

**Does Use of a Dual-task cognitive game based treadmill platform improve  
balance and gait in Parkinson Disease?**

**A feasibility study**

by

**Bhuvan Mahana**

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## **Abstract**

**Introduction:** There is an early deterioration of balance and gait functions in Parkinson Disease (PD). In addition to this, participants with PD show deterioration in one or more cognitive areas. The combination of these results in more than 60% of PD participants reporting recurrent falls. To prevent such falls, there is a need to develop and validate affordable rehabilitation program that target both walking and executive cognitive performance in participants with PD. To answer this need, we have developed and validated, engaging, Game-based treadmill platform (GTP), which provides an integrated approach to assess and treat a decline in balance, mobility, visuomotor control and visuospatial executive cognitive function.

**Purpose:** The primary purpose of this study was to examine the feasibility of the GTP program concerning the process, resources and management for conducting a future randomized controlled trial with GTP. The secondary purpose of this study was to evaluate the experience of the participant with the intervention program and provide an estimate of treatment effect size on various standing balance, gait and cognitive outcome measures.

**Methods:** We aimed to recruit 20 participants with PD for the 10 weeks, twice a week GTP program. Standing balance, spatiotemporal gait variables and visuospatial search and visuomotor executive cognitive performance was evaluated at baseline and after 10 week of GTP intervention. Semi-structured interviews were conducted for all eligible participants to explore the user experience of GTP program.

**Results:** Fifteen participants diagnosed with PD, stage 1-3 on Hoehn and Yahr scale were screened for the study. All participants completed 10 weeks, twice a week dual-task intervention program with the GTP program. We observed excellent feasibility regarding recruitment,

retention to program, study procedures and study management for conducting a future RCT with GTP. Medium to large effect sizes for all significant improvements in standing balance, gait, and cognitive performance were observed.

**Conclusion:** We obtained favourable results for the feasibility of GTP to conduct RCT with an appropriate control group. The embedded semi-structured interviews also showed that GTP was highly appreciated among patients with PD. The substantial improvement in standing balance and gait of patients with PD shows the effectiveness of GTP for targeted rehabilitation.

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## **Dedication**

I would like to dedicate this thesis my parents and my brother – Mr. Jitendra Mahana, Mrs. Jyoti Mahana and Mr. Rachit Mahana

## **List of Abbreviations**

6MWT	6-minute walk test
ABC	Activities-Specific Balance confidence Scale
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AP	Anterior-Posterior
BBS	Berg-Balance Scale
BG	Basal Ganglia
COP	Centre of Pressure
COV	Coefficient of Variation
CPU	Central Processing Unit
CST	Card Sorting Test
CTSIB	Clinical test of sensory integration of Balance
DFT	Design fluency Test
D-KEFS	Delis-Kaplan Executive Function System
DST	Digit-Span test
DT	Dual Task
EC	Eyes Closed

ECF	Executive Cognitive functions
EO	Eyes Open
fNIRS	function near-infrared spectroscopy
FOG	Freezing of Gait
FOGQ	Freezing of Gait Questionnaire
FSA	Force Sensor Array
GTP	Game based treadmill platform
HC	Healthy Controls
HR	Heart Rate
LCD	Liquid Crystal Display
LSVT	Lee-silverman Voice treatment
MCI	Mild Cognitive Impairment
ML	Medio-Lateral
MoCA	Montreal Cognitive assessment
MRI	Magnetic Resonance Imaging
PD	Parkinson Disease
PFC	Pre-frontal Cortex
RCT	Randomised controlled Trial

RMS	Root Mean Square
SOT	Sensory Organisation Test
SrT	Stroop Test
TC	Tai-Chi
TMT-A	Trail Making Test-A
TMT-B	Trail Making Test-B
ToL	Tower of London
TT	Treadmill Training
TUG	Timed-up and Go Test
TV	Television
UPDRS	Unified Parkinson Disease Rating Scale
USB	Universal Serial Bus
VCG	Visuo-cognitive Game
VF	Verbal fluency
VMTH	Visuo-Motor Tracking Horizontal
VMTV	Visuo-Motor Tracking Vertical
VR	Virtual Reality
WO	Walk only



## **List of Tables**

Table 1: Participant's Demographics.....	48
Table 2: Anonymized Participant's demographic data.....	52
Table 3: Mean, SD, t-value, effect size and p-value of RMS measure of COP displacement before and after intervention.....	58
Table 4: Mean, SD, t-value, effect size and p-value of average gait measures before and after intervention.....	59
Table 5: Mean, SD, t-value, effect size and p-value of gait variability measures before and after intervention.....	61
Table 6: Mean, SD, t-value, effect size and p-value of gait entropy measures before and after intervention.....	62
Table 7: Mean, SD, t-value, effect size and p-value of VCG1 and VCG2 task outcome measures before and after intervention.....	64
Table 8: Mean, SD, t-value, effect size and p-value of VMTH and VMTV task outcome measures before and after intervention.....	65
Table 9: Sample size for cognitive outcome measures based on effect size observed.....	66
Table 10: Sample size for motor outcome measures based on effect size observed.....	67

## **List of Figures**

Figure 1: Wireless scoop pointer air mouse from Hilcrest Lab (Rockville,MD) mounted on Helmer worn by participants.....	27
Figure 2: Computer games for treatment.....	30
Figure 3: Sitting, Standing and treadmill walking positions for assessment at baseline and post intervention.....	36
Figure 4: Participants playing computer games in standing and treadmill walking.....	37
Figure 5: Standing balance data collection recording and raw COP signals.....	40
Figure 6: Gait data collection and raw COP signals during walking.....	41
Figure 7: VCG1 and VCG -2 task display and raw game data.....	42
Figure 8: VMT horizontal and vertical task and raw game data.....	43
Figure 9: Recruitment flow diagram.....	48
Figure 10: Standing balance single task performance.....	66
Figure 11: Standing balance dual task performance.....	67
Figure 12: Walking COP displacement scatter plots for different walking conditions.....	68
Figure 13: Visuo cognitive task performance.....	69
Figure 14: Visuo Motor tracking task performance.....	70

## **Table of Contents**

<b>Abstract.....</b>	<b>i</b>
<b>Acknowledgment.....</b>	<b>iii</b>
<b>Dedication.....</b>	<b>iv</b>
<b>List of Abbreviations .....</b>	<b>v</b>
<b>List of Tables .....</b>	<b>viii</b>
<b>List of Figures.....</b>	<b>ix</b>
<b>Chapter 1: Introduction .....</b>	<b>1</b>
<b>Chapter 2: Literature Review .....</b>	<b>3</b>
<b>2.1 Standing balance, Gait, and Gait Stability .....</b>	<b>3</b>
<b>2.2 Executive Cognitive Functions.....</b>	<b>6</b>
<b>2.3 Dual-task interference in Parkinson Disease.....</b>	<b>9</b>
<b>2.5 Summary.....</b>	<b>20</b>
<b>Chapter 3: Study Purpose and Objectives.....</b>	<b>22</b>
<b>3.1 Purpose: .....</b>	<b>22</b>
<b>3.2 Objectives: .....</b>	<b>22</b>
<b>Chapter 4: Methods .....</b>	<b>23</b>
<b>4.1 Study Population:.....</b>	<b>23</b>
<b>4.2 Sample Size:.....</b>	<b>23</b>
<b>4.3 Ethical Approval:.....</b>	<b>23</b>
<b>4.4 Participants: .....</b>	<b>23</b>
<b>4.4.1 Inclusion Criteria:.....</b>	<b>23</b>
<b>4.4.2 Exclusion Criteria:.....</b>	<b>23</b>
<b>4.4.3 Recruitment:.....</b>	<b>24</b>
<b>4.5 Research Site: .....</b>	<b>24</b>
<b>4.6 Research Design: .....</b>	<b>24</b>

4.7 Primary Outcome measure .....	24
4.8 Secondary Outcome measures .....	25
4.9 Study Equipment's.....	25
4.9.1: Standing Balance Assessment.....	25
4.9.2: Gait Assessment .....	26
4.9.3: Computer Gaming Substation.....	26
4.9.4: Computer-based cognitive task .....	27
4.9.5: Computer games for intervention .....	29
4.9.6: Compliant surface for standing balance challenge during intervention.....	30
4.9.7: Treadmill for intervention .....	30
4.9.8: 6 minutes walk test.....	31
4.9.9: Overground Walking Speed Assessment.....	31
4.9.10: Screening Tool and Questionnaires .....	32
4.10 Study Procedure.....	32
4.11 Data Quantification .....	39
Chapter 5: Analysis.....	45
5.1 Feasibility Analysis .....	45
5.2 Qualitative Interview Analysis.....	45
5.3 Quantitative Analysis.....	46
Chapter 6: Results.....	47
6.1 Feasibility analysis .....	47
6.1.1 Study Procedures .....	47
6.1.2 Study Resources .....	49
6.1.3 Study Management .....	49
6.2: Experience of participants with GTP .....	50
6.3: Estimate treatment effect size and sample size calculation.....	58
6.4 Result figures.....	68
Chapter 7: Discussion .....	73
7.1 Feasibility of GTP .....	73
7.2 Experience of Participants with GTP.....	75
Chapter 8: Conclusion, Study strengths, Study limitations and future studies .....	83

<b>8.1 Conclusion:</b> .....	83
<b>8.2 Study strengths:</b> .....	84
<b>8.3 Study Limitations:</b> .....	85
<b>References</b> .....	88

## **Chapter 1: Introduction**

Parkinson Disease (PD) is the second most prevalent adult neurodegenerative disorder in North America after Alzheimer's disease (1). It affects more than 100,000 Canadians currently (2). The number is expected to cross 163,000 by the year 2031 (3).

In PD, there is a marked loss of dopaminergic neurons and the presence of Lewy bodies (alpha-synuclein) in substantia-nigra (4,5). This results in the depletion of dopamine in Basal Ganglia(BG) and associated dopaminergic pathways(6). The Basal Ganglia (BG) is an extensive group of subcortical nuclei. It consists of caudate and putamen; the striatum, as the input zone of BG, and the globus pallidus and substantia nigra pars reticularis as the output zone of BG (7). The BG has extensive connections with all brain areas. There are three main loops of BG connections defined in the literature, namely, the executive (cognitive) loop, the limbic loop and a motor loop (8). The most important role of BG is motor planning for the desired task. Loss of dopamine neurons and degeneration of dopaminergic pathways does not remain limited to BG, but the degeneration is also extended to both motor and cognitive processing centres of the cerebral cortex. This results in the development of not only motor but also many non-motor symptoms such as executive cognitive dysfunctions in PD (8).

Executive cognitive functions (ECF) are the specialized brain functions required for acquiring and processing vital information from surroundings while performing various activities of daily living (ADLs) (9). With the disruption of dopaminergic networks in PD, the BG connections with frontal cortex are affected, resulting in 60% of the PD population developing at least one, or more executive cognitive dysfunctions (10,11). For safe community ambulation, there arise numerous occasions when ECF such as navigation, negotiating terrains, and obstacles,

reading and visual tracking must be combined with walking (12,13). This calls for the ability to dual-task (DT) efficiently while walking, without losing balance. In PD, DT walking further deteriorates the spatiotemporal gait variables, increase chances of freezing of gait (FOG) and resultantly, increase chances of fall (14–16).

Anti-Parkinson medications such as Levo-dopamine, are effective for improving bradykinesia and reducing tremors and rigidity but have very limited scope to improve balance and executive cognitive functions in people with PD (17–20). Several recent studies have reported that providing multi-modal therapy training by combining motor and ECF aspect of dual-tasking, leads to improvement of both gait and executive functions (21–23).

My thesis research will evaluate feasibility, acceptability and an estimate treatment effect with game-based treadmill program (GTP), for improving DT gait and balance in people with PD.

## **Chapter 2: Literature Review**

### **2.1 Standing balance, Gait, and Gait Stability**

Apart from the three cardinal signs in PD, there is marked deterioration in balance and gait stability with the progression of the disease (24). Approximately 60% of PD patients report at least one fall in a year and a significant number of report multiple falls. The result of these falls is usually devastating, resulting in disabilities (15,16).

Several studies have evaluated the body sway metrics during standing balance in PD under many different conditions. The Sensory Organization Test (SOT) has been widely used to quantify an individual's ability to use visual, proprioceptive and vestibular cues to maintain balance (25). Nocera, Hovav and Ray 2009 (26) compared the performance of 10 PD participants with ten age-matched normal controls during SOT. All PD participants were in stage 2-3 on the Hoehn-Yahr scale and were tested on 'on phase' phase of medications. The results showed that there was a significant increase in body sway as measured by analysis of the center of foot pressure (COP) displacement under condition 4-6 of the SOT. Other researchers have conducted SOT in PD and found similar results (27,28).

Clinical test of sensory interaction on balance (CTSIB) is a low-cost clinical version of the SOT and an equally valid tool to assess standing balance in any population under similar conditions as that of SOT (29–31). Researchers have used a modified version of CTSIB to evaluate standing balance in PD (32,33). This version examines the body sway metrics while a person is standing with their eyes closed and then open, first on a firm surface and then on a compliant surface. Kaylena Martens et al. 2016 (34) examined standing balance performance during modified CTSIB in PD. They recruited 21 healthy controls and 31 PD participants. The



results from the study showed that participants with PD had significantly greater COP displacement than age-matched healthy controls. There was no statistically significant difference observed in COP displacement while standing on a foam surface with eyes closed among the two groups. This highlights the importance of vision and visual information of surroundings required by our brain to maintain standing balance.

A recent study by Bekkers et al. 2018 (35) examined standing balance performance under DT condition in individuals with PD, with and without freezing of gait (FOG) history. They conducted all four mCTSIB conditions and added a cognitive task of listening to a number sequence, memorizing it and repeating the number sequence. This study used a standard sponge as a compliant surface. The results demonstrated that PD participants with FOG had significantly greater COP displacement during eyes open sponge condition and DT sponge condition as compared to PD participants without FOG.

In PD, apart from standing balance, gait dysfunctions are also observed in early stages of PD (36). Classical gait for an individual with PD can be described as a slow, short-stepped, shuffling gait with a forward-stooped posture and an asymmetrical arm swing (37). With disease progression and loss of automaticity of movements in PD (38,39), there is a significant loss of pace and walking rhythm (40). Several researchers have compared spatiotemporal gait variables such as step length, step time, single and double support time, and coefficient of variation for step length and step time among PD and normal healthy age-matched adults (41,42).

Wahid et al. 2015 (43) compared the spatiotemporal gait variables of individuals with PD, in stage 2-3, with healthy normal adults. They recruited 23 PD participants, with a mean age of 68.5 years and 26 healthy adults, with a mean age 69.5 years. An 8-Camera video motion analysis system with two force platforms was used to record the gait of PD participants. This can

only record 3-4 consecutive steps. Participants were asked to walk ten times across this walkway to provide data for 30 steps. Mean walking speed was similar in both groups, 1.1m/s for PD groups and 1.2m/s for healthy controls. The results showed that PD participants had significantly smaller stride length and step length ( $p<0.05$ ) and smaller double support time too ( $p<0.05$ ) when compared to healthy controls. Smaller step length and decreased double support time are indicators of shuffling of gait in PD. Many other studies have evaluated the spatiotemporal gait variables in PD and found similar spatiotemporal gait deviations when compared to normal healthy controls (44–46).

Another common gait problem in PD is FOG. FOG is defined as “brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk” (47). A FOG episode typically lasts for a few seconds. These small episodes of cessation of walking are more frequent in the late stages of diseases and increase as patient approach the “off” phase of medications (48,49). Freezing most commonly occurs while turning, passing through a narrow corridor or while approaching a destination, such as a chair (50). Pieruccini- Faria et al. 2015 (51) compared spatiotemporal gait variables between PD participants with and without FOG history. They recruited 21 PD participants with FOG and 26 PD participants without FOG history. Participant’s 15-20 non-consecutive steps were analyzed for average step length and step time, and step length variability by walking five times over 5m GAITRite carpet (52). The results showed PD participants with FOG history had significantly higher step time and step length variability, and a reduced average step length.

Such deterioration of spatiotemporal gait variables has been an independent predictor of future falls in older people with and without neurological disorders (53,54). Falls are among one of the biggest problems in PD, with approximately 60% of PD participants reporting at least one

fall per year (55). Lord et al. 2016 (56) conducted a 36-month prospective follow up study with 77 PD participants in stage 2-3 to evaluate the relationship between falls and step time, and step length variability of PD participants that reported falls and that did not report falls. Falls were prospectively measured with the help of “Fall Diaries” that were collected monthly. After 36 months of follow up, 47 participants reported at least one fall and 30 participants reported no falls. It was found that participants that reported falls had significantly slower gait speed and significantly higher step time and step length variability. Other studies have shown similar results of deterioration in spatiotemporal gait variable as a predictor of future falls in PD (57,58).

Okuma et al. 2018 (59) conducted a 6-month prospective study to evaluate the contribution of FOG episode to falls experienced by PD participants. They followed 36 PD participants with a mean age of 67.5 years, in Hoehn and Yahr stage 2-4 for six months. All 36 PD participants experienced FOG, as per the FOG questionnaire (FOGQ). Participants were asked to log fall incident in a diary and categorize their fall reason to FOG or loss of balance. Thirty-six participants reported a total of 252 falls and a significant 172 falls were related to FOG, irrespective of medication state of PD participants. Several other studies have also found a significant correlation of FOG with falls in PD individuals (60,61).

## **2.2 Executive Cognitive Functions**

Executive cognitive functions (ECF) can be defined as specialized brain functions involved in acquiring and processing the information for making decisions (62). Some examples of ECF include process planning as assessed by tower of London test (ToL), concept formation as assessed by card sorting test (CST), response inhibition as assessed Stroop test (SrT), working memory as assessed by digit-span test (DST), set-shifting as assessed by trial-making test A and

B (TMT-A and TMT-B) and multi-tasking (10,63). The pre-frontal cortex (PFC), specifically medial and lateral PFC, is highly associated with performance on various ECF tests like TMT, WCST, DST, and ST etc. (64). Several studies show that PFC volume and thickness is highly correlated with better performance on various ECF tests. It is reported that 20%-50% of individuals with PD develop at least one form of cognitive impairment, including executive cognitive dysfunctions, broadly known as mild cognitive impairment (MCI) in PD (65–67).

Bezdicek et al. 2017 (68) examined the performance of PD participants on the frontal assessment battery (FAB) and compared it to age-matched healthy normal adults. FAB consisted of 6 subtests for ECF like TMT-A and TMT-B, ST, CST and VF (69). They recruited 73 participants with PD and 73 age-matched healthy controls for the study. PD participants had a significantly lower mean composite score of 14 as compared to normal healthy controls with a mean composite score of 17, demonstrating that PD participants had impaired ECFs. A resting state MRI examination was carried out on 37 PD participants and 31 control participants. There was atrophy in the prefrontal cortex of PD participants possibly explaining the reason for lower performance on all ECF tests.

Another study by Kudlicka et al. 2013 (70) evaluated the pattern of ECF impairment in PD. They recruited 34 participants with PD, in stage 1-3 on Hoehn and Yahr scale and mean age of 72.6 years. ECF was assessed on the Delis-Kaplan Executive Function System (D-KEFS) which consists of a set of 9 subset examinations like TMT A and B, VF, ST, CST, design fluency test (DF), 20 questionnaire test, ToL and proverb recognition test. All tests were performed in the sitting position. A cluster analysis was performed on all subtests scores and by stage of the disease. This revealed that PD participants had maximum difficulty in performing a task requiring cognitive flexibility, set-shifting and visuospatial search, as tested by TMT-A and

TMT-B. Also, participants in stage 3 had the lowest composite scores as compared to stage 1 and 2. Another study by Olchik et al. 2017 (71) evaluated the performance of PD participants on TMT-B test for visuospatial search and set-shifting and compared to that of normal healthy age-matched controls. The results showed that PD participants took significantly greater time (301sec) to complete the TMT-B test as compared to normal-healthy age-matched controls (224sec). PD participants also had a significantly high cut-off point (297.5sec) on TMT-B test, as analyzed by ROC curve analysis, thus indicating that TMT-B can be used to differentiate patients with PD from healthy controls.

Several longitudinal prospective studies in the past have proposed that executive cognitive dysfunction in PD is progressive. Pedersen et al. 2013 (72) conducted a three-year prospective study with 182 PD participants to evaluate the progression of MCI or executive dysfunction to dementia. A series of ECF tests like WCST, TMT- A and B, VF, ST and total immediate recall test were administered at baseline, 1 year follow up and at three years follow up to keep a record of performance of participants. Participants were diagnosed with MCI based on Movement Disorder Society (MDS) diagnostic criteria for MCI in PD (73). Dementia was diagnosed as per MDS clinical diagnosis of dementia in PD (74). After following up, it was found that 27.8% of PD participants progressed to dementia in 1 year and a significant 45.5% participants progressed to dementia at three years follow up. Also, participants that developed dementia had significantly lower performance on ST and TMT-B test at baseline, and 1-year follow up. Many similar studies have related lower performance on ECF test at baseline to progressive dementia in PD (67,75,76).

### **2.3 Dual-task interference in Parkinson Disease**

Safe, independent community ambulation requires a series of a complex interactions between mobility skills and cognitive flexibility to manage a variety of environmental challenges such as talking or navigating in busy environments and avoiding obstacles while walking on a street or looking around while shopping (77–79). There have been several studies in the past two decades that explore the effect of dual-tasking on over ground walking of older people with and without any neurodegenerative disease (80–82). Reduction in walking speed while performing an added secondary cognitive task has been a common finding in all over ground DT walking studies. Majority of such studies have used a 5m long GateRite carpet that can record spatiotemporal gait variables of 4 to 6 consecutive steps, which takes about 5-7 seconds. This provides a very limited window for cognitive task performance while walking to study the DT interaction (83). There are limited studies which have studied the DT walking interaction in PD (84,85). Rochester et al. 2014 (86) conducted a study to evaluate the DT interference in PD as compared to healthy controls (HC) during overground walking. They recruited 121 participants with PD in stage 1-3 and 184 age-matched HC. They used a GAITRite carpet (52) that recorded only 4-5 steps for analysis of step velocity and steps length variability during walk only or ST and while walking and performing secondary cognitive task or DT walking. Serial 7 subtraction or digit span test was selected as the secondary cognitive task evaluating working memory capabilities of participants both in sitting as ST and DT walking. Error percentage while performing the secondary cognitive task was calculated to quantify performance on the cognitive domain of DT walking. An analysis of co-variance (ANCOVA) revealed a significant reduction in step velocity and a significant increase in step length variability during DT walking as compared to ST walking in both PD and HC. The error rate in the digit-span test was also

significantly higher while performing DT walking as compared to ST. There was no significant group effect seen for both gait and cognitive outcome measures. It should be noted that only a few consecutive steps were recorded for the analysis with the GAITRite mat (52) and the cognitive task was done only for a few seconds. There was likely prioritization to gait function as participants in both groups showed reduced step velocity or slowed down during DT walking.

Another study by Salazar et al. 2017 (87) evaluated the DT walking in PD with verbal-TMT. They recruited 19 participants with PD in Hoehn and Yahr stage 2-3 and 13 age-matched healthy controls (HC). Participant's walking speed, and stride length were recorded for 4 to 6 consecutive steps using Optotrack motion camera system. A 2-way ANOVA was performed that revealed a significant group, condition and group-condition effect on walking speed. A significant reduction in walking speed during DT walking was found in PD participants as compared to ST walking. Upon comparison with HC, PD participants had reduced walking speed, both ST and DT condition. Both HC and participants with PD produced significantly fewer set shifts under DT walking conditions as compared to ST, but no significant group effect was observed. It should be noted that the number of set-shifts produced was not standardized during analysis and number of set-shifts possible in 4 to 6 steps is very low.

All studies which have evaluated DT interference effect during overground walking in PD report reduction in walking speed. Several types of research in the past have shown that change in walking speed can affect the spatiotemporal gait variables (88–91). A recent study by Cole et al. 2017 (92) evaluated the effect imposed fast and slow walking on step length and stride time variability of people with PD. They recruited 20 PD participants in stage 2-3 on Hoehn and Yahr scale and ten age-matched HC. Participants were asked to walk for 60 seconds on a treadmill with 70%, 100% and 130% of their preferred walking speed. A total of 20 consecutive

steps were analyzed using inertial motion sensor system and Vicon motion analysis system surrounding the treadmill. The results showed a significant effect of treadmill speed on stride length and stride time variability in both groups, with no significant between-group effect. There was an increase in stride length and reduced COV stride time seen with an increase in walking speed. Therefore, it is very important to control walking speed while evaluating the effect of a secondary task on walking in any patient population.

A study by Fernandez-Lago et al. 2015 (93) evaluated DT interference effects in a group of PD participants while walking on a treadmill. They recruited 19 PD participants in stage 1-2 on Hoehn and Yahr scale, and 19 age-matched HC. Participants were asked to walk on a treadmill for 1 minute, and 25-30 consecutive steps were recorded, and average stride length (m), and stride length variation (%) were computed. Participants were asked to listen to an audio recording via earphones for 1 minute and count the number of times two-predefined words occurred in that recording. Percentage of error in counting was determined while both ST in sitting and DT while walking. The audio-recordings in both ST and DT were different to avoid learning effect. However, as a major limitation of this study, all participants walked on a treadmill while holding on to the side railings during both ST and DT walking trails. Adopting such a method can make it difficult to interpret the results and evaluate the true DT effect. A one-way ANOVA revealed no significant difference in stride length during ST and DT condition. PD participants walked with higher variation in stride length during DT walking as compared to ST walking. Also, when compared to HC, PD participants had significantly higher stride length variation during DT walking task. The cognitive task results revealed a significant group effect with PD participants having significantly higher error percentage as compared to HC.



Such deterioration in spatiotemporal gait variables in PD while DT walking or complex further increases the fall risk in PD (53,54,56,94). Most of the DT interaction studies use digit span (Serial 7 subtraction), Verbal TMT, phenome counting and verbal fluency as the secondary cognitive test of assessment. These cognitive tests do not consider the visual-cognitive aspect of interaction with the surroundings. Some studies in the past with older adults have reported that cognitive tasks requiring visual processing (e.g. Brook's visuospatial tasks) affect gait more than tasks requiring working memory and set-shifting (95,96).

Thesis research by Mayank Bhatt and Tony Szturm 2018 (97), University of Manitoba evaluated DT interference during DT walking and performing a visual-cognitive task on two different stages of PD according to Hoehn-and-Yahr scale. They recruited 26 PD participants, with 13 in stage 2 and 13 in stage 3 for PD. Participants were asked to perform a computer-based visual-cognitive task that required participants to control a game paddle with the help of wireless motion mouse to catch a target object and avoid distractor while walking on a treadmill for 1 minute. Step length, step length variability and Medio-lateral (ML) drifting was evaluated for 25-30 consecutive steps with help of a pressure mat nested under the belt of the treadmill. Cognitive performance was evaluated for success rate and neck rotation movement variation to move the paddle for catching the target object. A significant within-group effect was seen for step length variability and ML drifting during DT walking as compared to ST walking. This shows that PD participants gait further deteriorated when performing an added visual-cognitive task. A significant between-group effect was seen for all 3 gait variables during DT walking. Stage-3 participants showed significantly higher DT interaction as compared to stage 2. Therefore, with disease progression, there is an associated decline in DT walking in PD. The visual-cognitive

game performance showed significant within-group effect but no significant between group effect for success rate and movement variation as compared to performance in sitting to walking.

This shows that during multitasking, apart from age-related deterioration in motor performance, people with PD show greater DT interaction with both motor and cognitive performance deterioration. A DT interaction results in a greater threat to gait stability during community ambulation and thus increase in fall incidence in the PD population.

These findings led to the thought that development of a DT walking training protocol may prevent and prospectively reduce such fall incidences.

## **2.4 Current Exercise Therapy Programs in Parkinson Disease**

Apart from the pharmacological treatment for patients with PD, the latest Canadian guidelines on PD treatment also stress the importance of exercises for improvement of muscle strength, standing balance and gait function (98). Several studies in the past have shown that standing balance and gait stability respond better to exercises as compared to standard pharmacological treatments (99–102).

A study by Smania et al. 2010 (103) evaluated the effect of a balance training program on people with PD. They recruited 64 participants with PD and randomized them into two groups of balance training (n=33) and a control group (n=31). The balance training program group consisted of a variety of exercises that produced destabilization of the body center of mass. The movements involved were standing on toes, heels, standing on a compliant surface with eyes open and eyes closed, and while performing various upper limb movements. The control group received lower limb strengthening exercises and stretching on the bed. Both groups received the interventions for 21 days, and the duration of each session was 50 minutes. The primary outcome

measure for this study was performance on the Berg- balance scale (BBS) and on Activities-Specific Balance Confidence Scale (ABC). Only the balance training group showed significant improvement in performance on BBS and ABC scale. The controlled group showed no statistically significant improvement. Hence, physical therapy exercises that are challenging enough to produce a threat to body stability improve standing balance in PD. However, the effects of this exercise program on gait performance was not examined.

Lee-Silverman Voice treatment (LSVT) – BIG is another form of approved exercise regime for patients with PD (104). It consists of high-amplitude, big rhythmic movements of arms and legs that aims to improve general body movements required during daily living activities such as dressing etc. (105). A recent study by Isaacson et al. 2018 (106) evaluated the effectiveness of LSVT-BIG exercise program to improve balance as measured by timed up and go test (TUG). They recruited 93 PD participants with a mean age of 68.4 years and in Stage 1-3 on Hoehn and Yahr scale. LSVT-BIG training was provided to each participant for 4weeks, four times each week and each session lasting for 1 hour. A significant improvement in TUG scores was seen after 16 sessions of LSVT-BIG. It is critical to note that no control group undergoing an active treatment was included in this study. Other studies in the past have shown a similar effect of LSVT -BIG on patients with PD (107,108). But unfortunately, no study in the past has reported the effect of LSVT-BIG on gait performance of PD participants.

Tai Chi (TC) is another exercise program that is gaining popularity in ageing and in PD to improve standing balance and body awareness (109). TC consists of a series of slow and sustained movements of the upper and lower extremity. TC emphasis on the relaxation of muscles by breathing and reducing tremors by attempting to maintain certain positions for a set duration of time (110). A study by Gao et al. 2014 (111) conducted an RCT to evaluate the effect

of TC to improve balance in people with PD. The recruited 76 PD participants with a mean age of 69.54 years and in stage 2-3 on Hoehn and Yahr scale. Participants were distributed into TC group (n=37) and no- treatment group (n=39). Participants in the intervention group received 24 TC sessions, each session lasting for 60minutes. The TC group showed significant improvement in balance as evaluated by berg-balance scale (BBS). Only a paired t-test was conducted, and no ANOVA was conducted to evaluate a between-group effect. There was no significant change in TUG scores following the intervention. Other studies in the past have shown TC to be beneficial for PD (112–114), but no study has compared TC to another exercise program or used any gait outcome measure to evaluate the effect on gait function.

An emerging exercise program for PD is boxing (115). Customary boxing training in PD involves various patterns of upper body punching motions and lower-extremity footwork in multiple directions. It is believed that high-speed punching motions in boxing initiates trunk rotations and facilitates anticipatory postural control in PD (116). However, there is very limited evidence in the form of randomized control trials on the effectiveness of boxing in PD. A case series study by Combs et al. 2011 (117) provided evidence for the feasibility and safety of Rocksteady boxing® training in PD to improve balance and activities of daily living in six PD participants.

In a review of current exercise programs in PD, Mehrholz et al. 2015 (118), concluded that although various therapy protocols are proposed for balance and gait rehabilitation in PD, only the therapy protocols that challenge stability produce beneficial results. A recent study by Nadeau et al. 2017 (119) evaluated if an aerobic cycling protocol has any effect on walking speed, cadence, and step length and step length variability of PD participants. The results from this study showed significant improvement in only overground walking speed after 12 weeks of

cycling but no improvement in any other gait outcome measure. Although improvement in overground walking speed was statistically significant, the mean change was from 1.1 m/s at baseline to 1.18 m/s post-intervention. The change of 0.08 m/s is very small (not clinically significant).

Treadmill training (TT) in PD has been seen as an effective training program to improve gait in PD (118,120). A study by Nadeau et al. 2014 (121) evaluated the effect of 24 weeks of a treadmill training program on the gait of PD participants. They recruited 93 participants with PD in Stage 1-3 on Hoehn and Yahr scale and randomized the participants into three groups namely control group (n=34), speed only TT group (n=29) and, mixed TT group (n=30). Each group received pre-defined exercise protocol for, three times per week for 24 weeks and each session lasting for 1 hour. The control group received 1 hour of general aerobic exercises like cycling, Tai-chi and tennis ball dribbling. In the speed-only group, only treadmill speed was progressed every week. In the mixed-TT group, treadmill speed and treadmill inclination were progressed. Participants were allowed to hold on to handrail support while walking. Participant's spatiotemporal gait variables were analysed using GAITRite carpet (52). A 6MWT was also conducted to evaluate walking endurance. Overground walking speed was evaluated by time take to travel 10 m. There was a significant effect of time observed on cadence, stride length, step with and double support time for all three groups. There was no significant group effect observed. A significant group interaction was seen for walking endurance and walking speed with both TT groups showing significant improvement.

Another study by Shulman et al. 2013 (122) evaluated the effect of three different training protocols to improve walking endurance. They recruited 67 PD participants in Hoehn and Yahr stage 2-3. Participants were randomized into one of three treatment arms. The three

treatment arms were high-intensity TT targeting 70%-80% of HR for 30minutes, a low-intensity TT targeting 40%-50% HR but for an increased time of 50 minutes and a group receiving resistance and stretching exercises for leg muscles. All three groups received therapy for 12 weeks, three times every week. It is interesting to note that participants were allowed to hold the side rails during TT if needed. The primary outcome measure was the participant's walking endurance was measured with 6MWT. Only the low-intensity TT group showed significant improvement in walking endurance, whereas the other two groups showed no significant improvement. Thus, long duration TT is more effective than high-intensity training to improve over ground walking endurance. Several other studies in the past have provided similar results on the effectiveness of treadmill training in PD (123–125).

Community ambulation involves not only motor processing of walking but also performing many other visuomotor and cognitive activities. Many multicomponent exercise programs or DT training programs are emerging for people with PD to improve both mobility functions (i.e. balance and gait) and cognitive functions (126,127). Addition of various secondary cognitive tasks or sensory stimulation, cueing, or music also, can further enhance the benefits from such targeted therapy protocols.

Mirelman et al. 2016 (128) evaluated the effect of DT training in PD by comparing virtual-reality (VR) based TT program to traditional TT program to reduce fall risks and improve gait performance during obstacle negotiation in individuals with PD. They recruited 130 participants with PD and randomized them into either of two groups, VR + TT or only TT. A customized video-graphic illustration of an outdoor scene was displayed on a large monitor placed in front of the treadmill. The VR+TT environment consisted of various virtual obstacles to step over while walking on the treadmill. A Microsoft Kinect camera was also placed in front

of the treadmill to detect the foot motion. This information was used to lift the foot in the virtual world to overcome the obstacles in the VR walking path. To note that there was no description of the frequency and size of obstacles presenting in the training environment. This makes it difficult to comment on the degree of cognitive and motor challenge. The intervention lasted for six weeks, three times every week and each session lasting for 45 minutes. An overhead body harness was used during the intervention and participants were allowed to hold on to side rails of the treadmill. Falls were measured over six months at baseline and after the intervention. Gait speed and step length variability were evaluated for overground walking, both with and without obstacles using a 7 m Zeno walkway carpet. The VR+TT showed significant improvement in the number of falls, and there was a significant group effect seen after the intervention. TT group showed no significant improvement in the number of falls. Both groups showed significant improvement in gait speed and step time variability during overground walking with and without obstacles, but there was no significant group difference observed.

A follow-up study with the aforementioned VR+TT program was done by Maidan et al. 2018 (129). They evaluated the change in prefrontal cortex activity following six weeks of VR+TT program and only TT program with the help of functional near-infrared spectroscopy (fNIRS). The results from this study showed a significant reduction in prefrontal cortex activity in both groups, but a significant group effect was seen. The VR+TT group showed significantly greater reduction in activation as compared to only TT group.

Geroin et al. 2018 (130) compared the effect of integrated and consecutive DT training in PD. They recruited 120 PD participants in stage 2-3 on Hoehn and Yahr scale. The participants were divided into two groups; one received integrated DT training, and the other received consecutive DT training for 12 weeks, two times every week. In integrated DT training

participants performed various cognitive tasks while walking over ground. Cognitive tasks chosen for intervention were digit span and verbal fluency. The performance on a cognitive task and walking speed was not standardized during the intervention. In the consecutive training group, participants performed the cognitive task in sitting for 20 minutes and received an overground gait training by a therapist for 20 minutes. Participants stride length, step length and step length variability were evaluated for 4-5 consecutive steps using GAITRite carpet (52) while normal walking and walking while performing an auditory Stroop test. An ANOVA performed on the outcome variables revealed a significant time effect of an intervention for both groups, in particular, improved step length and stride length and a significant reduction in step length variability after 12 weeks. There were no significant group differences observed.

Compliance with a prescribed exercise program is a critical key factor associated with the effectiveness of the protocol. To maintain long-term compliance for the therapy program, it should be engaging and stimulating. Computer games are gaining popularity in recent literature as a medium to increase focus, attending and engagement toward various therapy programs (131). Coupling of computer games with a suitable physical activity is known as “Exergaming.” Other researches in the past has coupled standing balance exercises on Wii-board, Kinect 3D depth camera and pressure mats with computer games as a DT training program in older adults, patients with multiple sclerosis and PD (132–136). There has been no study in PD till date, providing DT walking training by combining cognitive computer games and walking



## **2.5 Summary**

A large percentage of patients with PD report balance and mobility limitation in the early phase of the disease and a significant amount of those report multiple falls during community ambulation (137,138). Apart from motor complications of the disease, there is a significant deterioration in ECF (66). Community ambulation requires a person to couple various executive cognitive activities with walking.

Most of the current therapy programs like LSVT, TC and PD boxing requires PD patients to perform various standing balance activities with a stationary base of support. Several studies in the past have shown that improvements in standing balance capabilities do not transition into gait improvement under ST and DT walking conditions (132,139,140). Very few DT walking therapy studies have been performed with PD participants. The majority of these studies use overground walking and limited cognitive activities such as verbal fluency and the digit span test (135,141). Such cognitive task provides very limited challenge, and there is no method to control or standardize the performance on every treatment session. One of the main effects of DT walking in PD is a reduction in walking speed, and so overground walking speed needs to be controlled in therapy protocols. Treadmills have been used in the past for DT walking therapy in PD, e.g. the VR+TT protocol has shown to reduce fall risks and increase gait speed during over ground obstacle negotiation in patients with PD (128,142). But a major limitation of the VR+TT program was a lack in knowledge of the degree of ECF challenge imposed by the virtual environment to produce effective DT interaction required for DT walking training and fall reduction.

Researches has shown that playing computer games require the use of multiple ECFs like cognitive flexibility, response inhibition and response generation, and working memory etc. (131,143,144). To answer this need, our research team has developed a game-based treadmill platform (GTP), which provides an integrated approach for rehabilitation of mobility skills and various executive cognitive activities required during community ambulation. The GTP consists of 1) a standard treadmill instrumented with a pressure mapping system capable of computing various gait stability measures like average step length, average stride length and gait variation; 2) an interactive computer gaming sub-station providing medium of dual-tasking while walking; 3) a customized assessment software with advanced data logging system to quantify participant's cognitive performance on targeted assessment games during DT treadmill walking (97,145,146). This makes GTP an ideal platform for both assessment and treatment of DT walking difficulties in a patient population.

Thesis research of Akshata Nayank and Tony Szturm (2015) (147) at University of Manitoba, evaluated the feasibility and preliminary treatment effects of a similar combination of treadmill and cognitive computer games ([www.bigfishgames.com](http://www.bigfishgames.com)) for DT walking training in older adults, aged 70-80 years. The results from this research work showed the treatment method was highly acceptable among the target population and showed excellent feasibility. The preliminary treatment effects were positive for both motor and cognitive outcome measures. My thesis research work will compute the feasibility of GTP protocol in PD, and the mean improvement and variability in outcome measures will help to perform a sample size calculation for future RCT with GTP. The validity and reliability of all cognitive, standing balance and spatiotemporal gait outcome measures used in the study for the people with PD have been tested in the thesis work by Mayank Bhatt and Tony Szturm (97).

## **Chapter 3: Study Purpose and Objectives**

### **3.1 Purpose:**

The purpose of this pilot study is to provide evidence of the feasibility of conducting a full-scale randomized controlled trial (RCT) with GTP for DT walking training in PD. For this, we will recruited 15 PD participants in stage 2- 3 on the Hoehn and Yahr scale.

### **3.2 Objectives:**

There are three main objectives of this study:

1. **Objective 1:** Evaluate the feasibility of conducting full-scale RCT with GTP by assessing the recruitment rate with current inclusion and exclusion criteria's, retention rate, drop out rate; study procedures and study management.
2. **Objective 2:** Evaluate the experience of participants undergoing the intervention and acceptability of the GTP program among PD population with the help of semi-structured interviews after the ten weeks of intervention.
3. **Objective 3:** Evaluate an estimate of the treatment effect size of the intervention program to improve DT walking in PD. The mean and variances of outcome variables pre to post-intervention will be used for sample size calculation of future RCT with patients with PD for the power of 0.80 or 80% and an alpha value of 0.05 or 5%.

## **Chapter 4: Methods**

**4.1 Study Population:** Individuals with diagnosed Parkinson Disease.

**4.2 Sample Size:** In accordance with literature for an adequate sample size of a pilot and feasibility study (148,149), we will aim to recruit 20 individuals with PD.

**4.3 Ethical Approval:** This research study has been approved by the Health Research Ethics Board (HREB), Research Ethics-Bannatyne, University of Manitoba (H2018: 338)

### **4.4 Participants:**

#### **4.4.1 Inclusion Criteria:**

- Diagnosed with PD according to UK brain bank criteria (150).
- In PD stage 1-3, according to PD Hoehn and Yahr scale (151).
- Achieve a minimum score of 26 or higher on Montreal Cognitive Assessment (MoCA), to be regarded as non- MCI PD (152).
- On stable PD medications for the past three months (153).
- Able to walk for a minimum of 6 minutes continuously overground.

#### **4.4.2 Exclusion Criteria:**

- Any diagnosed psychiatric co-morbidity.
- History of any other neurological disorder apart from PD.
- Any orthopedic or cardiovascular disorder limiting participant to walk on a treadmill or overground for a minimum of 6 minutes continuously.

- Any other associated medical condition limiting participant to play computer games for a minimum of 10 minutes continuously.

#### **4.4.3 Recruitment:**

- Recruitment was done through 2 movement disorder clinics in the province of Manitoba.
- Recruitment was also be done through the University of Manitoba annual Neuro-rehabilitation clinic organized by the college of Rehabilitation Science.
- Additionally, we also advertised the study to various PD support groups in Winnipeg (U-Turn Parkinson and Parkinson Canada – Manitoba).

#### **4.5 Research Site:**

All aspects of this research study was conducted in room RR327 on the 3<sup>rd</sup> floor of Rehabilitation Hospital, 800 Sherbrook Avenue, Winnipeg.

#### **4.6 Research Design:**

This was a single group feasibility and pilot study with a “baseline and post-intervention” study design.

#### **4.7 Primary Outcome measure**

The primary outcome of this study was to evaluate the feasibility of GTP program for standing balance and gait rehabilitation in individuals with PD.

#### **4.8 Secondary Outcome measures**

The secondary outcome measures of this study was to evaluate the experience of participants with GTP program and provide an estimate of intervention effect size on various standing balance, spatiotemporal gait and cognitive outcome measures.

#### **4.9 Study Equipment's**

##### **4.9.1: Standing Balance Assessment**

A flexible piezo-resistive force sensor application (FSA) pressure mapping carpet by Vista Medical Private Ltd., Winnipeg, was be used to compute the centre of pressure (COP) displacement in anterior-posterior and medial-lateral directions. The square pressure mat consists of 256 piezo-resistive sensors (16 X 16), each sensor capable of recording an area of 2.8cm<sup>2</sup>. The flexibility of this pressure mat allows it to be placed easily on any compliant surface. We evaluated the standing balance on a compliant sponge surface during both the ST and DT condition.

The compliant surface used for assessment was a 6- inch thick sponge with density 22.66kg/m<sup>3</sup>. We will place a wooden board over the top of the sponge with dimensions 16inches length and 11inches of width. The pressure mat was be placed over the sponge and board for standing balance assessment on a compliant surface.

Post-assessment was done on the same 6-inch sponge as pre-assessment.

#### **4.9.2: Gait Assessment**

Assessment of gait was conducted on a standard treadmill, nested with a pressure mapping system to compute various spatiotemporal gait variables both during normal walking and while walking and performing a secondary cognitive task. We used a Model T635 treadmill from SportsArt Fitness Ltd. (Mukilteo, Washington) with a belt with 22inches and the total length of 61inches. This treadmill was equipped with front and side railing for holding on if needed. For the safety of participants, an overhead harness system was be used, without body weight suspension.

The pressure mapping system nested beneath the treadmill belt was be a flexible-piezo-resistive FSA walking carpet. This recorded various spatiotemporal gait parameters and COP displacement during treadmill walking. This mat has 512 piezo-resistive units, each unit capable of recording an area of  $2.8\text{cm}^2$ . This is a single wire mat, so it does not hinder walking on a treadmill. This is like many conventionally available pressure mats like GAITRite (52), GaitMat (154) and Zenowalkway (155). Placing the mat underneath the treadmill mat allowed us to record spatiotemporal gait data at a constant treadmill speed, both pre and post intervention.

#### **4.9.3: Computer Gaming Substation**

A thirty-two-inch LG LCD TV monitor connected to windows CPU was placed approximately 1m in front of the treadmill. This computer was used as a medium to conduct computer game based cognitive task for assessment and for playing commercial computer games as a part of DT intervention. This computer station was connected to the internet to access multiple commercial computer games through [www.bigfishgames.com](http://www.bigfishgames.com) (156).

A wireless optical air mouse from Hillcrest Lab (Rockville, MD) was connected to this substation with a standard USB. This air mouse was secured by Velcro on a plastic helmet, which was worn by participants. With the help of an air mouse placed on the helmet, participants were able to interact with the computer by head rotations. Studies (145,146) in the past have established the usability of this air mouse of interacting with a computer to perform a similar cognitive task and playing commercial computer games while walking on a treadmill.



*Figure 1: Wireless scoop pointer air mouse from Hilcrest Lab (Rockville, MD) mounted on  
Helmet worn by participants*

#### **4.9.4: Computer-based cognitive task**

A custom assessment software application with a visual-cognitive game (VCG) module and a visuomotor tracking (VMT) module was used to assess the cognitive domain. All participants wore the helmet, having the air mouse for interaction with the computer. Both VCG and VM task required participants to perform gentle neck rotation to left and right.

1. **Visual-Cognitive game (VCG):** This task will evaluate the ECFs such as response inhibition, information processing and visuospatial search abilities. The fundamental objective of this task was to align a computer paddle by catching the dropping target (soccer ball) and avoid distractor (black dotted sphere). The computer paddle was



enslaved to the left and right head rotations by the participants. There were two different types of VCG tasks performed by the participants. Both these tasks varied in difficulties of visuo-spatial search and response generation. The two types of VCG tasks are:

- **VCG TASK 1:** In this, a target (soccer ball) and a distractor (dotted sphere) fell from top of the screen to bottom screen at a fixed speed and in straight path length. The background for this task will be solid grey, and both target and distractor were easily visible on the grey background. Participants controlled the paddle at the bottom of the screen and attempted to catch all target objects.
- **VCG TASK 2:** In this task, same target and distractor were falling from the top of the screen at a fixed speed (faster than VCG1) but in diagonal trajectory. Also, an optokinetic background to produce optical illusion was used in this task. The duration of both VCG1 and VCG2 remained the same.

The target object (soccer ball) and distractor (dotted sphere), both appeared at an interval of 1.5 seconds. The duration of the VCG task was 45 seconds in sitting, sponge standing and 60 seconds while walking on a treadmill. The sampling frequency was set at 100Hz.

2. **Visuomotor Tracking Task (VMT):** This task evaluated ECFs such as response generation, visual motor tracking with eye-head coordination. In this task, participants were asked to overlap a rectangular paddle over a computer controlled yellow sphere. The rectangular paddle was enslaved to the participant's head rotation by wireless air mouse. The computer controlled yellow sphere was set to move left and right (horizontal) or up and down (vertical) at a set frequency and amplitude. The horizontal and vertical VMT task was played for 30 seconds during sitting and sponge standing. During treadmill walking, horizontal VMT task was played for 45 seconds.

The computer controlled yellow sphere moved at a pre-set frequency of 0.5Hz and amplitude of 0.60 or covering the middle 60% of the screen. During treadmill walking, the amplitude was changed to 0.50 or covering the middle 50% of the screen. The background for the VMT task was solid grey. The sampling frequency was the same as 100Hz. The software recorded and compared the movement trajectory of both the yellow sphere and rectangular paddle and provided the quantitative outcome of difference between two trajectories.

#### **4.9.5: Computer games for intervention**

Commercial computer games from [www.bigfishgames.com](http://www.bigfishgames.com) were selected for DT training during walking over treadmill and sponge standing. Games like Action ball, Birds town, Jet Jumper, Luxor, Digby's donuts, Bricks of Egypt etc. were selected for the program (156). All games will be capable of being controlled by a wireless air mouse, previously used for assessment. A total of 30 games were selected, that required participants to utilize various complex ECF such as response inhibition, response generation, visuospatial search and visuomotor tracking. The participant was asked to play interactive commercial computer games while standing on a sponge for 10-15 minutes and while walking on the treadmill for 20-30 minutes.



i) *Jet Jumper*

ii) *Action Ball*

iii) *Luxor*

*Figure 2: Computer Games for Treatment (www.bigfishgames.com)*

#### **4.9.6: Compliant surface for standing balance challenge during intervention**

For intervention, two different compliant surfaces were used to provide a standing balance challenge. All participants started with the 6-inch sponge used during the initial assessment. Progression was made to air bladder or Swiss disk (J/fit, Vancouver, Canada). An air bladder is a circular 12-inch diameter rubber disk, filled with air. Progression was made if the participant no longer felt challenged in standing balance while dual-tasking on the 6-inch sponge. This was a self-reported challenge to standing balance.

#### **4.9.7: Treadmill for intervention**

A standard treadmill without the pressure mapping system was used for the study. We used Model T635 treadmill from SportsArt Fitness limited (Mukilteo, Washington) with a belt width of 22 inches and the total belt length of 61 inches. An overhead safety harness without body weight support was worn by participants to ensure safety during treadmill walking. Participants were allowed to hold the side railing during initial treatment sessions, although the objective was to progress the participants to walking without support if possible. Increasing treadmill speed was not the object of DT treadmill training.

#### **4.9.8: 6 minutes walk test**

Six minutes walk test (6MWT) was conducted on a 30m long straight corridor on the 3<sup>rd</sup> floor, Rehabilitation hospital, 800 Sherbrook Ave, Winnipeg, MB. Cones were placed at both ends. The participant was asked to walk at their regular pace for 6 minutes in the 30m path and turn from the cones. Total distance covered in 6 minutes was documented at Pre and Post assessment. A Casio stopwatch was used to keep track of 6 minutes. Participants was allowed to take rest if required. This method has been shown to be valid and reliable in individuals with PD (157).

#### **4.9.9: Overground Walking Speed Assessment**

Overground walking speed was calculated pre and post assessment over 25m. Participants was asked to walk in a 30m long straight corridor at 3<sup>rd</sup> floor, Rehabilitation Hospital, 800 Sherbrook Ave, Winnipeg, MB. Walking speed was evaluated over middle 25 m of 30m walking track. A Casio stopwatch was used to keep a record of time taken to cover 25 m. Overground walking speed evaluation over short distance is valid and reliable outcome measure in individuals with PD (158).

#### **4.9.10: Screening Tool and Questionnaires**

##### ***Unified Parkinson Disease Rating Scale (UPDRS):***

The Unified Parkinson Disease Rating Scale has been the gold standard scale to measure the severity of PD in an individual (157). It also helps in the staging of the individual in PD in stage 1-5 based on Hoehn and Yahr scale. UPDRS is a 5-point scale (0 to 4) in which zero denotes the absence of impairment and 4 denotes high severity of impairment. Higher the score more is the disease severity. For this study, we calculated the scores for part 3 (motor examination) during both pre and post-assessment. UPDRS has shown excellent test-retest reliability with ICC of 0.90 for part 3 with PD population (159,160).

##### ***Montreal Cognitive Assessment (MoCA):***

The MoCA is one of the most widely used screening tools to assess any significant cognitive impairment in participants with PD. It consists of multiple cognitive tests like TMT-B, VF, short term memory test and digit span test. MoCA has a total score of 30 points, and as a part of inclusion criteria, a participant were expected to score more than 26, to be rated as non – MCI PD (152).

#### **4.10 Study Procedure**

All components of the research study were conducted at the research laboratory of Dr. Tony Szturm at RR345, Rehabilitation Hospital, 800 Sherbrook Ave, Winnipeg, MB. The study consisted of a Pre-assessment, ten weeks of the intervention program with GTP and post-assessment. A semi-structured interview was conducted after post-assessment of all participants by the study investigator to determine the experience of participants with using GTP.

## **Assessment Protocol**

**1. Baseline Assessment:** Baseline assessment lasted for approximately 90 minutes.

All participants were provided with a brief explanation of the research study and the tasks that they would be required to perform. Informed consent and inclusion screening measures were explained in detail. To check for walking capabilities, the participant was asked to walk in a straight hallway of 100 m without assistance. As a part of the screening to meet the inclusion criteria of the study, the cognitive assessment was done using the Montreal Cognitive Assessment (MoCA) scale. Participants scoring less than 26 were not included in the study. After responding to all questions, the participants had regarding the study and study procedures, the participant was asked to sign the statement of consent.

A brief demonstration of assessment and intervention methodology was shown to the participant. When the participant was ready to start the study protocol, the participant was asked to sit on a standard chair, placed at 2 meters from 32-inch LG LCG TV monitor attached to computer substation as described above. Upon participant approval, the lightweight plastic helmet with the wireless optical mouse placed on top was placed on their head.

There were three testing positions for each participant, namely sitting, standing on sponge surface and treadmill walking.

**Sitting Position:** A standard chair with seat cushion, backrest and bilateral armrest was placed on the centre of the treadmill. Participants were asked to sit comfortably on a chair with back straight and supported, both arms on the arm rests and feet flat on the treadmill floor. The distance of TV screen from centre of the treadmill was approximately two meters. The height of TV screen was adjusted to minimise excessive neck extension of the participant. Participant then

performed the VMT task in both horizontal and vertical settings for 30 seconds each. A 1-2 minutes rest was given to the participant in between two tasks. Then the VCG task was performed. Both VCG1 and VCG2 task were performed for 45 seconds each, with 1-2 minutes rest in between. The performance files were coded and stored in the computer hard disk.

**Standing on the unstable surface:** A standard sponge with mentioned characteristics was placed in between the side rails of the treadmill with a wooden block of mentioned dimensions on top. The viewing distance of TV screen from sponge was approximately two meters. An FSA pressure mat was placed on top of the sponge. The participant was made aware of side rails and front handles of the treadmill, which participant could hold on to in case they lose balance on the sponge. A 6-inch sponge was selected based on the participant's ability to balance on without support. The same sponge was used at baseline and after the intervention. Participants were expected to complete all procedures without any external support. A therapist was always standing behind the participant to check for any adverse event of fall.

Before the VCG and VMT tasks, participants were requested to stand on the sponge under two conditions, eyes open (EO) and then eyes closed (EC). Participant's body sway under both conditions were recorded for 30 seconds each. The participant was then made to rest for 2-3 minutes on a comfortable chair.

Following the EO and EC task, participants again stepped on the same sponge and performed the VCG and VMT task. Participants performed both the horizontal and vertical VMT task for 30 seconds each and both the VCG1 and VCG2 for 45 seconds each while standing on the sponge surface without any support. 1-2 minutes of rest was offered to participants in between tasks.

**Treadmill Walking:** Only for this task, an overhead safety harness was provided to the participants. The purpose of the safety harness was to prevent any falls or any undesirable event during treadmill walking and performing the assessment tasks. The distance of TV screen from centre of treadmill was approximately two meters.

Participants were allowed to practice walking on the treadmill for 5-10 minutes and become familiar with treadmill walking. Treadmill speed was adjusted to the comfort level of the participant. After the participant was comfortable on the treadmill, participant's walk-only (WO) data was collected for 60 seconds. The participant was instructed to look at the computer screen in front and requested to not to talk during data collection of WO task. After this, the participant was allowed to rest for 2-3 minutes. Following rest, participants performed the VCG1 and VCG2 task for 60 seconds each and the horizontal VMT task for 45 seconds, while walking on a treadmill at the same speed as set during WO task. During all data collection on the treadmill, participants was requested to walk unsupported.

Upon completion of testing, participants rested for 3-5 minutes. After rest, the Unified Parkinson Disease Rating Scale (UPDRS) was administered. For this study, we computed part 1-3 of UPDRS.

Assessment of 6MWT and overground walking speed was done on the day of a first treatment session to control for fatigue from assessment in one single day.





*i) Sitting Position*



*ii) Sponge standing*



*iii) Treadmill walking*

*Figure 3: Sitting, Standing and treadmill walking positions for assessment at baseline and post intervention*

## **2. Intervention Protocol**

The intervention lasted for ten weeks, two times every week, making a total of 20 intervention sessions. Participants wore the plastic helmet having the wireless motion mouse secured by Velcro and connected to the computer sub-station. Participants were asked to play the commercial computer games as a part of DT intervention under two different physical conditions of standing in compliant surface and walking on a treadmill. Each session lasted for 45 minutes and included the following:

1. Five minutes of warm-up exercise consisting of large rhythmical movements of forward, backward and sideward stepping and head movements. The was similar to LVST large movements.
2. Fifteen minutes of the dynamic core standing balance training on 6 inch or 8 inch sponge while performing commercial computer games. The difficulty levels of games and the compliant surface were progressed based on the participant's performance and

documented. This acts as a warmup to participants to get familiar with different commercial computer games and how they will play the games by head rotations.

3. Twenty-five minutes of treadmill walking while performing DT cognitive tasks. Before playing the computer games, participants normally walked on the treadmill without any support for 2-3 minutes to familiarize to treadmill walking. The difficulty levels of commercial games and treadmill speed were progressed based on participant's performance and documented. A safety harness was worn throughout the treadmill walking task for the safety of participants. Also, participants were allowed to take as many rests they required during treadmill walking.



*i) Sponge Standing*



*ii) Treadmill walking*

*Figure 4: Participants playing computer games in standing and treadmill walking*

3. **Post-Assessment:** Post assessment was scheduled within one week after completion of 10 weeks of intervention with GTP. Post-assessment was performed in the same sequence as that of pre-assessment for every participant.
4. **Semi-structured Interview:** Upon completion of the post-assessment, all participants underwent a short interview describing their experience with GTP program. The intent of this embedded qualitative component was to gain insights to the experience of participants with GTP. There has been an increase in use of qualitative methods to evaluate experience of and gather view points of health care recipients, to better evaluate an intervention (161,162). Various qualitative studies have been done with individuals with PD with an intent to understand their experience with a new exercise program and better design the program (163,164).

The interviews were conducted in a small closed room with table and chairs. A semi-structured format of interview was used with five support questions and prompts will be provided to extract the information if needed (165) . Five support questions were used to explore the experience of participants:

- 1) When you agreed to participate, how did you hope you would benefit from the therapy program?
- 2) Were there things about the game or exercise program you liked and things you did not like?
- 3) What did you think about the computer games that you were asked to play? Did you enjoy the game? Were there games which you did not enjoy?
- 4) Did you feel that this therapy program helped you?
- 5) If you were provided with the right settings, would you continue with these exercises?

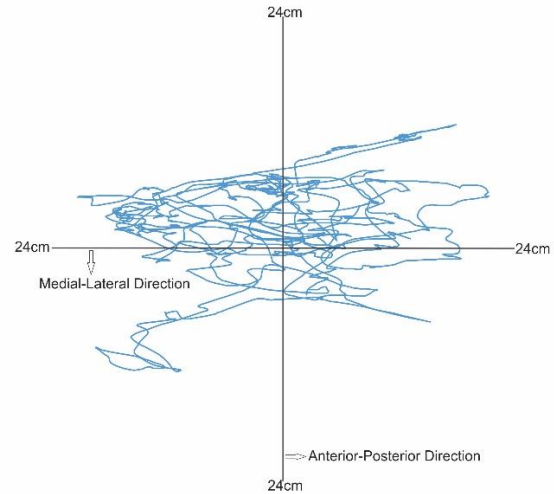
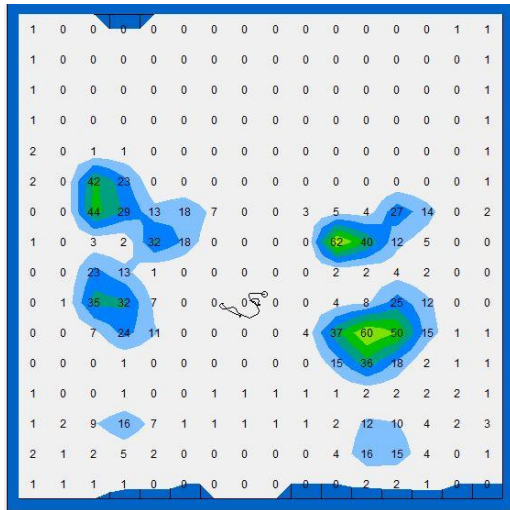
All the interviews were audio recorded with help of an audio recorder. These recordings were backed up with the research data. These audio recording were transcribed into a written format by a research assistant.

The post-intervention assessment of overground walking speed and 6MWT was performed on the last intervention day. After complete DT assessment, participants were allowed to rest for 3-5 minutes and then UPDRS was administered.

#### **4.11 Data Quantification**

- **Balance Assessment**

The balance FSA pressure mat recorded the centre of pressure (COP) displacement in anterior-posterior (AP) and medial-lateral (ML) direction. The displacements were quantified for root mean square (RMS) amplitude values of total COP displacement in both AP and ML direction. A lower RMS amplitude value indicated reduced body sway and better standing balance (146).



i) FSA Pressure Mat Recording Balance Data

ii) COP Excursion during Standing

*Figure 5: Standing balance data collection recording and raw COP Signals*

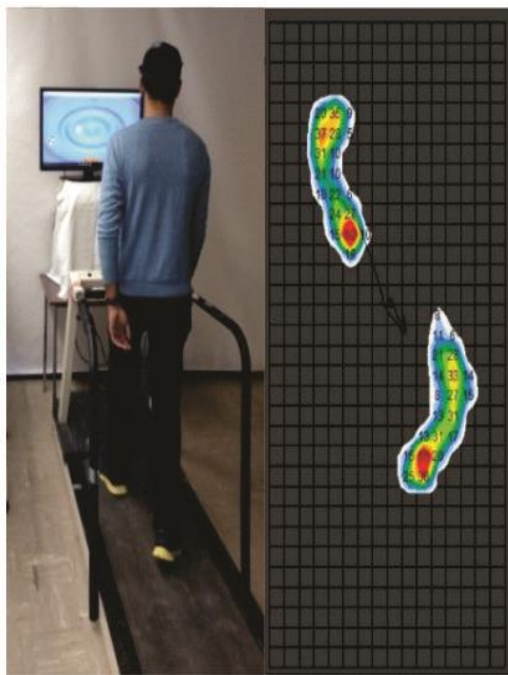
### • Gait Assessment

A standard treadmill (Sports Art Fitness Ltd, Mukilteo, Washington) nested with a pressure mapping carpet (Vista Medicals Ltd., Winnipeg, Manitoba) was used. Participants walked on this treadmill at their desired speed and the COP displacement in AP and ML direction was recorded for approximately 30-35 steps. The COP displacement data was analyzed through specialized MATLAB scripts (Math Work, MA) and the following spatiotemporal gait variables was obtained:

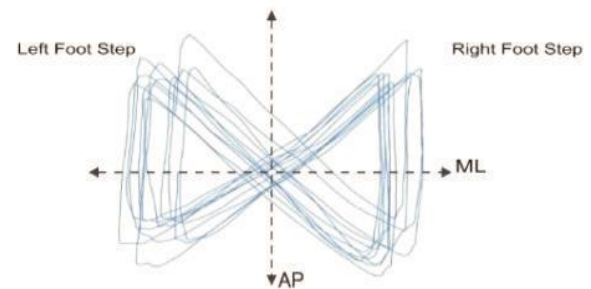
1. Average Step length
2. Average Step time and Stride time
3. Coefficient of Variation (COV) of step length, COV of step time and swing time.
4. COV of AP and ML footstep drifting on the treadmill belt.
5. Entropy measures in ML and AP direction.

These gait variables have been widely used by many studies to compute gait stability in PD and have shown excellent test-retest reliability and convergent validity (166,167).

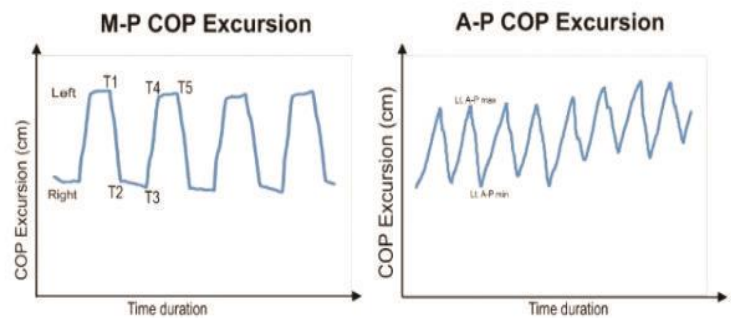
## Treadmill instrumented with a pressure mapping system



Pressure Mat Recording While Walking Over Treadmill



Scatter Plot Depicting AP and ML Excursion During Treadmill Walking



Gait outcome measures from AP and ML COP data

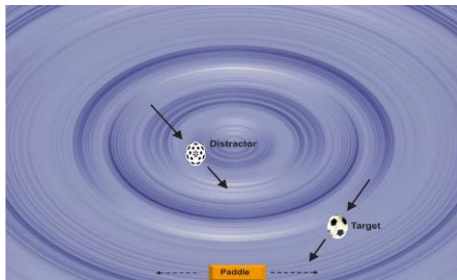
1. T2-T3 : Rt. Single Support time (ms)
2. T4-T5: Rt. Swing time (ms)
3. T1-T5: Rt. Stride time (ms)
4. Lt. A-P max - Lt. A-P min. : Rt. step length (cm)

Figure 6: Gait Data collection and raw COP signals during waking

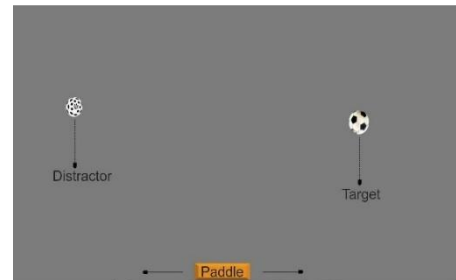
- **Visuo-Spatial Search (VCG) task analysis**

The computer software provided a detailed report card at the end of both VCG1 and VCG2 task. The report card provided a quantified measure of various outcome measures and provide a detailed graph of movement trajectories (145,146). The outcome measures of interest in the present research study were:

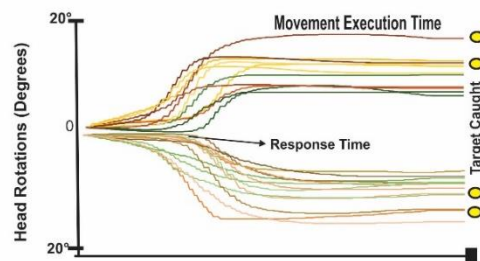
1. **Average Response Time (sec):** The average time is taken by a participant to initiate the movement on the paddle in the response of target (Soccer ball) appearance on screen.
2. **Movement Variation (percentage):** The variability in each paddle movement initiated by neck rotations to catch the target object.
3. **Success Rate (percentage):** Measure of a number of successful catches of target objects by the participant on paddle by neck rotations.



i)VCG-1



ii)VCG-2



iii) Raw Game Data

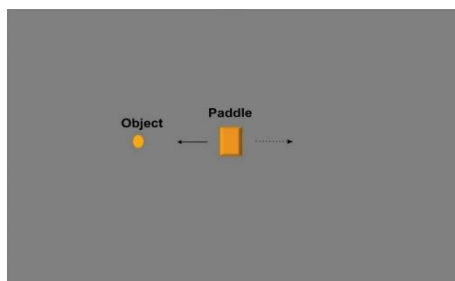
*Figure 7: VCG-1 and VCG-2 task display and raw game data*



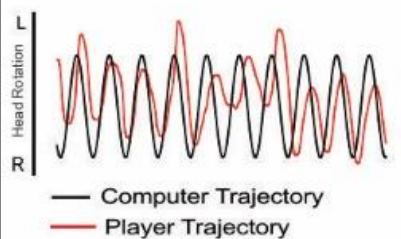
- **Visuomotor Tracking (VMT) task:**

The computer software developed a detailed report card after both VMT horizontal and vertical task. The report contained two sine wave graphs and quantified values of participant performance on tasks. There was one black coloured sine graph depicting the computer-controlled sphere movement (reference graphs) and overlapping this graph was the participant movements on the red colour graph. The outcome measures of interest were:

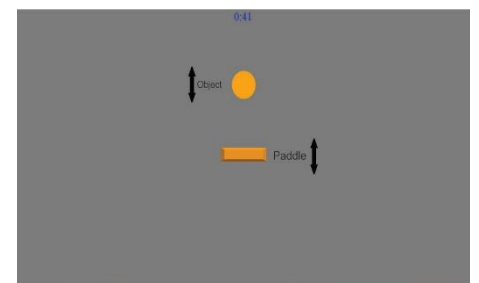
1. Total Residual Error (Percentage): The percentage of variation between participant-controlled paddle to-and-fro movements and computer-controlled sphere to-and-fro movements.
2. COV Amplitude Variation (Percentage): The variation in amplitude of movement between a participant-controlled rectangle and computer-controlled sphere. During sitting and sponge standing task, approximately 15 sine waves were analyzed for amplitude variation, and during treadmill walking, approximately 22 sine waves were analyzed.



i) VMT-H



ii) Tracking Raw Data



iii) VMT-V

*Figure 8: VMT Horizontal and Vertical task and raw game data*



Thesis research by Mayank Bhatt and Tony Szturm, 2018 (97) at University of Manitoba, evaluated the test-retest reliability of all standing balance, gait, visuomotor and visuospatial executive cognitive assessments. All outcome measures reported high to moderate test-retest reliability in patients with PD.

## **Chapter 5: Analysis**

### **5.1 Feasibility Analysis**

Feasibility of this GTP program were evaluated using the model proposed by Goldsmith et al 2010 (168) . According to this model, feasibility assessment of study protocol requires testing of three domains namely; study procedures, study resources used, and study data management. Evaluation of study procedures involve assessing for recruitment rate, dropout rate, feasibility of recruitment with eligibility criteria and compliance of participants to the program. Evaluation of study resource materials involve evaluating time taken to complete the study related paperwork like consent form and questionnaires, baseline and post intervention assessment, safety of study protocol, technical breakdown and troubleshooting incidences. Evaluation of study data management involve assessing data collection, storage back up process, and developing excels, other supporting documents for assessing and management of study results

### **5.2 Qualitative Interview Analysis**

The responses from all fifteen participants were analysed using interpretive descriptive method (169–171). A blinded research assistant will transcribe audio recordings of interviewed participants. The analysis of transcripts was done by the two study investigators. Narrative summary of transcripts was sent to all participants by electronic mail for trustworthiness. All transcripts were then coded depicting experience of participants with GTP program. Similar codes were then categorised to form defining themes. Direct quotes representing the themes were used to describe the data. A narrative summary was made explaining the experience of participants with GTP program.

### **5.3 Quantitative Analysis**

The aim of quantitative analysis was to estimate the treatment effect size on all cognitive, standing balance and spatiotemporal gait outcome measures. Normality of data was evaluated by the Shapiro-Wilk test (172). A paired t-test was conducted on all parametric variables to obtain the t-value. Effect size was calculated in form of Cohen's 'd' by dividing the t-value with square root of number of participants (173). For non-parametric variables, the Wilcoxon's signed rank test was done to obtain the Z-value. Effect size was calculated by dividing Z-value with the square root of number of participants (173).

Effect size and variance obtained from this study data was used to evaluate the sample size outcome variables of interest. Outcome variables of interest for sample size calculation were average step length, average step time, COV step length, COV step time, ML entropy, ML COP RMS value, average response time and amplitude variation. These outcome measures were selected based on improvement reported in mentioned variables by previous studies of DT training in individuals with PD.

Sample size calculation was done by using SAS version 9.1 sample size calculation extension and G-power of sample size calculation (174).

## **Chapter 6: Results**

### **6.1 Feasibility analysis**

#### **6.1.1 Study Procedures**

The recruitment of participants for the study was initiated in November 2018 and lasted until April 2019. A total of 20 participants were screened for the study during this period. One participant was not eligible for the study due to a progressed PD stage. Four participants who came for screening were not able to commit to coming for intervention twice a week for ten weeks because of their busy schedule. The study was completed with 15 participants, reaching 75% of the proposed target 20. The recruitment ended after 15 participants due to time constraints. The recruitment rate was 2.5 participants per month. All 15 participants attended all assessments and intervention sessions, twice a week, for ten weeks. With 75% recruitment in 6 months, study procedures were found to be highly feasible with recruitment. The inclusion and exclusion criteria did not pose any difficulty for recruitment.

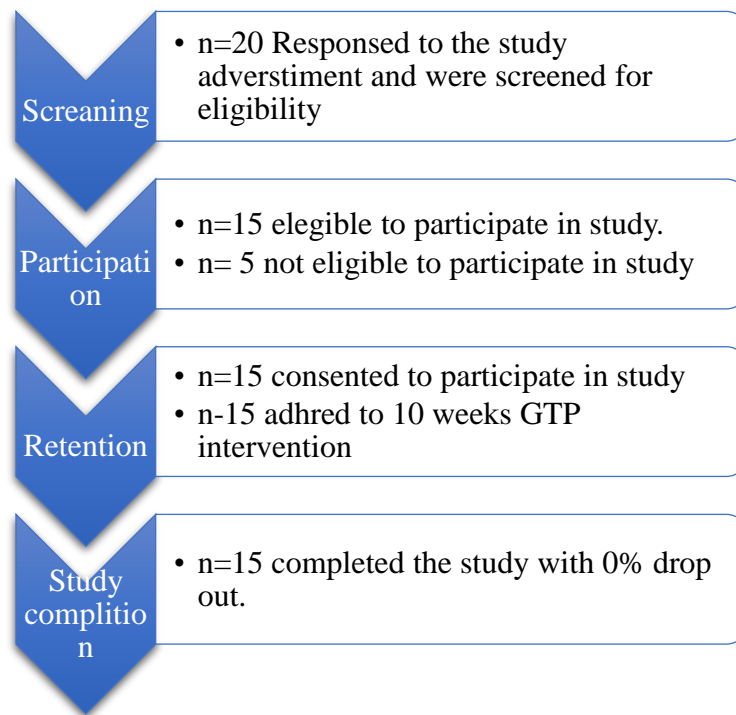
Table 1 presents the demographics of 15 participants that took part in the study. Out of 15 participants, 13 were males and two females with a mean age of 68.11 ( $\pm 5.2$ ) years. All participants had been clinically diagnosed with PD prior to the study. Of these 15 participants, 10 were stage two PD, and five were at stage 3 PD of the Hoehn and Yahr scale. The average UPDRS motor component score was 29.2 ( $\pm 8.9$ ) at baseline, which improved to 28.4 ( $\pm 10.6$ ) after ten weeks of GTP intervention. All participants met the inclusion requirement of MoCA with an average score of 28.7 ( $\pm 1.03$ ).

**Table 1: Participant's Demographics**

<b>Number of Participants</b>	15
<b>Age Median, IQR (Years)</b>	69, 7
<b>Age Mean <math>\pm</math> SD (Years)</b>	68.11 $\pm$ 5.2
<b>Male/Female</b>	13/2
<b>Hoehn and Yahr PD Stage 2/3</b>	10/5
<b>Average Hoehn and Yahr PD Stage <math>\pm</math> SD</b>	2.3 $\pm$ 0.4
<b>Average MoCA score <math>\pm</math> SD</b>	28.7 $\pm$ 1.03
<b>Disease Duration Median, IQR (Years)</b>	7, 8.5

*IQR-interquartile range, SD- standard deviation, PD-Parkinson disease, MoCA-Montreal Cognitive Assessment*

**Figure 9: Recruitment Flow Diagram**



### **6.1.2 Study Resources**

Participants were able to understand and complete the informed consent in 15-20 minutes. It took ten minutes to administer motor section of UPDRS and five minutes to administer MoCA. The outcome assessor requires five minutes each to complete scoring of UPDRS part three as well as the MoCA. The assessment took 30-45 minutes including rest for every participant. Each intervention session lasted for approximately 45-50 minutes. No participant reported objection to any time commitment requirements during any phase of the study.

The GTP program requires the use of various sensor systems to record spatiotemporal gait variables and cognitive performance while walking on the treadmill such as the pressure sensing mat, wireless mouse and embedded software. The pressure sensing mat was not required during DT walking treatment. There was no technical breakdown reported throughout the study during the assessment, or during intervention. There was no need for any troubleshooting steps related to the use of the internet and online gaming. The wireless motion mouse used reported no breakdown of wireless sensors or any other operational malfunction. All resources used in the study were hence found to be highly feasible.

### **6.1.3 Study Management**

It was easy to maintain the study data in hard and soft copies of all study related forms. All participant data was coded to numbers, and a master sheet with participant name and code was kept in one password protected computer. Electronic transcripts of all audio recorded interviews were created and stored on the same computer. An external hard drive was required to back up all study data. Overall, it was highly feasible to manage the study.

## **6.2: Experience of participants with GTP**

All fifteen participants that completed the study were interviewed regarding their experiences with the program. Interviews were conducted in a quiet room after the post-assessment and were audio recorded. The audio recordings of the interviews were later transcribed into a word document for analysis. All transcripts were anonymized with participant codes. An inductive approach for qualitative data analysis was used. As a part of the analysis, transcripts were coded according to significant statements for the program and later, similar codes were grouped into categories. From related categories, five major themes emerged to summarise the experience of participants with GTP program.

Overall, all participant had a positive experience with the GTP program. Eight out of fifteen participants felt the GTP program had a well-designed protocol that challenged their gait and standing balance in a similar sense as that in the real world. A beneficial effect of the program was observed as 13 of 15 participants who reported improvement in both their standing balance and gait. Self-perceived improvement from participants is considered essential feedback for any new intervention as it is directly related to compliance of participants to a program. It was also seen as the GTP program beholds a favourable future in community centres and various supervised fitness centres because 13 of 15 participants also reported that they would like to continue with GTP if necessary, equipment is provided.

The use of digital media in the form of commercial computer games helped in maintaining compliance of participants with the program. Twelve of the 15 participants appreciated the use of these games and found it as a factor that encouraged their compliance for ten weeks. Some participants also provided valuable feedback in regards to the place of intervention and digital media used in the study that can further improve the program. Most fundamentally, participants

wanted some immediate feedback and target oriented gaming so that they could see if they were improving in games on an everyday basis.

Table 2 presents the demographic information such as age, gender, stage of PD according to Hohen and yahr scale and time since first diagnosis of PD for each participant. Participant's personal information has been coded to numeric numbers and response by each participant has been presented.



**Table2: Anonymized demographic information of each participant for the interviews**

<b>Participant Code</b>	<b>Age</b>	<b>Gender</b>	<b>Stage</b>	<b>Time since diagnosis</b>
001	69	Male	2	7 years
002	69	Male	2	3 years
003	76	Male	2	4 years
004	66	Male	2	13 years
005	71	Female	2	8 years
006	72	Male	2	3 years
007	57	Male	3	11 years
008	71	Male	3	5 years
009	77	Male	3	14 years
010	69	Male	2	20 years
011	73	Female	2	15 years
012	66	Male	2	3 years
013	63	Male	2	5 years
014	62	Male	2	4 years
015	67	Male	3	4 years

Following are the five themes that emerged and there supporting statements:

**1. Challenging Program:**

*Participant 001: "It's a good physical and mental workout."*

*Participant 002: "I enjoyed all the games. Some were more challenging for me than others"*

*Participant 004: "It became a challenge and I wanted to better myself from the week before and I wanted to get better."*

*Participant 005: "It was a pretty challenging task to walk on the treadmill and balance at the same time."*

*Participant 006: "It's challenging, a real challenge and I guess the other thing is I realize what I am doing isn't really going to help me any outside of my balance and surface area, but the program is going to help me move down the road and that appealed to me."*

*Participant 008: "I thought he program was entertaining and challenging for me."*

*Participant 009: "The rest of the games were challenging and fun to do."*

*Participant 013: "I didn't like the sponge or whatever that is made my foot or muscle sore whatever but other than that it was fine. It was a challenge."*

**2. Self-perceived Improvement in Gait and balance:**

*Participant 001: "I noticed that my balance improved dramatically"*

*Participant 002: "I feel the program has helped me. It has helped with my self-awareness."*

*Participant 002: "Feel that it helped me with my balance, helped me with my eye hand foot coordination."*

*Participant 003: "I got better as it went along so that felt good."*

*Participant 004: "Yes. I did. From stamina to balance to fatigue improvement to steadying your head."*

*Participant 006: "Oh yeah, I do feel program improved my balance. Since I was diagnosed and taken in exercising."*

*Participant 006: "I guess my motivation is getting better a little bit at a time."*

*Participant 008: "In some respects, yes program did help me. It has opened my eyes in terms of what it is that I need to think about when I am in a balance situation."*

*Participant 009: "Did program improve my walk? I will say yes."*

*Participant 010: "I believe it improved my balance issues somewhat"*

*Participant 010: "Yes, program di helped me to improve balance and walking"*

*Participant 011: "Yeah, well, I guess just the knowledge that I can beat a little bit. I can do something with my maneuvering with things and picking them up."*

*Participant 012: "I think it increased my physical fitness. It increased my balance too. Improved is a better word than increased."*

*Participant 013: "Yes, program did helped me improve walking."*

*Participant 013: "Most probably helped me in maintaining my balance. Specially notice the difference on the foams. Like over the course, the different games we played on the foam, I found myself steadier."*

*Participant 014: “Yeah. I talked to my son-in-law on Friday when we were playing squash and it did improve my reaction time. I saw a difference in my squash game.”*

*Participant 015: “Yes. I think I told you. It’s the 8th week. It’s hard for me to quantify, but I think it has been a benefit, yeah.”*

### **3. Future Compliance to the Program**

*Participant 001: “Yes, I would like to continue with program”*

*Participant 002: “Yes, for sure, I plan to continue this at home.”*

*Participant 003: “Oh yeah. I plan to. I think they are helpful and probably essential.”*

*Participant 005: “Yes, I would. Yeah, because of all the things I’ve found, this one got to me in a certain way.”*

*Participant 007: “I think I would take program if available.”*

*Participant 008: “Yes, I will take the program if I am not too busy.”*

*Participant 009: “Sure, I will like to take the program.”*

*Participant 010: “Yes, I will continue the program If settings provided”*

*Participant 012: “Definitely, yes. It was all fun and helped me”*

*Participant 013 “Yes, I would like to continue with exercise program”*

*Participant 014: “Yes, I would continue with program if available”*

*Participant 014: “I think I would. Like you can get a treadmill at home”*

*Participant 015: “Absolutely will continue with program”*

#### **4. Feedback to Digital Media Used and Compliance to the Program**

*Participant 001: “Starting with a small thickness sponge for example so that I wasn’t overwhelmed at any point. I think that worked out well.”*

*Participant 002: “I liked all the games.”*

*Participant 003: “I actually enjoyed everything”*

*Participant 004: “Once I started this program, I am much more positive about it.”*

*Participant 005: “I like the fact that it is fun to do actually.”*

*Participant 007 “There were a variety of games and if one was too difficult, we could skip it and go on to something else.”*

*Participant 009: “The games I didn’t enjoy, they were hard I guess, I might say. At the end, though I think you get to a point where you learn to like them.”*

*Participant 010: “I enjoyed everything. I had no problem. Certainly, I was better at it, the more I used it.”*

*Participant 011: “I enjoyed the games. There were some I enjoyed more than other games. I didn’t not like any of the games. I actually enjoyed the ones that involved using several facilities.”*

*Participant 012: “I enjoyed them all. Some of them, I was not very good at but some others I was starting to learn how to do it.”*

*Participant 013: “Well, all the games were ok. Some games I liked more than other games. But I don’t that has anything to do with the intended results, just some were more fun than others especially the ones you are better at.”*

*Participant 014: “I pretty much enjoyed everything. Like I am not computer savvy on some of them but it was a little mindboggling for me at times. But, other than that everything was good.”*

*Participant 015: “Overall, it was enjoyable and good test allowing me to multitask”*

## **5. Feedback and Suggestions**

*Participant 002: “What I found is I had frustration levels where one day I could do a certain game and the next time I came, for whatever reason, I couldn’t manipulate or see the ball or whatever game I was playing.”*

*Participant 005: “I mean I know the importance is not how I did it on the gaming, it’s how I did on the balance and walking. But to keep up my motivation, I need some sort of visual proof that I was doing better.”*

*Participant 008: “Sometimes I think when I was playing the games, I could see I was in a little bit of control but a lot of it was just luck or a draw if I hit. So I didn’t really know how much I was benefiting by it.”*

*Participant 010: “I didn’t like the location. It’s too far from my home. No parking. Not very easy to get to somebody.”*

### **6.3: Estimate treatment effect size and sample size calculation**

The normality of data was tested with the Shapiro-Wilk test. Out of 15 dependent variables tested, 13 were normally distributed. The two exceptions were COV step time and COV ML drift. For all normally distributed data, a paired t-test was used to assess the difference pre to post GTP intervention. The effect size was calculated as Cohen's  $d$  (173). For non – normally distributed data, the Wilcoxon-Signed rank test was used to assess the difference pre to post GTP intervention.

Table 3 represents pre and post mean, SD, t-value, p-value and effect sizes of the RMS COP displacement in AP and ML direction. There was a significant reduction in the magnitude of ML-COP displacement for all ST and DT conditions. There was a significant reduction in the magnitude of AP-COP displacement for only two tested conditions, namely, eyes open standing (ST) and VMTV tracking task (DT). Large effects sizes were observed for the improvement in ML-COP displacement for eyes open standing and VMTH condition. Medium effect sizes were observed for all other conditions that demonstrated significant improvement.

**Table 3: Mean, SD, t-value, effect size, and p-value of RMS measure of COP displacement before and after intervention**

Condition (Sponge Standing)	Baseline Mean (SD)	POST Mean (SD)	t-value, p-value	Effect Size 'd'
<b>RMS ML</b>				
<b>Eyes Open</b>	3.3 (2.2)	0.5 (0.3)	4.3, <b>0.0004</b>	>1
<b>Eyes Closed</b>	3.13 (2.5)	1.1(1.0)	2.814, <b>0.006</b>	0.72
<b>Standing + VCG1</b>	11.0 (12.1)	6.02(9.4)	1.806, <b>0.04</b>	0.5
<b>Standing + VCG2</b>	8.2 (10.8)	4.18 (7.11)	1.865, <b>0.001</b>	0.5
<b>Standing + VMH</b>	4.09 (2.8)	0.9 (0.7)	3.822, <b>0.001</b>	>1
<b>Standing + VMV</b>	3.22 (2.19)	1.38 (1.6)	2.842, <b>0.006</b>	0.73
<b>RMS AP</b>				
<b>Eyes Open</b>	2.1 (1.4)	1.0(1.2)	1.8, <b>0.04</b>	0.52
<b>Eyes Closed</b>	1.6 (1.0)	1.2 (1.2)	1.3,0.1	0.35
<b>Standing + VCG1</b>	1.7 90.7)	2.0 (2.0)	0.7,0.2	0.2
<b>Standing + VCG2</b>	1.8 (0.5)	1.3 (1.0)	1.387,0.09	0.37
<b>Standing + VMH</b>	2.0(0.7)	1.7(1.7)	0.3,0.35	0.1
<b>Standing + VMV</b>	2.3(1.6)	1.2(1.3)	1.752, <b>0.05</b>	0.46

*SD- Standard Deviation, VMH- Visuo-Motor Tracking Horizontal, VMV- Visuomotor Tracking Vertical, VCG- Visuocognitive Game, RMS- Root mean Square, AP-Anterior Posterior, ML- Medial Lateral*

Table 4 presents group means (SD), statistical results and effect size for average step length and average step time during walk-only (ST walking) and DT walking. A significant increase in average step length and average step time was observed during walk-only (ST walking) and while playing the VCG2 game (DT walking 2). A significant increase in average step time was also observed while playing the VCG1 game (DT Walking 1). Medium effect sizes were seen in all improvements.



**Table 4 Mean, SD, t-value, effect size, and p-value of average Gait measures before and after intervention**

Condition	Baseline Mean (SD)	POST Mean (SD)	t-value, p-value	Effect Size 'd'
<b>Average Step Length (cm)</b>				
<b>Normal Walking</b>	45.4 (21.2)	51.9 (23.9)	1.9, <b>0.03</b>	0.53
<b>Walking + VMT</b>	48.5 (20)	49.4 (20.2)	0.55,0.29	0.14
<b>Walking +VCG1</b>	49.4 (21.2)	51.6 (21.9)	0.86,0.2	0.22
<b>Walking + VCG2</b>	45 (22.3)	49.6 (20.9)	1.7, <b>0.05</b>	0.5
<b>Average Step Time (sec)</b>				
<b>Normal Walking</b>	0.6 (0.1)	0.7 (0.1)	2.6, <b>0.008</b>	0.7
<b>Walking + VMT</b>	0.6 (0.1)	0.7 (0.1)	0.9,0.19	0.23
<b>Walking +VCG1</b>	0.6 (0.09)	0.7 (0.09)	2.2, <b>0.02</b>	0.6
<b>Walking + VCG2</b>	0.6 (0.09)	0.7 (0.11)	2.4, <b>0.01</b>	0.6

*SD- Standard Deviation, VMT- Visuo-Motor Tracking, VCG- Visuocognitive Game, cm- centimeters, sec- seconds*

Table 5 presents group means (SD), statistical results and effect sizes for normally distributed gait variability measures and group median (IQR), statistical results, and effect sizes for non-normally distributed data. A significant reduction in COV step length, COV step time, and COV AP drift were observed in the walk-only task (ST walking). A significant reduction in COV step length, COV AP drift, and COV ML drift were observed while VMTH task and walking (DT walking). A significant reduction was observed in COV ML drift while walking and performing VCG1 task (DT walking). A significant reduction was observed in COV step length while walking and performing VCG2 task (DT walking). All significant improvements in ST and DT walking showed a medium to large effect sizes.

**Table 5** Mean, SD, t-value, effect size, and p-value of Gait variability measures before and after intervention

Parametric Variables	Baseline Mean (SD)	POST Mean (SD)	t-value, p-value	Effect Size 'd'
<b>COV Step Length (%)</b>				
<b>Normal Walking</b>	23.4 (16.9)	18.7 (12.7)	1.8, <b>0.03</b>	0.5
<b>Walking + VMT</b>	27.1 (16.6)	20.3 (11.1)	2.1, <b>0.02</b>	0.56
<b>Walking +VCG1</b>	27.2 (22.2)	23.7 (15.7)	1.4,0.08	0.41
<b>Walking + VCG2</b>	29.3 (19.6)	24 (15.2)	2.3, <b>0.01</b>	0.6
<b>COV AP Drift (%)</b>				
<b>Normal Walking</b>	14.9 (20.6)	13.6 (14.7)	,0.24	0.25
<b>Walking + VMT</b>	12.8 (5.0)	10.3 (3.7)	2.0, <b>0.02</b>	0.54
<b>Walking +VCG1</b>	17.4 (6.1)	16.6 (5.6)	0.6,0.25	0.19
<b>Walking + VCG2</b>	15.2 (6.1)	13.3 (3.9)	1.1,0.15	0.3
Non-Parametric Variables	PRE Median (IQR)	POST Median (IOR)	z-value, p-value	Effect Size 'r'
<b>COV Step Time (%)</b>				
<b>Normal Walking</b>	6.0 (12.9)	4.5 (5.7)	3.1, <b>0.001</b>	0.8
<b>Walking + VMT</b>	5.6 (3.6)	4.4 (4.4)	1.1,0.12	0.3
<b>Walking +VCG1</b>	7.2 (6.2)	6.1 (7.0)	1,0.15	0.26
<b>Walking + VCG2</b>	5.4 (7.8)	6.0 (8.9)	0.7,0.24	0.2
<b>COV ML Drift</b>				
<b>Normal Walking</b>	5.4 (8.0)	5.3 (3.4)	1.1,0.12	0.33
<b>Walking + VMT</b>	12.8 (10.2)	8.4 (7.4)	2.7, <b>0.002</b>	0.74
<b>Walking +VCG1</b>	10.5 (13.3)	7.0 (6.3)	1.7, <b>0.03</b>	0.45
<b>Walking + VCG2</b>	7.0 (7.3)	9.05 (5.5)	0.9,0.2	0.25

*SD- Standard Deviation, COV- Coefficient of Variation, VMT- Visuo-Motor Tracking, VCG- Visuocognitive Game, AP- Anterior-Posterior, ML-Medial- Lateral, IQR- Interquartile Range*

Table 6 presents group means (SD), statistical results, and effect sizes for gait entropy measured in ML and AP directions. A significant reduction in ML entropy was observed while walking and performing VMTH and VCG1 tasks (DT walking). There was no significant improvement observed in AP entropy for any conditions. The significant improvements in ML entropy for two conditions showed medium effect sizes.

**Table 6** Mean, SD, t-value, effect size, and p-value of Gait Entropy measure before and after intervention

Condition	Baseline Mean (SD)	POST Mean (SD)	t-value, p-value	Effect Size 'd'
<b>Entropy ML</b>				
<b>Normal Walking</b>	0.08 (0.01)	0.07 (0.01)	1.09,0.15	0.3
<b>Walking + VMT</b>	0.09 (0.02)	0.08 (0.03)	2.2, <b>0.01</b>	0.61
<b>Walking +VCG1</b>	0.1 (0.01)	0.09(0.01)	1.9, <b>0.02</b>	0.51
<b>Walking + VCG2</b>	0.1 (0.01)	0.1 (0.01)	0.39,0.34	0.1
<b>Entropy AP</b>				
<b>Normal Walking</b>	0.12 (0.04)	0.11 (0.04)	0.7,0.25	0.3
<b>Walking + VMT</b>	0.13 (0.03)	0.12 (0.04)	1.07,0.15	0.5
<b>Walking +VCG1</b>	0.15 (0.03)	0.14 (0.03)	0.05,0.47	0.01
<b>Walking + VCG2</b>	0.15 (0.02)	0.15 (0.02)	1.3,0.09	0.36

*SD- Standard Deviation, VMT- Visuo-Motor Tracking, VCG- Visuocognitive Game, AP-Anterior Posterior, ML- Medial Lateral*

Table 7 presents group means (SD), statistical results, and effect sizes for VCG1 and VCG2 cognitive tasks during both ST and DT conditions. There was a significant increase in success rates for both VCG1 and VCG2 task performance in sitting (ST), while on the sponge (DT), and during walking (DT walking). A significant reduction in response time was observed for VCG1 task in sitting (ST), while standing on the sponge (DT), and during walking (DT walking). A significant reduction in response time was observed for the VCG2 task in sitting

(ST) and while walking (DT walking). A significant reduction in movement variation was observed for the VCG1 task only in sitting (ST). A significant reduction in movement variation was observed for VCG2 task in sitting (ST) and while standing on the sponge (DT). A medium to large effect size was observed for all improvements.

**Table 7 Mean, SD, t-value, p-value and effect size of VCG1 and VCG2 task outcome measures before and after intervention**

Task (Condition)	PRE Mean (SD)	POST Mean (SD)	t-value, p-value	Effect Size 'd'
<b>Success Rate (%)</b>				
VCG 1 (Sitting)	93.3 (10.9)	97.1 (8.6)	2.9, <b>0.005</b>	0.78
VCG 2 (Sitting)	83.7 (16.1)	91.6 (10.6)	3.2, <b>0.003</b>	0.84
VCG1 (Sponge)	92.8 (12.5)	97.5 (8.5)	2.9, <b>0.005</b>	0.75
VCG 2 (Sponge)	84.0(13.8)	93.8 (8.8)	3.7, <b>0.001</b>	0.89
VCG 1 (Treadmill)	83.4 (19.3)	89.7 (14.4)	2.7, <b>0.02</b>	0.72
VCG 2(Treadmill)	69.9 (24.3)	85.0 (15.3)	3.9, <b>0.001</b>	0.95
<b>Response Time (ms)</b>				
VCG 1 (Sitting)	576.7 (56.2)	527.7 (67.3)	2.8, <b>0.006</b>	0.76
VCG 2 (Sitting)	627.6 (66.0)	581.4 (63.2)	3.4, <b>0.002</b>	0.88
VCG1 (Sponge)	555.3 (101.8)	508.5 (72.4)	2.5, <b>0.01</b>	0.7
VCG 2 (Sponge)	602.6 (62.3)	5778.7 (53.2)	1.3,0.09	0.3
VCG 1 (Treadmill)	632.8 (82.9)	552.6 (60.0)	4.0, <b>0.0005</b>	0.99
VCG 2(Treadmill)	663.3 (63.1)	610.2 (63.7)	3.7, <b>0.001</b>	0.92
<b>Movement Variation (%)</b>				
VCG 1 (Sitting)	16.1 (2.6)	14.4 (2.1)	2.1, <b>0.02</b>	0.6
VCG 2 (Sitting)	18.7 (3.3)	16.5 (2.3)	3.73, <b>0.003</b>	0.75
VCG1 (Sponge)	16.1 (2.5)	15.5 (1.8)	1.2,0.11	0.34
VCG 2 (Sponge)	19.6 (3.2)	17.8 (3.02)	2.5, <b>0.01</b>	0.66
VCG 1 (Treadmill)	18.3 (3.6)	17.0 (3.17)	1.5,0.06	0.4
VCG 2(Treadmill)	22.05 (3.72)	20.6 (3.2)	1.4,0.09	0.4

*SD- Standard Deviation, VCG- Visuocognitive Game, ms- milliseconds*

Table 8 presents group means (SD), statistical results and effect sizes for the VMTH and VMTV cognitive tasks during both ST and DT conditions. There was a significant reduction in total residual error and amplitude variation was observed for all conditions with medium to large effect sizes.

**Table 8** Mean, SD, t-value, effect size, and p-value of VMTH and VMTV task outcome measures before and after intervention

<b>Task (Condition)</b>	<b>PRE Mean (SD)</b>	<b>POST Mean (SD)</b>	<b>t-value, p-value</b>	<b>Effect Size 'd'</b>
<b>Total Residual Error (%)</b>				
<b>VMH (Sitting)</b>	9.4 (1.7)	8.3 (1.8)	3.2, <b>0.003</b>	0.82
<b>VMV (Sitting)</b>	10.8 (3.8)	7.9 (2.2)	3.2, <b>0.003</b>	0.88
<b>VMH (Sponge)</b>	12.5 (4.03)	10.3 (4.2)	3.7, <b>0.001</b>	0.97
<b>VMV (Sponge)</b>	12.4 (3.8)	9.54 (2.7)	4.3, <b>0.0005</b>	>1
<b>VMH (Treadmill)</b>	12.8 (2.5)	10.0 (2.7)	4.4, <b>0.00001</b>	>1
<b>Amplitude Variation (%)</b>				
<b>VMH (Sitting)</b>	19 (9.9)	13.2 (4.9)	2.4, <b>0.01</b>	0.65
<b>VMV (Sitting)</b>	18.8 (6.7)	14.1 (4.5)	2.4, <b>0.01</b>	0.66
<b>VMH (Sponge)</b>	20.6 (5.9)	14.5 (4.6)	3.8, <b>0.001</b>	0.9
<b>VMV (Sponge)</b>	25.2 913)	13.7 (6.5)	3.5, <b>0.001</b>	0.88
<b>VMH (Treadmill)</b>	31.9 (6.8)	22.6 (8.4)	4.0, <b>0.001</b>	0.99

*SD- Standard Deviation, VMT- Visuo-Motor Tracking, VMH- Visuomotor Horizontal, VMV- Visuomotor Vertical*

Overground walking distance, as measured by 6MWT, also increased statistically from an average of 566.5m (97.6) to 607.5m (122.5) (t-value- 3.61, p-value- 0.002). Overground walking speed as measured over 25m also increased significantly from 1.5m/s (0.2) to 1.7m/s (0.2) (t-value- 3.65, p-value- 0.001). A large effect size was observed for both improvements.

Table 9 and 10 shows estimate effect sizes and calculated sample sizes required for the GTP group to perform an RCT. Table 9 presents the estimate effect sizes and sample size needed for all cognitive outcome measures of interest. Table 10 presents the estimate effect sizes and sample sizes required for gait and balance outcome measures of interest. Sample size calculation was only done if the effect size was medium or large by Cohen's effect size interpretation (175). The largest calculated sample size required is 40. Adding the 20% drop out rate evaluated during feasibility analysis of the study, the minimum sample size required for GTP group is 48.

**Table 9 Sample size for cognitive outcome measures based on effect size observed**

<b><u>CONDITION</u></b>	<b><u>SAMPLE SIZE</u></b>	<b><u>EFFECT SIZE</u></b>
<b>Response Time</b>		
Sitting	9	0.88
Sponge Standing	17	0.3
Walking	7	0.92
<b>Amplitude Variation</b>		
Sitting	16	0.65
Sponge Standing	10	0.9
Walking	8	0.99

**Table 10 Sample size for motor outcome measures based on effect size observed**

<b><u>CONDITION</u></b>	<b><u>SAMPLE SIZE</u></b>	<b><u>EFFECT SIZE</u></b>
<b>Average Step Length</b>		
Normal Walking	25	0.53
Walking with VMTH	NA	0.14
Walking with VCG2	40	0.50
<b>Average Step Time</b>		
Normal Walking	20	0.70
Walking with VMTH	NA	0.23
Walking with VCG2	16	0.6
<b>COV Step Length</b>		
Normal Walking	27	0.50
Walking with VMTH	21	0.56
Walking with VCG2	19	0.60
<b>COV Step Time</b>		
Normal Walking	14	0.80
Walking with VMTH	20	0.30
Walking with VCG2	NA	0.20
<b>Entropy ML</b>		
Normal Walking	NA	0.3
Walking with VMTH	27	0.61
Walking with VCG2	NA	0.10
<b>RMS ML</b>		
Eyes open standing	7	>1
Standing with VMTH	8	>1
Standing with VCG2	27	0.50



## 6.4 Result figures

Figure 10

### STANDING BALANCE SINGLE TASK PERFORMANCE

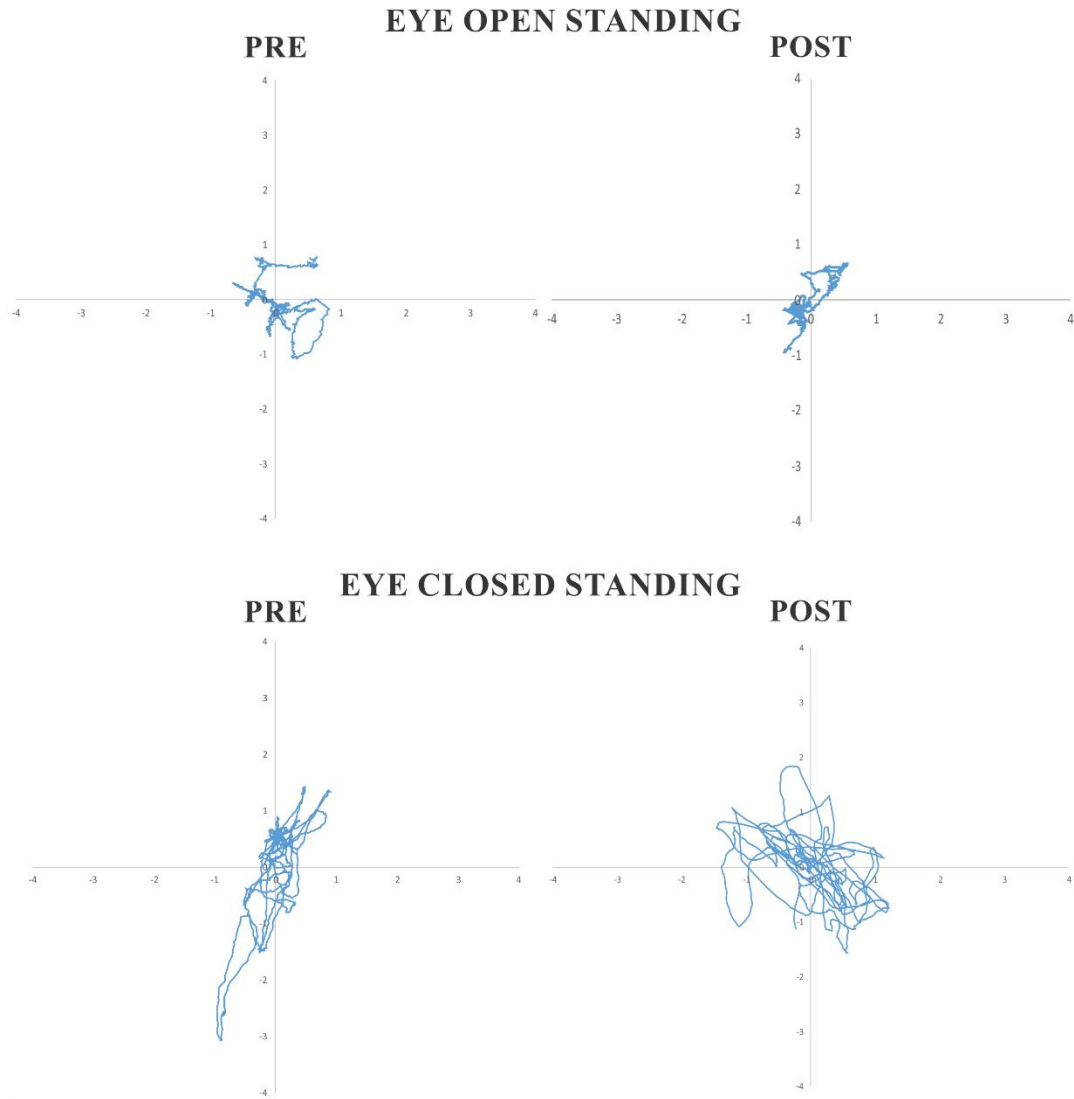
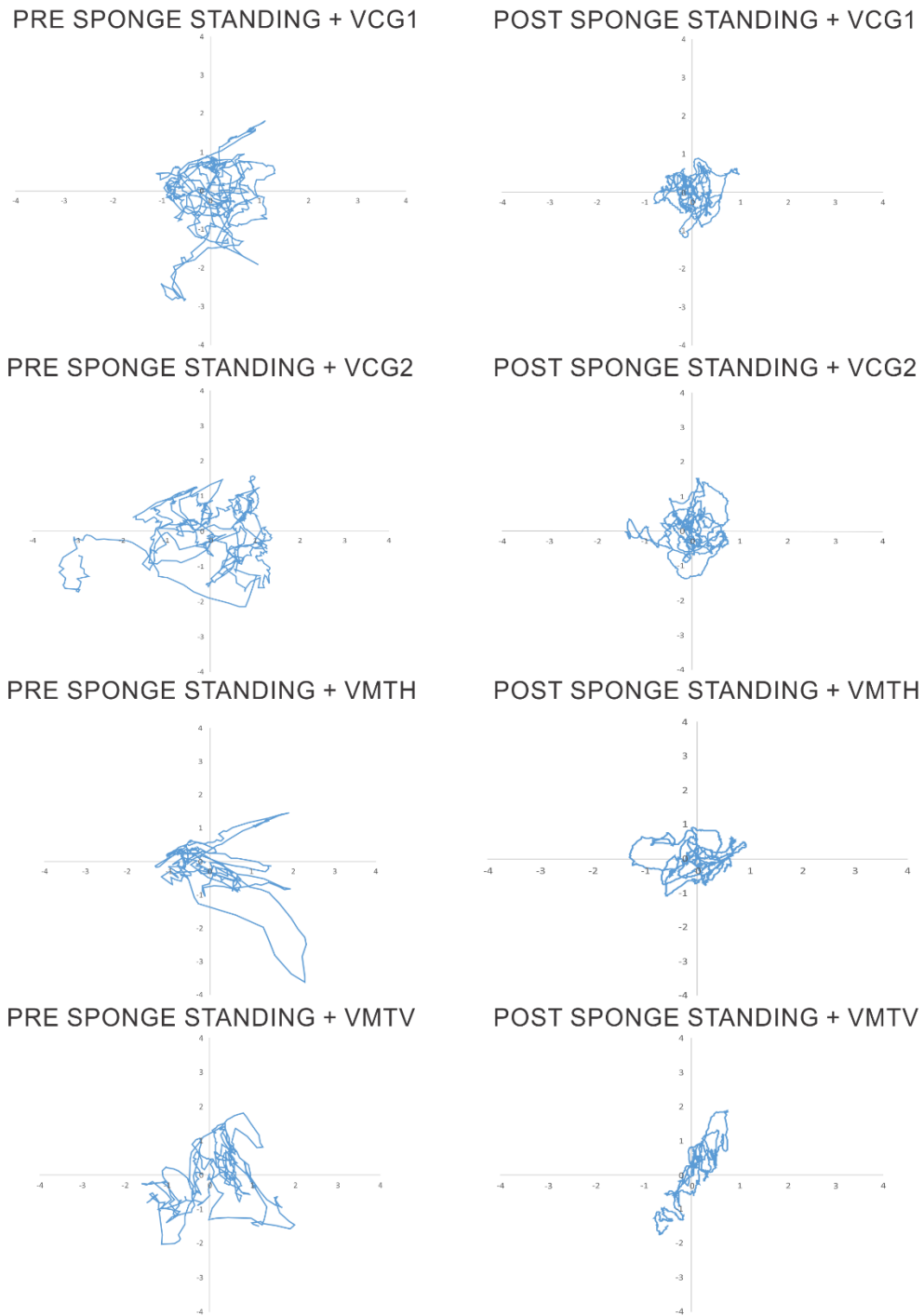


Figure 10: Standing Balance single task performance

*The blue string shows raw COP excursion during eyes open and eyes closed standing before and after intervention*

**Figure 11**

**DUAL TASK STANDING BALANCE ON SPONGE**



**Figure 11: Standing Balance dual task performance**

*The blue string shows raw COP excursion during dual task performance while standing on sponge before and after intervention*

Figure 12

## **WALKING COP DISPLACEMENT DATA**

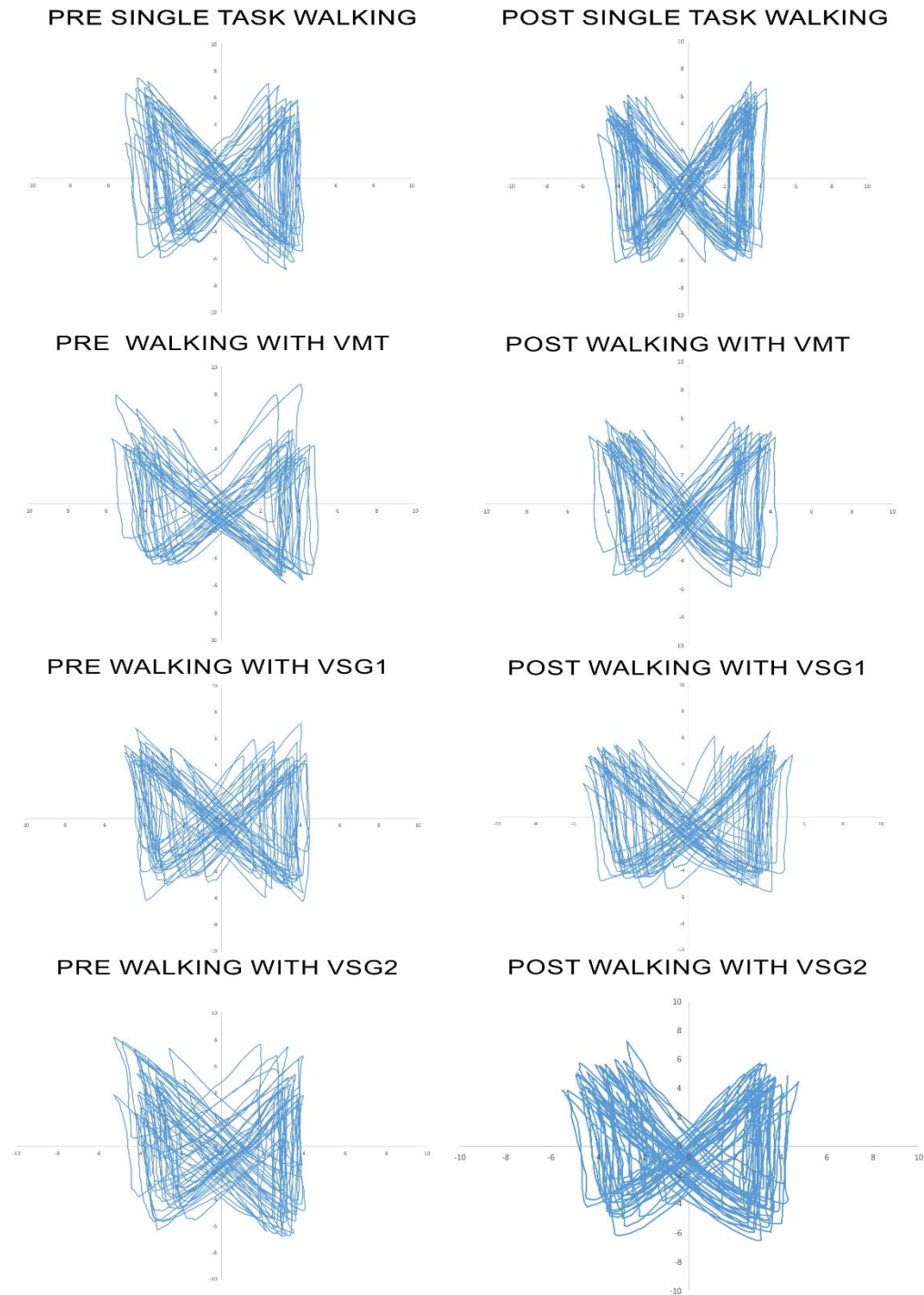


Figure 12: Walking COP displacement scatter plots for different walking conditions

*Scatter plot of COP excursion in AP and ML direction during walking only and Dual Task walking conditions before and after intervention*

Figure 13

## VISUOCOGNITIVE GAME PERFORMANCE

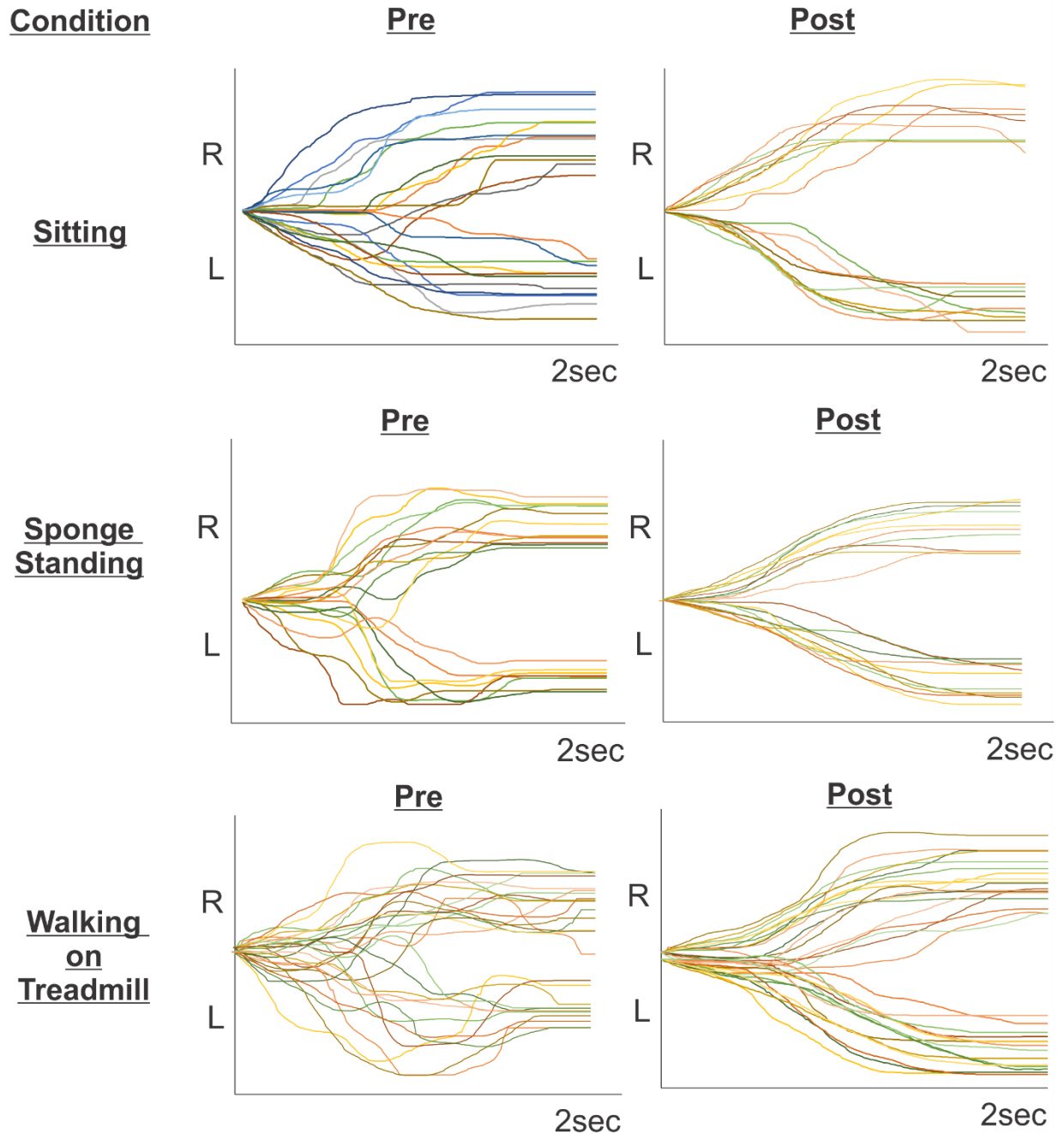


Figure 13: Visuocognitive task performance

*Raw VCG task performance data in sitting, sponge standing and during treadmill walking before and after intervention*

Figure 14

## VISUOMOTOR TRACKING GAME PERFORMANCE

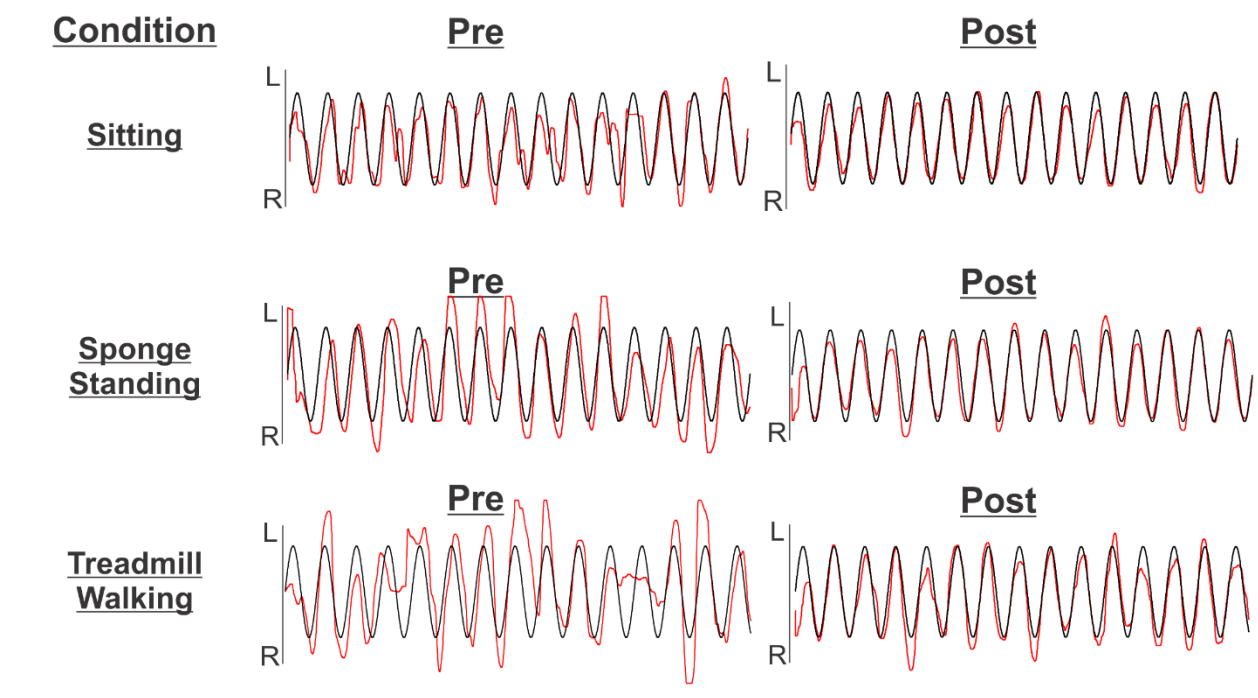


Figure 14: Visuomotor tracking cognitive task performance

*Raw VMT task performance plot in sitting, sponge standing and treadmill walking before and after intervention.*

## **Chapter 7: Discussion**

The primary purpose of the present study was to evaluate the feasibility of conducting an RCT using the DT treadmill walking program and to obtain a preliminary data to estimate the effect size of the program in people with Parkinson Disease.

### **7.1 Feasibility of GTP**

The recruitment target for this study was to enrol 20 eligible participants. We were able to screen 20 potential participants over 6 months. Fifteen participants completed the program because 5 out of 20 screened participants did not enter the program. Vergara-Diaz et al. 2018 (112) reported a recruitment rate of 2.1 participants per month for their Tai-Chi program to improve DT walking in people with PD. The present study reported a higher recruitment rate of 2.5 participants per month. A possible reason for this can be the difference in the population of two different cities where the study took place. For the present study, the recruitment occurred in the city of Winnipeg, the town of Brandon and surrounding rural communities, so the total population adds up to near 800,000 (176). The study by Vergara-Diaz et al. had their recruitment from neurology practice clinics and PD support groups in the Boston area, MA, that recorded a population of just over 667,137 in 2016 (177). Unfortunately, data on the number of people suffering from PD in either of the cities is not available. This study observed a zero percent drop out rate which is commendable.

Recruitment for this study was mostly limited to the city of Winnipeg, MB, Canada because the GTP was set up at the Health Science Centre, Winnipeg, MB, Canada. Three participants also came from the city of Brandon in the province of Manitoba, Canada and travelled between the cities for 20 intervention sessions with GTP. Nine out of fifteen

participants (60%) came from the local Movement Disorder Clinic. The present study was also advertised in various Parkinson's exercise support groups though the turn-up from these exercise support groups was not substantial as only three out of 20 participants screened came from these groups. An important factor affecting recruitment from exercise groups could be time commitment to another exercise program apart from the one they are already doing. Based on current recruitment rate, we propose a minimum of 19 months for the recruitment of 48 PD participants for GTP from the province of Manitoba, Canada.

All 15 participants completed the ten-week program. No adverse events were reported with any participant during the program. A review by Treweek et al. 2013 (179) emphasized on recruitment and retention of participants in RCTs. The review clearly stated that retention of participants into the program is more challenging than recruitment. In the present study, all fifteen participants that started the program maintained 100% compliance to the program. One possible strategy that helped to maintain compliance and retention to the program was a regular meeting of study investigators with the participants during treatment sessions. This helped in increasing the trust of participants with the program and therapist. The digital media used in the present study in the form of commercial computer games also helped in the retention of the program. The versatility of the GTP program in terms of challenge to balance, treadmill speed and a large variety of digital media/games, allows tailoring of the program according to individual needs. There was no cost for participation or any financial coverage for this study, which is a big issue to address in future. In addition, three participants were willing to travel twice a week from Brandon, (more than 100Km from the research site) supporting the impression of strong compliance with the GTP program.

Multiple electronic resources are required to complete GTP set-up like treadmill, a computer system and an inertia based wireless motion mouse. A treadmill and a computer system connected to the internet is readily available now in most rehabilitation centers and inertial motion mouse used in the present study is now commercially available. In this study, no technical breakdown of any study-related instrument occurred.

## **7.2 Experience of Participants with GTP**

Previous studies have evaluated the experience of people with PD with an exercise program (163,164,180,181). A study by Kunkel et al. 2017 (182) evaluated the experience of 51 PD participants with ballroom dancing to improve gait and balance. No significant improvement in standing balance as measured by Activities-specific balance confidence (ABC) scale and overground walking endurance as measured by 6MWT was observed after ten weeks, twice a week of ballroom dancing. Only 19% of PD participants reported “self-perceived” improvement in gait and standing balance with the protocol. This is in contrast with the present study in which 86% of participants reported “self-perceived” improvement in standing balance and gait. A study by Galna B et al. 2014 (164) evaluated the experience of 10 PD participants who played Kinect games for 30 minutes (one session) as a part of a rehabilitation protocol to improve standing balance and gait. Six out of ten participants reported that Kinect game they played was not challenging enough. Three out of ten participants did not even consider it as an exercise.

In the present study, a trend of contrasting experience with the program was observed with PD participants. Eight out of 15 participants (53%) in the present study appreciated the simultaneous motor and cognitive challenge by GTP. With the help of inertial motion mouse in the present study, participants were able to experience hands-free cognitive gaming, while simultaneously adjusting for standing balance on a compliant surface or while walking on a



treadmill. Thirteen out of 15 participants (86%) showed interest to continue with GTP if they were provided with the right technology. Also, five of fifteen participants (33%) in the present study purchased the inertial motion mouse to continue the DT training on a compliant surface in their home.

The rehabilitation needs of patients with PD vary greatly. It is necessary for any rehabilitation program to be flexible in regard to challenge to both motor and cognitive domains. In the present study, five out of 15 (33%) of participants commented on the flexibility of the program concerning both gait training and cognitive challenges. In the present study, a large variety of more than 40 commercial computer games were used. Selection of these computer games was based on cognitive demand imposed by the game. They required participants to perform color-matching, visual-spatial search for objects, target selection and shooting. The game-sprite in most of the games could be controlled by head-rotations by participants. Shooting and target selection games required participants to use a wireless clicker with both left and right mouse buttons and all games varied in levels of difficulty and progression. New and exciting games that provide similar cognitive challenges can be added to this pool as they emerge. Apart from the variety in the cognitive challenge, this study also used three different compliant surfaces to challenge the standing balance. This allowed the therapist to vary the challenge to standing balance according to the potential of the participant. By the end of ten weeks, all participants reached the same level of standing balance challenge. Similarly, the use of the treadmill allowed variability in walking speed according to the potential of the participant. Participants were allowed to hold on to the treadmill during DT walking during initial sessions but were progressed to hand-free DT walking by the end of 10 weeks. Together, these factors contribute to the versatility of the GTP as a therapy program for PD.

Some participants also had some valuable feedback for the future development of the GTP. Three out of 15 participants had a common problem with the lack of a daily progression tracker in the GTP with regards to commercial video games used. They requested a standardized tracker to provide them with feedback of their daily improvement. One participant also raised a concern with the location of the GTP program and the difficulty they faced with parking their car. Unfortunately, all components of the GTP in its preliminary stage cannot be delivered unsupervised. Therefore, participants had to travel to HSC for one-hour sessions twice a week for this study. The induction of the GTP into community centers and fitness centers has the potential to solve this problem.

### **7.3 Estimate treatment effect size**

A beneficial effect of GTP was observed on standing balance, gait and executive cognitive functions in participants. Significant improvements with medium to large effect sizes were observed for most of the outcome measures. A recent systematic review by T.B. DE Freitas et al. 2018 (183) concluded that a very few studies with people with PD had evaluated the effect of an intervention on standing balance of patients with PD during DT conditions. Additionally, the available studies do not evaluate standing balance and compliant surface in individuals with PD.

A study by Fernandes et al. 2015 (184) evaluated the effect of a standing DT intervention on COP displacement in ML, and AP direction during eyes open and eyes closed standing on a flat surface in people with PD. Unfortunately, they did not quantify COP displacement during DT condition. The present study was able to successfully quantify both cognitive measures and COP displacement measures in both ST and DT conditions on a compliant surface. In the present study, we observed participants showed a greater effect on ML-COP displacement as compared

to AP-COP displacement. There can be many reasons for such observation. One of the possible reasons can be the design of commercial computer games used during intervention. Most of the commercial computer games required participants to perform left to right head rotation to control the game sprite. These left-and-right head rotations produce more ML-COP displacement and participants had a greater practice in dealing with ML-body sway as compared to AP-body sway. Also, previous studies (185,186) have shown that ML-COP displacement is more sensitive to change when standing balance conditions challenged in individuals with PD.

Improvement in AP-COP displacement was observed only for two conditions; the eyes open standing (ST condition) and while playing VMTV task (DT condition). Improvement in VMTV task was a remarkable finding because very few commercial computer games used in the study required participants to perform up and down head rotations, thus challenge the AP-body sway. No previous study has documented improvement in AP-COP displacement for both ST and DT conditions previously in individuals with PD.

Gait performance measures also improved significantly during both walk-only condition and DT-walking conditions. Average step length improved significantly during the walk-only condition and during VCG2 conditions. A trend of increasing step length was also observed during VCG1 and VMTH conditions, but it did not reach a statistically significant level. The present study observed a 14% improvement in average step length during walk-only and a 10% improvement in average step length in VCG2 conditions. These magnitudes of improvement were greater than improvements documented in previous DT walking intervention studies.

Geroian 2018 (178) reported a 6% improvement in average step length after a 6 week DT gait training program. The intervention consisted of overground walking while performing cognitive tasks such as verbal fluency as well as a memory test however this intervention lacked

standardization; there was no control of overground walking speed while dual-tasking, number of words formed during verbal fluency, and errors during both the digit span and verbal fluency task. Of note, treadmill walking itself has shown to increase step length in individuals with PD (187,188). A recent study by Alcock et al. 2018 (189) determined that a longer step length in PD patients is directly be associated with better minimum toe clearance while walking over ground. The authors suggested that this would help to reduce future falls associated with tripping during walking.

The present study observed significant increase average step time during the walk-only condition, during VCG1 and VCG2 conditions. The increase in average step time would be related to increased average step length. Previous studies have characterized shuffling gait in individuals with PD as the gait of short step length and small step time (43,44,46). A significant improvement in both average step time and average step length indicates reduced shuffling gait in individuals with PD.

Gait variability measures are important outcome measures as they reflect gait stability (40,167) and are independent predictors of future falls in individuals with PD (53,54). In the present study, a significant reduction in COV step length and COV step time measures were observed during the walk-only condition and during all DT walking conditions. The improvement in gait variability during walk-only condition is in contrast to previous studies (121,124) that evaluated the effect of a 12 week treadmill training program on COV step length and COV step time in individuals with PD. They used a 5m long GAITrite carpet (52) to evaluate COV step length and COV step time. They reported no significant improvement in COV step length and COV step time in the variables above after 12 weeks. To note, they allowed participants to hold the side rails of the treadmill during intervention thus there was very limited

walking balance challenge to participants. In the present study, all participants walked without handrail support during treadmill walking.

Mirelman et al. 2016 (128) evaluated the effect of a virtual reality-based DT treadmill training as compared to traditional treadmill training on gait variability and future falls in individuals with PD. They evaluated variability in overground gait speed during usual walking and walking overground with obstacle negotiation. While walking on the treadmill, the participants viewed a moving video outdoor scene and an avatar of person walking on a path. This was referred as virtual environment for walking. Various obstacles were presented on the walking path of the moving outdoor scene. A Microsoft Kinect 3D camera was used to record the vertical position of the participant's feet while walking. In order to avoid obstacles, participants were required to lift the foot and this would raise the foot of the avatar walking in the virtual environment. During the training there were several obstacles to overcome, but the critical information like shape and size of obstacles was not provided. Gait variability was assessed using a 7m Zeno walkway. Various obstacles were placed on the walkway, but critical information on size and distance between obstacles was not provided. Overground obstacle negotiation was regarded as the DT walking. The main finding from this study was significant reduction in falls measured over 6 months period for VR treadmill training program. There was no significant effect on falls for treadmill only group. A non-significant reduction in gait speed variability during ST walking and during obstacle negotiation was reported. In the present study, a significant reduction in variability of step length and step time was documented during all DT walking conditions. A possible reason for significant reduction in gait variability in present study can be greater cognitive load by commercial computer games. The commercial computer games

required participants to use multiple executive cognitive functions like visuospatial search, visuomotor tracking, dividing attention and response generation.

The visuomotor and cognitive outcome measures also showed significant improvement during both ST and DT conditions following the intervention. A limited number of DT intervention studies quantify cognitive performance while dual tasking. Strouwen et al. 2017 (153) evaluated the performance of 121 PD participants on auditory Stroop task after six weeks, twice a week DT intervention. The participants were randomized into two groups. One group performed the cognitive task during overground walking for 30 minutes and other group performed cognitive tasks and overground walking separately. The cognitive tasks for intervention were verbal fluency and working memory task. A clear description of the working memory task was not provided by the authors. Percentage correct responses during auditory Stroop task were calculated while walking on a 5m GAITrite carpet (52). As stated earlier a 5m GAITrite carpet (52) can only assess 5-6 steps, so participants would have been presented with a small number of presentations for auditory Stroop and hence very limited responses made. Also, percentage of correct responses does not tell how many responses actually made by participants. No significant improvement was reported in the percentage of correct responses for either group. Several other DT intervention studies have also used cognitive tasks such as verbal fluency, the digit span and serial subtractions for intervention and assessment of DT overground walking and reported no significant improvement in cognitive performance (130,135). This is in contrast with findings from the present study. A reason for such contrasting results can be the nature of cognitive task for both assessment and treatment and the methodology of assessment. The cognitive tasks such as verbal fluency, the digit span and serial subtraction were not standardized or controlled during DT walking. Also, use of treadmill for assessment of DT walking makes a

critical difference. Individuals with PD have shown a significant reduction in walking speed when dual-tasking and use of treadmill prevents change in walking speed. A review by McIsaac et al. 2015 (190) stressed on the importance of standardization of cognitive task for DT training. The author also suggested to include cognitive tasks requiring visual-cognitive skills than cognitive skills alone. In the present study, the cognitive tasks for intervention and treatment required use of visuospatial search, visuomotor tracking and attention to playing the commercial computer games and the assessments game also.

Maidan et al. 2018 (129) evaluated the effect of similar virtual reality-based treadmill training on prefrontal cortex activity using functional near-infrared spectroscopy, in individuals with PD. They recruited 64 participants with PD in stage 1-3 on the Hoehn and Yahr scale. Thirty-four participants received virtual reality-based treadmill training, and thirty participants received usual treadmill training for 45 minutes, three times each week for six weeks. Prefrontal cortex activation reduced significantly by 18% during obstacle walking in PD participants receiving virtual reality-based treadmill training. An increased dependence on cognitive resources to maintain motor performance is observed in individuals with PD (191,192). Authors suggested enhanced utilization of striatal-thalamic-cortical-motor circuit responsible for the automaticity of walking, after 18 sessions of DT treadmill training. In the present study, we observed better results concerning average step length, average step time and variability in step length and step time during both ST and DT walking. It is possible that 20 sessions with GTP can produce similar neuroplastic changes in the brain.

## **Chapter 8: Conclusion, Study strengths, Study limitations and future studies**

### **8.1 Conclusion:**

The games-based treadmill training platform, or GTP, was found to be highly feasible with regards to participant recruitment, retention, study resources, and management. Embedded qualitative interviews revealed that participants appreciated the GTP program and had an enjoyable experience. Participants also showed interest in continuing with the GTP program in their home with regular follow-ups. Compliance of participants with the GTP is worth mentioning with no participant leaving the study in the middle due to disinterest or adverse events. A significant improvement in standing balance, gait, and cognitive outcome measures was observed during both single and dual task conditions. All significant improvements had medium to large effect size, demonstrating that improvements were not only significant but also substantial. The magnitude of improvement in average and variability spatio-temporal gait variables was greater in the present study as compared to previous dual-task gait training studies.

There is an urgent need to develop a dual-task gait training program for individuals with PD that provides continuous visual-cognitive and physical challenge. Most of the DT gait training interventions proposed for individuals with PD consisted of performing cognitive tasks with overground walking for a limited distance. Performing a cognitive task with overground walking results in participants slowing down or even coming to a standstill. The present study showed that the use of a treadmill could provide a solution to this problem. A moving treadmill belt provided a continuous stimulus to walk, and commercial computer games kept participants engaged in cognitive activity, demonstrating true dual-task walking. The proposed GTP program



can go to any fitness or community center with a treadmill and a computer system. It can be used as a method of continuous gait and cognitive rehabilitation for individuals with PD.

## **8.2 Study strengths:**

The majority of studies proposing DT standing balance interventions consist of participants performing a cognitive task or arm movement while standing on a fixed surface with a very limited cognitive or physical challenge. The evaluation of such an intervention is also performed while standing on a firm surface. In the present study, standing balance training included participants standing on a compliant sponge surface and playing highly challenging cognitive commercial computer games. The assessment of both ST and DT standing balance was also performed on a sponge surface.

Similarly, dual task walking intervention studies proposed in the past involve participants performing cognitive tasks during overground walking and the reduction of gait speed is associated with dual task walking in individuals with PD. In the present study, the use of a treadmill provided a solution to standardized walking speed during dual task walking intervention in PD. A moving treadmill belt provided a strong external stimulus to continue walking while performing cognitive tasks.

The cognitive tasks used in the present study were also superior and for the first time, challenged visuospatial and visuomotor executive cognitive functions. Previous dual task intervention studies have used cognitive tasks such as verbal fluency, the digit span and serial subtraction for intervention. These task does not challenge the visuospatial and visuomotor domains for executive cognitive functions. Also, the performance on these tasks cannot be standardized or controlled and may be affected by multiple factors such as educational

qualifications and prior knowledge. The computer-based task used in the present study provided continuous cognitive load while walking, and the results cannot be affected with the factors mentioned above.

### **8.3 Study Limitations:**

There were some limitations associated with the present study.

1. The present study did not have a control group by which to compare the improvements in standing balance, gait, and cognitive performance with the GTP program to an appropriate exercise program. An appropriate intervention program to compare with the GTP program could be conventional treadmill training in individuals with PD.
2. In the present study, no standardized test for the executive cognitive function was included. This makes a claim of cognitive improvement potentially questionable. Future studies should include an appropriate executive cognitive function test such as trail making test or Stroop test.
3. In the present study, no scale evaluating outdoor walking confidence in individuals with PD was included. Since one of the objectives of the GTP program is to improve community ambulation, there is a need to include a method that evaluates confidence in community ambulation in individuals with PD. One scale that has been used in the past in PD is the Ambulatory Self-Confidence Questionnaire (ASQC).
4. In the present study, all assessments and interventions were conducted with “on” stage of Parkinson’s medication, as reported by the participant. Thus, the results cannot be interpreted as same when on “off” state of Parkinson’s medication.

5. The gender ratio of a participant in the present study was highly biased towards the male population with PD. Interpretation of results in the female population suffering from PD requires caution.

#### **8.4 Future studies**

1. A powered RCT should be performed comparing the GTP program with an equivalent exercise program. An example of an equivalent exercise program with GTP can be conventional treadmill training or an overground DT gait training program. The present study has proposed the sample size for the GTP group in an RCT with 80% power.

2. Future studies can examine the effect of the GTP to reduce future falls in individuals with PD. For this, a prospective fall records for a fixed time could be done after the ten-week GTP program.

3. Future follow up study can examine if the improvement in standing balance, gait and executive cognitive function is maintained over time or it fades away after terminating the program.

4. Future studies can include a brain imagining technique such as positron emission tomography to study the possible neuroplastic changes in brain networks after ten weeks of the GTP program in individuals with PD.

5. Future studies can be conducted to study the effect of the GTP program to improve head rotations limited by axial rigidity in individuals with PD.

6. A trajectory analysis can be done to check for minimum intervention session required to produce similar improvements with GTP on standing balance, spatiotemporal gait variables and executive cognitive functions.

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