance? Yes / No

16. If yes, what kind of physical exercise (s) do you do? _____

How many hours per week? _____

17. How many Dance for Parkinson's classes have you attended at Canada's National Ballet School? _____

Date: _____

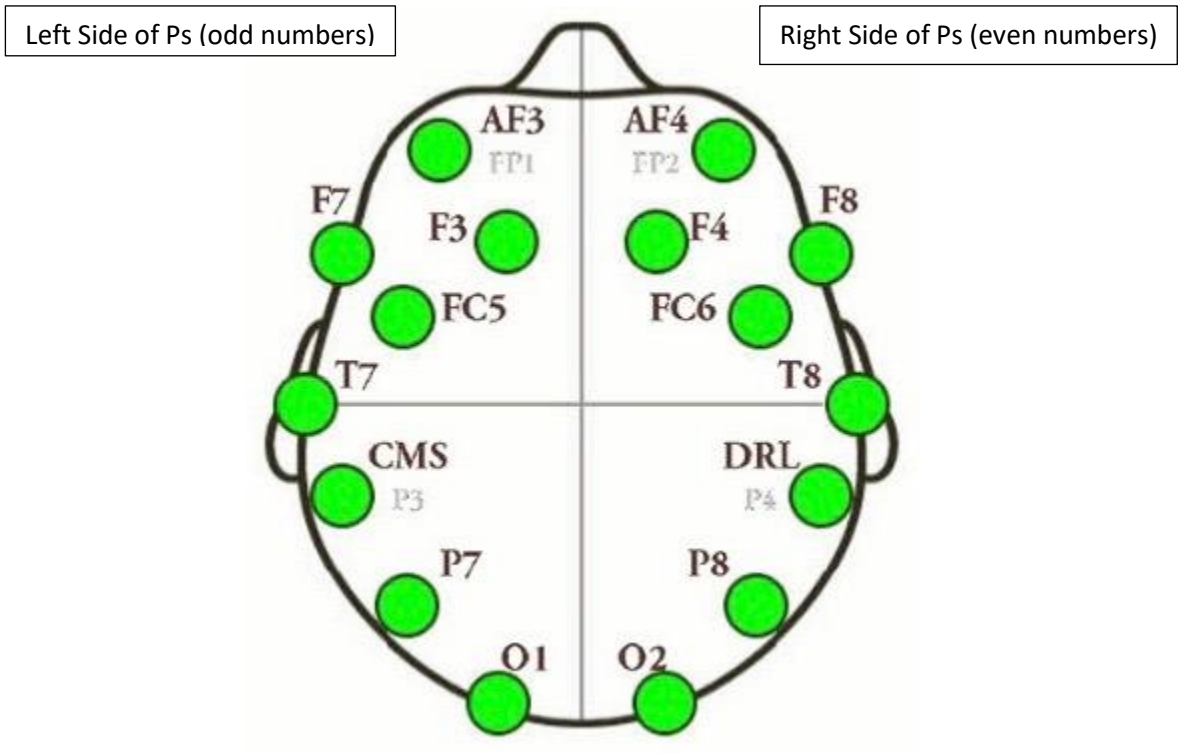
18. Of the classes you attended, were you able to participate fully in them? Yes / No

If no, how often did you have to sit out? _____

19. How many times per week do you practice visualizing the steps of the dance you are learning? _____

20. For how many minutes do you visualize? _____

Appendix I



Numbering and placement of EPOC 14-channel electrodes. Green signal in all indicates a good connectivity in each individual electrode and thus testing should proceed.

Appendix J

Nature Partnered Journal – Parkinson's Disease Rebuttal (Open Science Policy)

Prior to submission to *Brain Sciences* journal, our initial submission was to the *Nature Partnered Journal – Parkinson's Disease (npj-PD).* Our manuscript was accepted for review and was returned to us with a rejection and comments from Reviewers. The comments provided by the Reviewers incorporated factual mistakes and misinterpretations of the methodology, and as such set a ground for us to form and complete the Rebuttal process. In this Rebuttal process, large literature review was conducted which focused on published research which used the exact same measures as we did for this study, being UPDRS Parts I-IV, and that used dance as a form of intervention for PwPD. Presented below is the Rebuttal, including the Letter to Editors and the Appeal Letter.

4.9.1 Letter to the Editors

Dear Editor in Chief Prof. Ray Chaudhuri,

We are writing this letter in response to the rejection for our manuscript (No.NPJPARKD-00367) entitled "Parkinson's Disease Progression Halted Using Multinetwork Learning to Rhythmic Music over 3-years Compared to Controls: Assessed by MDS-Unified Parkinson's Disease Rating Scale". We have reason to believe that the comments from our reviewers contained factual mistakes and misunderstandings within the results and interpretation of our research findings. Thus, we are writing to ask for your reconsideration of the rejection of our manuscript.

In the following pages, we have laid out our appeal on a point-by-point rebuttal stemming from our reviewer comments while using great detail to show these factual interpretive mistakes. We further support our responses to the reviewer comments using scientific research that parallels our research (idea, design and methodology) and that have been successfully published in a wide variety of peer reviewed scientific journals.

The research presented in this manuscript is of novelty, as to our knowledge this is the first attempt of an ongoing longitudinal over 3-year pilot study design on the effects of dance as a complementary treatment for PD. Further our results showed positive life changes within our pilot dance cohort: where PD motor and non-motor symptoms remained stable while continuously participating in dance. With that, we strongly believe that the findings of our study reach the aims and scope of *npj Parkinson's disease* which is to "*publish original science……related to Parkinson's disease, including……therapeutic development and treatments*" Therefore we consider npj- Parkinson's disease an ideal platform from which to share our novel, validated research.

Given that PD exercise interventions are of high interest within PD research, and the fact that good longitudinal data is missing within this field, our study is the first research attempt to show the effects of an ongoing over 3-year longitudinal dance intervention for people with PD. Below we have addressed all reviewer concerns, and are more than happy to rerun, change, add or expand on any component within the manuscript to resolve and clarify any misinterpretations further.

We encourage the editorial team to review our appeal and reconsider your initial decision. We look forward to hearing back from the editorial team on their decision of the appeal in light of our responses to the reviewer comments. We sincerely appreciate all the time and effort going into this.

Sincerely,

Karolina A. Bearss and Joseph F.X. DeSouza

Appeal Letter

We would like to acknowledge and thank our reviewers for taking the time to precisely read and construct their insightful feedback and comments on our previous manuscript titled "**Parkinson's Disease progression halted using multinetwork learning to rhythmic music over 3-years compared to controls: assessed by MDS-Unified Parkinson's Disease Rating Scale**". The reviewers comments highlighted important areas of concern providing us with the opportunity to address and clarify them within the study, these incorporated changes both strengthened and improved the current version of our manuscript and we thank them for this.

Reviewer Comment	**Counterargument**
a) Exercise based interventions are of major interest within the PD field. The study however is too small and vulnerable to bias. This is shame as good longitudinal data is required within this field. In my opinion this renders the findings uninterpretable and I therefore cannot recommend publication	a) Most published dance studies in PD include relatively short-term research interventions of 10–13 weeks[5,9,19,31,34,50,63,85-90,102,109,117-130]. A few studies in PD have investigated longer intervention periods ranging from six months[30,83], twelve months[92,93,96,94], or as long as two years[96]. Duncan's (2014)[96] study included a total of *five(5)* PD participants that danced twice a week for the 2-year study duration. To date, this is the only longitudinal study that has been published withinthis field. Our current manuscript adds to this field of longitudinal literature that has last been updated since Duncan in 2014, not only does our manuscript expand the time duration of the research to include data for over a 3-year period but it also increased the sample size to be that of *sixteen(16)* PD participants. This has been added to our revised manuscript in lines 76-89.

b) Although the analysis strategy is sensible, there is no reference to whether this was a predefined analysis plan. c) There is no discussion of the distributions of the data and whether a parametric method is appropriate. There is no discussion of correction for multiple comparisons, no discussion of an a priori power calculation and no reference to how many analyses were undertaken. There is also no reference to whether coovariates were added to the model, although I realise given the samples were matched this may not have been necessary.	b) To clarify a predefined analysis plan, we have easily added this sentence to help clarify this reviewer comment within the manuscript. Please refer to sentences 169-171 for this addition. c) Multilevel models (also known as hierarchical linear models, linear mixed-effect models) are widely used for the analysis of correlated non-Gaussian data (non-normally distributed data) such as those found in longitudinal studies[42]. The total UPDRS score and the UPDRS subscale scores are not interval scales, which means that they are not quantified, equal distances between values on these scales. For example, a score of 4 is greater than 2 but does not necessarily indicate twice the degree of severity. Each part of the rating is a *rank order* measure rather than a precise interval change. This must be considered when using these data for statistical analyses –ordinal measures require a nonparametric test such as the linear mixed-effect/hierarchical linear model (HLM) that we used in our analyses. HLM is essentially an expanded form of regression; it can be quantitative and normally distributed, or it can be *qualitative or non- normally distributed*. Ordinal data like the UPDRS is qualitative data that is not normally distributed in our sample thus we used HLM as a non-parametric test[43]. The description of the

	distribution of our data and the reasoning for using a linear mixed-effects model for our analyses was added into the manuscript on lines 172-180
d) Whilst the matching of control and case groups by baseline characteristics is desirable, it is difficult in a sample of this size to directly compare UPDRS III results which are not assessed by the same raters.	d) We conducted a literature search of 41 published articles within the dance and PD field. Of these, 21 published articles used UPDRS Part III as either part of the study or the primary research assessment criteria for the entire study. Of these 21 studies, 5 studies[63,128,96,94] (23.8%) included a true no intervention control arm as a comparison with an average experimental group size of 15.2 and control group size of 15.4. These 5 studies measured UPDRS III on an average of ~11 month duration. Our study was above average in both of these categories; we compared PD Dancers (n=16) and non-dancers as controls (n=16) over a course of ~40 months, a duration that is four (4) times longer than the existing literature to date, while still holding an above average sample size! Even if the same size and variability of raters across two groups not consisting of the same raters acts as a downfall to our study, our PD Dancers show a decrease in their PD symptom progression alone without a comparison to another group. This is explained in lines

	190-192 and shown in Figure 1A. The addition of a comparable control group from the PPMI database helps to further strengthen our initial results and premise that PD subjects who dance progress much slower than those who do not participate in dance. Please refer to Table 1 below for a comparison of studies using UPDRS III as a research measurement.
e) The variability of even expert raters can be substantial (I note that the level of expertise is not defined).	The UPDRS demonstrates good reliability and validity as well as sensitivity to change[148]. Our 7-8 **blinded** raters were previously trained on scoring the UPDRS using the online Training Program: Certificate Exam developed by The International Parkinson and Movement Disorder Society (MDS). This program consists of a 4-8 hour training which trains on the use of this scale and includes 4 patients with Parkinson's disease at the end of the Training Program that you must pass to receive the certificate from MDS. All of our raters were successful in completing these exercises and received a certificate from MDS. Research has shown that reviewing exercises can improve the reliability of the measures in the UPDRS[135]. As per the MDS-UPDRS website, certified raters are eligible to rate UPDRS and all of our raters are certified and completed the MDS training.
f) This is especially pertinent given the raters of the intervention arm were not blinded. No attempt is made to address this point in the text, even though it is a major limitation.	f)It is our initial fault and intuitive assumption that we did not include this detail in our original manuscript and we thank the reviewer(s) for bringing this to our attention. In fact our UPDRS

	trained and certified raters were indeed blinded for scoring all portions of the UPDRS, it is only the PI and graduate student on the project (the authors) that were aware of the participants and their associated scores. In order to sufficiently blind the raters, we labeled all data and videos by non identifying terms (ex: 1000). From our literature review on the research within this field, it is to our knowledge that these published studies, which use the UPDRS assessment, did not use blind raters within their research protocol but instead used either clinicians or the experimenter themselves. To avoid this "major limitation", we have included a description of our trained raters on lines 154-160 of the revised manuscript.
g) There is major potential for ascertainment bias in this study: i.e the patients who carried on attending dance classes and were filmed are likely to be the ones who declined the least slowly.	g) Our subjects H&Y scale ratings ranged from 0-3 with a mean of 1.25, most studies that we have additionally reviewed for this appeal had H&Y that fall within this range (asymptomatic to moderate PD severity). Within our 16 PD-Dancers, we had individuals who were moderately severe, indicating that they are nearing most PD motor impairment and progressing in their disease. Despite their PD symptom being of moderate severity, these individuals still continued in the dance classes and our research for over 3 years. Our results indicate that our intervention works for PD patients within a certain H&Y score range.

h) progression rates of PD vary tremendously, even with subjects matched by age and disease severity.	h) Progression rates on PD do vary across PD patients, and we have previously acknowledged that in our manuscript in the Introduction on lines 77-88. The UPDRS, since its development in the 1980's has been the most widely used rating scale for tracking PD progression[57]. Aside from our results comparing our PD- Dancers to PPMI matched PD-Controls (or non-dancers), our manuscript initially showed a decrease in PD motor- and non-motor symptom progression *within* our longitudinal dance group alone (without a matched comparison group). This initial result provided us with the ability to then add a matched control non-dance group which we derived from PPMI as a comparison group in order to help strengthen this result further by showing that our PD-Dancers do not decline in motor and non-motor symptoms the same as those who do not dance and to that what is seen in the existing literature. The fact that our within PD-Dancer group showed no decrease in PD motor and non-motor symptomology over time allowed for these sixteen PD patients to behave as a control group for themselves.-thus reducing any errors associated with individual differences (such as variability of PD progression rates).
i) Conversely those who dropped out (only 16 subjects out of 110 underwent more than one repeat assessment) are likely to be those who are progressing faster. This is the biggest flaw in this study and unfortunately is an inherent limitation of the design.	i) We must report this comment that addresses our drop out rates as "the biggest flaw in the study" as a reviewer misunderstanding or a ***factual mistake.*** Our continuing longitudinal study incorporated a total of 110 individuals that was

	comprised of both people with PD (n=67) and healthy controls (n=43). Of those 67 PD dancers, 16 subjects *initially* agreed to volunteer for an ongoing, longitudinal study when we first introduced it. Thus, our drop out rate was actually 0% over the course of over 3-year research study. Due to this confusion, we have revised lines 120-125 in the hopes to avoid this misconception any further. Further, our results indicate that mild to moderate PD patients tend to be able to attend more dance training sessions and get the most benefit.
j) The scope of the interpretation of the discussion is completely unwarranted by the data displayed. I'm afraid I do not believe it is possible to draw any sensible conclusions as to the benefits of long term dance classes. At best this is interesting **pilot data** that might be used to design and power a more rigorously designed and executed study. Ideally this would be involving a properly randomised intervention and control arm.	j) We have also changed our manuscript title, which now indicates this study being a pilot study. We have further expanded on this within our manuscript by indicating that this is a small-scale preliminary study which is geared to investigate whether crucial components of a main study – a randomized controlled trial (RCT) – will be feasible to conduct a future full-scale project using the outcome measures that have been used in this manuscript (such as the UPDRS scales). In order to perform a good long term RCT project, it is crucial that we lay out our methodology and the key steps needed to conduct an RCT of this type to avoid wasting time and resources. This has been added to lines 92-96 within our manuscript.

k) This study suffers from the issue of selection bias, wherein motivated patients who enroll for these programs are unlikely to be representative of the larger population.	k) The data presented in our current, revised manuscript is a small scale preliminary study conducted in order to evaluate feasibility, duration and improve upon our study design prior to conducting a full-scale research study (aiming for a future RCT design), this manuscript is intended to be presented as a pilot project/study. As with all pilot studies, those that are not properly randomized and controlled for, there is the issue of selection bias. We have added lines 292-297 and a limitation section to our revised manuscript in order to clarify and acknowledge that we are aware of this limitation in this current preliminary study.
l) In addition, the study is comparing only 16 patients with a PPMI control group, which is clearly not an ideal active control condition.	l) As discussed above in comment *(d)*, we have conducted an extensive literature review on published research data that determine the effects of dance on PD symptomology using the same measures that we used in our current manuscript (UPDRS with all subsections I-IV). Comparing these 21 published studies (Table 1), we show that published research lasted on average 4.6 months, used a total N = 23 participants, where approximately 14 participants were in a dance group. Our manuscript lasted a total of approximately 40 months, used a total N =32 where 16 participants were in our dance group. Our manuscript clearly surpassed every dimension of the literature to date that looks at longitudinal dance effects on PD.

m) Despite covering the wide range of progression rates reported in the literature, the authors selectively emphasise those with higher progression. This needs to be strictly tempered.	m) Research has shown that improper randomization in PD clinical trials results in improper end-result interpretations. Importantly, PD heterogeneity due to underlying genetic factors creates variability between individual patients and between overall trial arms in areas such as disease progression. However, most clinical research trials lack genetic balancing[136]. There are a few clinical trials that underwent pre-trial genetic adjustment[137,138] for PD patients who carry the well-known PD risk variants such as GBA or LRRK2 mutations, however even these pre-genetically balanced studies showed large variations between patients. In fact, none of the PD and dance studies listed in Table 1 and our reference section took into account genetic balancing. Other research also looked at the lifestyle factors that influence PD motor progression, (such as caffeine or alcohol consumption, physical activity, or cigarette smoking). These studies show that all but physical activity have been inversely associated with PD onset[139-141] while others show no influence on PD motor progression[142-144] or variability in their results[145]. Many of these studies lack data on cognitive (or non-motor) PD progression. Further, a 9-year follow-up study showed that male gender, older age at diagnosis, akinetic-rigid subtype, cognitive impairment and lower baseline motor score were associated with greater progression

	of motor scores on the UPDRS[146]. In another study comparing "rapidly progressive" to "slowly progressive" patients showed that older patients at PD onset progressed more rapidly[147]. In our study we have controlled for these same variables of gender, age at diagnosis and baseline motor score- we added the variables of age; motor severity (H&Y) and disease duration to help stabilize the groups further. Our study was a first, preliminary study to understand how dance, a form of physical activity, contributes to the progression of PD for both the motor and non-motor symptoms over a long period of time using the measures of UPDRS as our assessment tool. Research has already shown the short-term positive motor effects of dance using the UPDRS. We are testing to see whether the UPDRS (and all of its subsections) can hold true over a longer period of time.
n) This paper's title is clearly misleading. All therapies (pharmacological, exercise, etc...) can improve UPDRS scores and do NOT mean that disease progression has been halted.	n) To avoid any future misleading words, we have changed our manuscript title to: **"*Improved* Motor Impairment in Parkinson's Disease Patients with Multisensory Training over 3-years: A P*reliminary* *L*ongitudinal Investigation"**

Conclusion of Appeal Letter

The Appeal Request was submitted on February, 9th 2021 and was accepted and passed Editorial Review, as such the updated manuscript and Appeal letter was sent for a new peer review and process on March 19th, 2021. The decision on our Appeal was sent on April 5th, 2021 indicating that it was not offered publication in *npj-Parkinson's Disease* based on the "*the basic crux of the reviewers' criticism centered on sample size. I take the author's point that this study is larger and longer than those published previously, however, the sample size of 16 still remains too small to draw any conclusions and the reader is left thinking that this is interesting but too preliminary"*. At that point we have moved onto submission to several other high impact journals such as *The Lancet, EClinical Medicine* (which is a sister journal of *The Lancet* and was suggested to us for article transfer by *The Lancet* Editors), *Science, Movement Disorders* and finally to *Brain Sciences* where it was accepted with minor revisions and successfully published.

Article Recognition

After a long battle and many years of revisions, it appeared we made the right decision to submit to *Brain Sciences* journal. After the article's online publication, the results and impact of our findings made an impression on the scientific community, several news report attentions, invitations as oral presenters to scientific conferences and social media releases:

1. 2021.11.10 – Science Line
2. 2022.01.24 – 2nd Global Summit on Neurology and Neuroscience. Invited Oral Speaker,
3. 2021.10.25 – CBS-U.S. News- Interview
4. 2021.07.21 - Dublin Ireland Radio Station Podcast- Could Dancing help Parkinson's? Interview begins at 29.00minutes. https://play.acast.com/s/room104/wednesdayjuly21st-hour3
5. 2021.07.16 – The Guardian. https://guardian.ng/features/health/more-studies-endorse-healing-with-arts-music-dance/
6. 2021.07.13 – Medscape. https://www.medscape.com/viewarticle/954679
7. 2021.07.11 – YFile: York Universities News. https://yfile.news.yorku.ca/2021/07/11/novel-research-shows-dancing-with-music-can-halt-debilitating-symptoms-of-parkinsons-disease/
8. 2021.07.09 – Clinical News. https://clinicalnews.org/2021/07/07/dancing-with-music-can-halt-

most-debilitating-symptoms-of-parkinsons-disease/amp/?__twitter_impression=true
9. 2021.07.08 – York University social media Twitter. https://twitter.com/YorkUnews/status/1413152620550623236?s=20
10. 2021.07.08 – Broadway World. https://www.broadwayworld.com/bwwdance/article/New-Study-Shows-Dance-Training-Can-Improve-Motor-Skills-in-Patients-With-Parkinsons-Disease-20210708
11. 2021.07.07– York University Media Release. https://news.yorku.ca/2021/07/07/dancing-with-music-can-halt-most-debilitating-symptoms-of-parkinsons-disease/
12. 2021.07.07 – CTV News. https://www.ctvnews.ca/health/dancing-can-improve-symptoms-of-parkinson-s-disease-in-some-patients-study-shows-1.5500250
13. 2021.07.07 – Medical Xpress. https://medicalxpress.com/news/2021-07-music-halt-debilitating-symptoms-parkinson.html
14. 2021.07.07 – Neuroscience News. https://neurosciencenews.com/parkinsons-dancing-18869/
15. 2021.07.07 – YorkU Twitter Social Media Video. https://twitter.com/YorkUnews/status/1413152620550623236?s=20