INVESTIGATING THERAPIES FOR FREEZING OF GAIT TARGETING THE COGNITIVE, LIMBIC, AND SENSORIMOTOR DOMAINS

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INVESTIGATING THERAPIES FOR FREEZING OF GAIT TARGETING THE
COGNITIVE, LIMBIC, AND SENSORIMOTOR DOMAINS

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Honours Bachelor of Science in Kinesiology, University of Waterloo, 2015

THESIS

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ABSTRACT

Freezing of Gait (FOG) is a highly disabling motor symptom experienced by individuals with Parkinson’s disease (PD). Yet, there are currently no effective treatments for FOG. Treatments which target the potential underlying mechanism of FOG may be the most effective strategy. According to the cross-talk model of FOG, competing demands from the cognitive, limbic, and sensorimotor domains may be the cause of FOG episodes. Thus, treatments of the cognitive, limbic, and sensorimotor cortical domains may be beneficial to FOG. This thesis is an exploratory investigation of these three different types of treatment in individuals with FOG. Specifically, computerized cognitive training, cognitive behavioural therapy (CBT), and proprioceptive training were employed as treatments towards the cognitive, limbic, and sensorimotor domains, respectively.

A single-blinded randomized crossover trial was conducted. Fifteen individuals with FOG were randomized into different groups with a counterbalanced order of interventions. Each of the three interventions involved eight one-hour sessions occurring twice weekly for a four-week period. A two-week washout period (cessation of intervention) was employed between intervention periods to prevent carryover effects. Severity of FOG and spatiotemporal gait parameters were objectively assessed using a gait paradigm which included three conditions evaluating walking when the cognitive, limbic, or sensorimotor domains were independently challenged.

Following the completion of the cognitive training intervention, participants demonstrated an improvement in severity of FOG, but only in the cognitive walking assessment. Interestingly, while there was no effect of cognitive training on freezing in the proprioceptive walking assessment, some gait characteristics did improve. After completing CBT, the severity
of FOG worsened over all gait conditions, except in the sensorimotor assessment condition, where there appeared to be no change. Gait characteristics, however, did show improvements in the proprioceptive and limbic walking assessments. Proprioceptive training results revealed improvements to FOG severity in all gait conditions except in the proprioceptive walking assessment, with additional improvements to specific gait parameters also demonstrated in the limbic walking assessment condition.

Collectively, the results indicated that all three types of treatment have the potential to improve different aspects of FOG. Thus, any one of these interventions could be a viable option for the treatment of FOG. When weighing the benefits of each intervention, it was determined that proprioceptive training would be the best and most relevant treatment option of the three, since it demonstrated improvements in the most number of outcomes. Furthermore, proprioceptive training was effective on its own, and combining additional interventions demonstrated no further benefit. Therefore, proprioceptive training would be the most ideal treatment for FOG.
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CHAPTER 1

Introduction

Parkinson’s disease and Freezing of Gait

Parkinson’s disease (PD) is a progressive neurodegenerative disorder characterized by a loss of neurons in the basal ganglia which results in a scarcity of dopamine, thus producing various motor symptoms (Petzinger et al., 2013). Freezing of gait (FOG) is one of these symptoms which is arguably the most debilitating motor feature of PD. It has been defined as “a brief episodic absence or marked reduction of forward progression of the feet despite the intention to walk” (Nutt et al., 2011). Generally, FOG episodes are characterised as a period of complete akinesia, but can also be demonstrated as festinating gait, which appear as a significantly shortened step length, increased cadence, increased stride variability, and decreased velocity (Nieuwboer et al., 2001; Iansek, Huxham, & McGinley, 2006). The severity of FOG is evaluated by quantifying the frequency and duration of FOG episodes (Morris et al., 2012).

Furthermore, the spatiotemporal characteristics of regular walking, exclusive to FOG episodes, are also affected in “freezers” (i.e. those who experience FOG) compared to “non-freezers” (i.e. individuals with PD who do not experience FOG). This is demonstrated by a decreased step length and increased stride-to-stride variability (Nanhoe-Mahabier et al., 2011; Hausdorff et al., 2003). Importantly, these changes to regular gait can also create difficulties in mobility and postural control.

In fact, FOG has been identified as an independent risk factor for falls in PD (Latt, Lord, Morris, & Fung, 2009; Rudzinska et al., 2013). Evidently, FOG is debilitating and lowers the quality of life in those who experience it (Walton et al., 2015). Advanced FOG does not respond
well to the treatments commonly used for PD, such as dopaminergic therapy and deep brain stimulation (Nutt et al., 2011; Vaamonde Gamo et al., 2010; Vorovenci, Biundo, & Antonini, 2015). This might suggest that areas of the brain other than the basal ganglia are also involved in the manifestation of FOG. Therefore, due to the disabling nature of FOG and lack of effective treatment, investigation of adjunct treatment options is highly warranted. In order to establish adjunct therapies, understanding the underlying mechanism causing FOG is critical and can provide objectives for treatment.

**Cross-talk Model of Freezing of Gait**

The mechanism underlying FOG is currently not well understood, however, several models have attempted to explain this phenomenon. One innovative model, known as the cross-talk model, proposed by Lewis and Barker (2009) suggests that FOG is caused by competing demands from the processing of the cognitive, sensorimotor, or limbic systems, which compete for processing resources. This causes an under-activation of the direct path and an over-activation of the indirect path, which leads to excessive output from the basal ganglia nuclei (globus pallidus internal and substantia nigra pars reticulata). As a result, a sporadic inhibition of the thalamus and pedunculopontine nucleus (PPN; which may be involved in the initiation, planning, and adaptation of gait [Lau et al., 2015]) occurs, and thus manifests as FOG (Lewis & Barker, 2009). This would suggest that producing an overload in any of these domains (i.e. cognitive, limbic, or sensorimotor) has the potential to be a cause of FOG behaviour. Importantly, this model is the most encompassing explanation for FOG, since it is the only model to consider the involvement of multiple domains. Although it is very difficult to parse apart the individual influence of the separate domains that project to the basal ganglia, the
contributions of each domain to FOG have been established in previous research, therefore providing further support for this model.

**Cognitive Contribution to FOG**

Given that the basal ganglia are believed to be largely involved in automatic control of walking, individuals with PD are forced to constantly focus attention (cognitive resources) towards regulating gait (Wu, Hallett, & Chan, 2015; Vandenbossche et al., 2012). Unfortunately, cognitive functioning also progressively declines in individuals with PD who experience FOG more rapidly than those individuals with PD who do not experience FOG (Hall et al., 2014; Vandenbossche et al., 2012; Plotnik, Giladi, & Hausdorff, 2009). As a result, when freezers perform two tasks simultaneously (dual-tasking), cognitive resources that are being used to control walking and complete a secondary task may become overloaded, and may lead to a freezing episode. More specifically, if there is a performance decrement in one or both of the tasks, then it can be assumed that the two tasks are in competition with one another for central processing resources, and therefore control of one task may interfere with control of the other. Therefore, since gait is more cognitively and consciously controlled in individuals with PD, performing a cognitive task (e.g. mentally counting numbers) and walking simultaneously has been found to cause impairment to gait (Pieruccini-Faria, Jones, & Almeida, 2014; Plotnik, Giladi, & Hausdorff, 2009). Due to the deficits in cognitive function identified in freezers (Peterson, King, Cohen, & Horak, 2015 for review), the availability of cognitive processing resources is even further reduced. Hence, performing a dual-task overloads cognitive resources, exacerbating gait impairment and causing FOG episodes to occur (Plotnik, Giladi, & Hausdorff, 2009; Spildooren et al., 2010; Maiden et al., 2015).
In addition to global cognitive decline, freezers are also impaired specifically in executive functions (control processes used to modulate subsets of cognitive function [Miyake et al., 2000]) compared to non-freezers (Amboni, Cozzolino, Longo, Picillo, & Barone, 2008; Giladi, Huber-Mahlin, Herman, & Hausdorff, 2007; Shine, Naismith, & Lewis, 2013). The most notable executive impairments include set-shifting (Naismith, Shine, & Lewis, 2010; Shine, Naismith, & Lewis, 2013), and response inhibition (Cohen et al., 2014; Vandenbossche et al., 2011).

Evidence shows that deficits in set-shifting (the cognitive ability to adaptively switch attention between different tasks) may contribute to freezing episodes. This has been demonstrated in an upper limb motor task, where PD participants were cued to switch between bimanual motor sets (i.e. in-phase movements or anti-phase movements). Individuals with PD showed a greater delay in switching and more episodes of upper limb freezing compared to a non-parkinsonian control group, which could reflect an inability to shift attention from one motor set to another (Almeida, Wishart, & Lee, 2003). Similarly, this set-shifting impairment could also contribute to freezing episodes of the lower limbs. This has been supported by findings demonstrating that greater time to complete (worse performance) the Trail-making Test (a neuropsychological assessment of set-shifting, TMT) predicted higher Freezing of Gait Questionnaire scores (a self-reported indication of FOG severity) (Naismith et al., 2010). Performance on the TMT was also correlated with objective measures of FOG, in that higher TMT scores were significantly correlated with a greater duration (percentage of time spent frozen) and frequency of FOG episodes during a timed up-and-go task (Shine, Naismith, Palavra, et al., 2013). Therefore, depleted cognitive resources may specifically present as a set-shifting impairment that could underlie the executive function deficits leading to FOG (Naismith et al., 2011).
Another possibility is that deficits to set-shifting in freezers may pose greater demand on already depleted processing resources (compared to individuals with PD who are non-freezers and non-PD controls), resulting in reduced availability of resources for processing of concurrent tasks, further contributing to FOG episodes.

Studies have also revealed that deficits in response inhibition can lead to FOG. This behaviour may be attributed to a failure in releasing an inhibition response (such as a “do not walk” response) when it is no longer needed (i.e. at the point of desired gait initiation or continuation) (Cohen et al., 2014). This is exemplified during performance on the Go-Nogo task. This paradigm requires participants to make a rapid and accurate button-press response to a “Go” stimulus, and inhibit that response when a “Nogo” stimulus appears. Freezers performing this task demonstrated a greater rate of errors primarily due to missed targets (i.e. inability to respond in the given timeframe) rather than false alarms, compared to non-freezers and healthy older adults (Cohen et al., 2014). This impairment in response inhibition might underlie some of the biomechanical features of FOG. During a freezing episode, freezers demonstrate difficulty in effectively releasing a desired response (stepping), while failing to inhibit an undesired response (weight-shifting), which represents multiple attempts at producing anticipatory postural adjustments (APA’s) (Cohen et al., 2014; Jesse V. Jacobs, Nutt, Carlson-Kuhta, Stephens, & Horak, 2009). Consequently, impairments in response inhibition may also require a greater consumption of cognitive resources, thus leading to gait impairments and FOG. Therefore, it may be possible that treatments focused on improving cognitive function, specifically in set-shifting ability and inhibitory control, may also lead to an improvement in gait behaviour and specifically FOG.
Limbic Contribution to FOG

A growing body of research has demonstrated that the limbic system (i.e. anxiety) may have an influence on movement control, and might also underlie many common situations that can instigate FOG (Caetano, Gobbi, Sanchez-Arias, Stella, & Gobbi, 2009; Ehgoetz Martens, Ellard, & Almeida, 2014). A virtual reality paradigm was used to experimentally induce anxiety by asking individuals with FOG to walk across a plank that appeared to be raised 8 metres above the ground (high plank). Freezers who walked across the high plank demonstrated a significantly greater frequency and duration of FOG episodes compared to a condition where walking across a plank appeared at ground level (Ehgoetz Martens et al., 2014). Furthermore, freezers reported higher ratings of anxiety (self-assessment manikins) than non-freezers irrespective of condition (high and low plank) (Ehgoetz Martens et al., 2014). To date, this paradigm has induced the greatest number of FOG episodes (300+ episodes) compared to any other experimental paradigms targeting other domains (Ehgoetz Martens et al., 2014), which might suggest that anxiety could have a robust influence on the occurrence of FOG episodes.

Interestingly, anxiety symptoms may be linked to specific motor symptoms in PD. Anxiety (indicated by the Hospital Anxiety and Depression Scale), was predicted by the postural instability and gait disturbance (PIGD) subtype, which is characterized by a predominant impairment in gait and postural control (Burn et al., 2012). Importantly, this subtype has been speculated to be more likely to progress to FOG, since FOG is associated with a more severe decline in postural control and gait deficits (Vervoort et al., 2015). Furthermore, freezers were also more anxious and depressed when assessed on the Hospital Anxiety and Depression Scale compared to non-freezers (Burn et al., 2012). This could suggest that anxiety is related to more severe gait impairments, and potentially FOG.
These motor deficits may be the result of anxiety competing for processing resources required for movement control in individuals with PD. Those with high trait anxiety who walked through a threatening environment demonstrated an improvement in gait while on dopaminergic medication compared to off medication, suggesting that the effect of anxiety on gait is modulated by dopamine (Ehgoetz Martens, Ellard, & Almeida, 2015a). Since a greater limbic load depleted these resources resulting in disturbances in gait, this lends further support to the influence of the limbic component in the cross-talk model. Given that there are well established treatments for anxiety such as cognitive behavioural therapy (Otte, 2011), it may be possible to ameliorate anxiety levels with a potential resulting decrease in limbic load, which might also improve FOG behaviour.

**Sensorimotor Contribution to FOG**

The cross-talk model suggests that the cortical-basal ganglia motor loop, mediated by sensory inputs from visual and somatosensory information, may be involved in FOG (Bartels & Leenders, 2008; Lewis & Barker, 2009). Individuals with PD demonstrate deficits in sensory processing, most notably in proprioception (sensory information regarding muscle length, contractile speed, muscle tension, and joint position), which has been argued to underlie motor impairments (Almeida et al., 2005; Jacobs & Horak, 2006; Konczak et al., 2009). This has been exemplified in a study by Keijers and colleagues (2005) in which individuals with PD pointed to remembered visual targets in two conditions that altered the level of sensory feedback available: i) In complete darkness (proprioception becomes the primary source of sensory feedback since visual information was not available) and ii) In complete darkness with an illuminated external frame of reference (such as a frame around the target) and limbs (vision
became the primary source of feedback). Individuals with PD pointed with significantly greater error compared to healthy controls in both conditions, but especially in the dark condition (Keijsers et al., 2005). These results indicated that individuals with PD have deficits in proprioception, which are exacerbated with a lack of visual feedback. These impairments can also translate to postural control deficits demonstrated in individuals with PD, such as impaired compensatory stepping triggered by a sudden loss of balance (Jacobs & Horak, 2006). When vision of the lower limbs is absent (i.e. causing a greater reliance on proprioception for motor control of lower limbs), PD subjects demonstrated significantly hypometric compensatory steps compared to when vision of the lower limbs is available, which suggests that the ability to use proprioceptive information to guide an accurately scaled motor response is dysfunctional (Jacobs & Horak, 2006).

This proprioceptive-motor deficit may also underlie FOG episodes. In fact, impairments in proprioception have been identified in freezers and are more severe than non-freezers (Ehgoetz Martens, Ellard, & Almeida, 2015b; Ehgoetz Martens, Pieruccini-Faria, & Almeida, 2013; Pereira, Gobbi, & Almeida, 2016; Tan, Almeida, & Rahimi, 2011). When walking through a completely dark environment (i.e. when utilizing proprioception as the primary source of sensory feedback), freezers displayed a greater number of FOG episodes compared to walking when an external frame of reference (illuminated doorframe) or limb position was visible (Ehgoetz Martens et al., 2013). This could be an indication that FOG is the result of defective proprioceptive processing, and that vision helps to override this faulty source of feedback. Notably, it has also been reported that freezers have a greater reliance on visual information during movement control, which may be the result of compensating for maladaptive proprioceptive feedback (Azulay et al., 1999; Beck, Martens, & Almeida, 2015; Demirici, Grill,
McShane, & Hallett, 1997; C. R. A. Silveira et al., 2015). This may also be the reason for greater errors in sensory-perceptual judgement demonstrated in FOG (C. R. A. Silveira et al., 2015), which could be due to the integration of visual information with distorted proprioceptive information. Collectively, these findings lend support to the role of proprioceptive functioning in the underlying mechanism of FOG. Since deficits in proprioception have been argued to play a large role in FOG behaviour, improving proprioceptive processing may also lead to improvements in FOG.

**Cross-talk between Cognitive, Limbic, and Sensorimotor Processing**

The element of cross-talk in this model implies that processing output from the cognitive, limbic, and/or sensorimotor domains conflicts with the processing between each other (Lewis & Barker, 2009). Understanding the interaction between these domains is important for elucidating the primary mechanism that potentially underlies FOG. It could be argued that impairments to proprioceptive and limbic processing may be attributed to deficits in executive function. For example, deficits in set-shifting may be causing a difficulty in maintaining the on-line processing and ability to shift between cognitive, limbic, and proprioceptive response sets, thus leading to an inadequate processing output (Naismith et al., 2010). Similarly, impairments demonstrated in proprioceptive processing may be the effect of impairments in motor planning, wherein utilizing somatosensory feedback alone to guide obstacle crossing could be placing demands on planning resources which are already strained due to this executive deficit (Pieruccini-Faria et al., 2014). Thus, inefficiencies in cognitive processing may be interfering with processing of limbic and proprioceptive inputs.
Similarly, anxiety, or a heightened limbic load, may be underlying impairments demonstrated in cognitive and proprioceptive processing. Anxiety caused by a fear of falling during locomotion can increase attentional cost, suggesting that it could reduce cognitive resources necessary for detecting and navigating around potential obstacles in the environment (Gage, Sleik, Polych, McKenzie, & Brown, 2003). Furthermore, anxiety has also been shown to interfere with the utilization of sensory feedback while walking (Ehgoetz Martens et al., 2015b). Consequently, processing of a limbic load caused by anxiety may create a deficit in processing resources necessary for accurate cognitive and proprioceptive processing.

Lastly, an underlying dysfunction in the integration of proprioceptive information has also been argued to underlie processing deficits in the cognitive and limbic domains (Ehgoetz Martens et al., 2013). Different triggers of FOG could be the product of a fundamental deficit in sensory processing. For example, individuals with PD use greater cognitive effort when walking to compensate for defective proprioception, which may cause a depletion of cognitive resources. Therefore, FOG episodes caused by a dual-task (which also recruits cognitive resources) could be the downstream effect of a proprioceptive impairment. Likewise, increased limbic load which can also produce FOG, may be due to elevated anxiety provoked by an inability to use proprioceptive information. Therefore, the cognitive and limbic contributions to FOG may be the consequence of impaired proprioceptive processing. Hence, improvements to one domain could be reflected as an improvement in the other domains. For example, an improvement to cognitive function may be revealed by improvements in limbic or proprioceptive tasks, since it could be argued that the cross-talk between domains is reduced.
Treatment for FOG

Although studies have identified the possible causes of FOG, research is limited in establishing potential treatments for this phenomenon. Treatment targeting the known triggers of FOG, or the upstream cognitive, limbic, and proprioceptive contributions, may be the most effective strategy. Previous studies have investigated the efficacy of therapies targeting each domain individually, although none have investigated the therapeutic benefits to FOG.

Cognitive Training

Treatment of the cognitive domain may be accomplished by training various cognitive and executive functions with guided practice focusing on specific skills (e.g. visuospatial processing, executive function, memory, language, and attention). Research has shown that pharmacological treatments for cognitive function have demonstrated inconclusive findings (Walton, Shine, Mowszowski, Naismith, & Lewis, 2014). Non-pharmacological interventions, such as cognitive training, may have the potential to alleviate FOG, although this has yet to be investigated. Cognitive training has been demonstrated to be effective in several studies involving individuals with PD (Leung et al., 2015; Naismith, Mowszowski, Diamond, & Lewis, 2013; París et al., 2011; Petrelli et al., 2014; Sammer, Reuter, Hullmann, Kaps, & Vaitl, 2006; Sinforiani, Banchieri, Zucchella, Pacchetti, & Sandrini, 2004). Furthermore, studies in individuals with PD have specifically shown improvements in executive functions including set-shifting and response inhibition which may also be responsible for FOG, as described above (París et al., 2011; Petrelli et al., 2014; Sammer et al., 2006). Improving cognitive and executive functioning may have a beneficial impact on FOG, potentially by improving processing of cognitive tasks, thus leading to better cognitive control of movement.
Cognitive training may be utilized as a therapy to address the cognitive contribution to FOG. Several studies involving individuals with PD have investigated this type of treatment, and have demonstrated improvements in general cognitive function (Leung et al., 2015; Naismith et al., 2013; París et al., 2011; Petrelli et al., 2014; Sammer et al., 2006; Sinforiani et al., 2004), as well as in the specific executive function domains which may be responsible for FOG (i.e. set-shifting ability and inhibitory control) (París et al., 2011; Petrelli et al., 2014; Sammer et al., 2006). Interestingly, a study conducted by Paris and colleagues (2011) which utilized a computerized cognitive training program (SmartBrain) demonstrated significant improvements in the greatest number of cognitive outcomes, including set-shifting ability and inhibitory control. In this randomized controlled study, 16 individuals with PD completed twelve 45-minute sessions, occurring thrice-weekly for 4 weeks, and were also given a set of 20 cognitive homework exercises each week. Results showed that participants in the Cognitive Training group significantly improved on the WAIS-III digit span, Stroop test, Rey-Osterrieth Complex Figure Test, RBANS Line Orientation test, Semantic Verbal Fluency, Trail-making Test Part B, and Tower of London (París et al., 2011). These findings demonstrated the efficacy of the SmartBrain program on individuals with PD, however, the functional benefits to motor performance or severity of FOG have yet to be investigated.

*Limbic Training (Cognitive-Behavioural Therapy)*

Theoretically, treatment of the limbic system in freezers may be accomplished by treating the underlying anxiety that may be depleting the reserve of processing resources. Common anxiety treatments involve pharmacological interventions, however, this may also have a higher risk of side effects (Pachana et al., 2013; Rabinstein & Shulman, 2000). Therefore, alternative
non-pharmacological treatments of anxiety, such as using the psychotherapy technique known as cognitive-behavioural therapy (CBT) would be more ideal. Currently, CBT is recognized as a “gold standard” treatment for many mental health disorders including anxiety (Otte, 2011). This type of therapy operates on the principle of modifying old, maladaptive thought processes by teaching cognizant strategies to reduce anxiety provoking thoughts. Therapeutic sessions may involve practices designed to help the individual recognize their own anxiety-related thoughts and facilitate the development of new thought processes. Changing the underlying thought patterns or “cognitions” to negative stimuli would therefore result in behavioural change.

Interestingly, CBT has also been demonstrated to be effective in the remediation of anxiety in individuals with PD (Egan, Laidlaw, & Starkstein, 2015; Feeney, Egan, & Gasson, 2005; Troeung & Gasson, 2013; Troeung, Egan, & Gasson, 2014). Recent meta-analyses revealed that individuals with PD may benefit less from antidepressant drugs than those without PD (Weintraub et al., 2005) and that CBT produced a larger effect size than antidepressant medication in PD patients, suggesting this type of therapy is superior to psychopharmacotherapy (Troeung, Egan, & Gasson, 2013). Therefore, alternative strategies to drug therapy, such as CBT, may be advantageous.

The neural mechanism underlying behavioural changes in CBT may be due to neuroplasticity. Changes in brain activation have been demonstrated in the limbic regions of the brain in individuals with anxiety disorders (See Frewen, Dozois, & Lanius, 2008 for review). In particular, increases in brain activity in areas associated with a relaxed state and improved emotional regulation (insula, right precuneus, posterior cingulate cortex, and inferior frontal gyrus), and decreases in activity in regions associated with processing of fear and negative affective responses (amygdala, hippocampus, and medial temporal lobe) have been noted in
adults with anxiety disorders (Frewen et al., 2008). Improving processing efficiency in these areas may lead to an enhanced ability to process a greater “limbic load” (i.e. greater demands placed on the limbic domain). This may be beneficial to individuals experiencing FOG, given the evidence that anxiety may provoke FOG. During periods of elevated anxiety (e.g. walking in a threatening environment), freezers will be able to more efficiently process this limbic load resulting in greater resources available for movement control.

Treatment of the limbic contribution to FOG may be achieved by treating the underlying anxiety that influences motor control, by using techniques such as cognitive-behavioural therapy (CBT). Studies utilizing CBT have been effective in reducing anxiety in individuals with PD (Egan, Laidlaw, & Starkstein, 2015; Feeney, Egan, & Gasson, 2005; Troeung & Gasson, 2013; Troeung, Egan, & Gasson, 2014; Calleo). However, it is important to note that these studies utilized CBT targeting both depression and anxiety symptoms. There are currently no studies which have investigated CBT designed for anxiety exclusively, therefore, it is unclear whether CBT only for anxiety could be effective in PD. Furthermore, the outcome measures for anxiety selected in these studies have not been validated in a PD population. Therefore, it would be more appropriate to use an anxiety rating scale that has been validated and demonstrated reliability in PD, such as the Parkinson Anxiety Scale (Leentjens et al., 2014). Furthermore, the effects of CBT on outcome measures related to motor function or FOG have not yet been demonstrated, although may be effective in ameliorating FOG behaviour, given the contribution of anxiety to FOG.
Sensorimotor Training (Proprioceptive Training)

The goal of proprioceptive training is to improve the integration of sensory processing. Previous studies utilizing functional magnetic resonance imaging (fMRI) in healthy adults demonstrated that chronic repetitive proprioceptive stimulation through passive limb movements resulted in increased activation of the supplementary motor area (SMA), which is involved in the processing of proprioceptive information (Escola et al., 2002), as well as the primary sensorimotor cortex (S1M1) (Carel et al., 2000). These improvements may be attributable to neuroplastic changes in sensorimotor brain regions. Proprioceptive training that involves active movements, as opposed to passive movements, has shown improved motor learning, however the movements must be self-initiated rather than externally guided (Marteniuk, 1973; Stelmach, Kelso, & McCullagh, 1976; Wong, Kistemaker, Chin, & Gribble, 2012). For example, active movements may include reproduction of a self-defined movement in the absence of visual feedback. According to a recent review by Aman and colleagues (2015), training involving a combination of passive and active limb matching, both with and without external feedback tends to have the greatest improvements to sensorimotor function. This type of training may be beneficial to FOG, since proprioceptive deficits have been found to contribute to FOG episodes. By improving proprioceptive processing, one would expect that when proprioception is challenged during locomotion (e.g. by removing visual feedback and preventing compensation of proprioception deficits), freezers would experience less decrements to gait due to an enhanced ability to process proprioceptive demands.

Currently, studies investigating the use of active or passive limb matching as proprioceptive training as a treatment are limited. This type of training has demonstrated effectiveness in neurologically healthy individuals (Hocherman, 1993; Robin, Toussaint,
and in individuals with osteoarthritis (a condition in which proprioception is altered) (Jan et al., 2008; Lin, Lin, Chai, Han, & Jan, 2007; Lin, Lin, Lin, & Jan, 2009). Only one study utilizing this type of training has been conducted in PD (Elangovan, Tuite, & Minneapolis, 2016). This study involved wrist proprioception training using a visuomotor task in five individuals with PD. All participants improved in wrist proprioceptive thresholds and four of the five participants demonstrated improvements in wrist movement precision as a result of the training (Elangovan et al., 2016). This study demonstrated that proprioception is trainable in individuals with PD, however, these effects were only examined specifically in the wrist joint which may not translate to overall improvements in gait. Multi-joint proprioceptive training in the upper and lower limbs, such as the methods used by Hocherman (1993) and Jan et al. (2008), could yield the greatest functional benefit to freezers. These studies utilized an active target-matching task, and demonstrated improvements in target reproduction accuracy in neurologically health adults. This type of training in both upper and lower limbs has yet to be investigated in FOG, and assessed on functional outcome measures, such as gait.

Although evidence demonstrates the value of therapies targeting each domain, to date, no study has evaluated the therapeutic benefits to FOG. Thus, the aim of the present study was to compare cognitive (SmartBrain computerized cognitive training), limbic (CBT), and proprioceptive (upper and lower limb target-matching) therapies in individuals with FOG, to determine which has the greatest therapeutic benefits and greatest improvements in FOG functional outcomes.
CHAPTER 2

Methods

Study Design and Participants

The current study was a prospective, single-blind, randomized cross-over design. After baseline assessments were completed, participants were block randomized into one of six groups with a counterbalanced order of interventions (Figure 1). Participants completed all three interventions over three separate phases in the study. A two-week washout period occurred between each intervention phase in order to prevent carryover effects. The complete flow of participants through the study is presented in Figure 1.
Participant recruitment was completed through the Movement Disorders Research and Rehabilitation Centre participant database at Wilfrid Laurier University (MDRC; Waterloo, Ontario). Inclusion criteria consisted of a diagnosis of PD and classification as a “freezer” (i.e. experiences freezing of gait), and either gender. FOG status was determined from a prior clinical assessment by a movement disorders specialist. Individuals were excluded if they were diagnosed with a neurological disease other than PD, or scored 19 or lower on the Montreal
Cognitive Assessment (MoCA) assessed prior to the start of the study, unable to walk at least 10 metres unassisted, and unable to understand verbal instructions in English. This study was approved by the Research Ethics Board at Wilfrid Laurier University. All participants provided written informed consent prior to beginning the study in accordance with the Declaration of Helsinki. This study is registered as a National Clinical Trial (clinicaltrials.gov NCT03065127).

Interventions

The three interventions each involved eight one-hour sessions occurring twice weekly for a period of four weeks. Participants completed the training while on dopaminergic medication since these were intended to be implemented as adjunct therapies.

Computerized Cognitive Training:

This treatment entailed computer aided cognitive training using the web-based version of the SmartBrain tool. Sessions were supervised by trained personnel, and were completed on an HP pavilion g6 laptop with a mouse. A program was designed containing 13 activities aiming to stimulate specific aspects of cognitive and executive function which are known to potentially contribute to FOG episodes (set shifting/mental flexibility, inhibitory control, and attention). The difficulty level of each activity increased as each participant progressed.

Limbic Training Group (Cognitive Behavioural Therapy):

Cognitive Behavioural Therapy (CBT) focusing on anxiety was conducted in one-on-one sessions with a trained psychotherapy Masters student supervised by a faculty member who was an experienced clinical psychotherapist. A total of seven psychotherapy students volunteered in
this study. All psychotherapists received weekly training with the supervisor who reviewed each session’s notes to ensure consistency with the treatment goals. The CBT treatment in the current study was designed using the recommendations of CBT for PD by Egan, Laidlaw, and Starkstein (2015). The content of the current treatment included components of psychoeducation, attention refocusing/cognitive shifting, behavioural activation, thought diaries, grief therapy, and behavioural experiments. Treatment activities were individualized to each participant’s needs.

*Proprioceptive Training Group:*

Proprioceptive training entailed a target matching task utilizing self-defined active movements and was completed in the upper and lower limbs separately. For the upper limb target-reaching task, participants were seated in front of a tabletop. Ten numbered targets were marked along the surface, with five targets placed symmetrically on the right and left sides of the participants’ midline. At the start of each trial, participants placed their hand at the “origin” located at the midline at the bottom of the surface. Participants first viewed the single target, and once blindfolded, instructed to reach towards the target, aiming to touch the centre of the target with their fingertip. The blindfold was immediately removed once the reach was completed to allow participants to view their error in joint angle production. This process was repeated for each target, and participants attempted to complete five rounds of the 10 targets in right and left upper limbs. The lower limb target matching protocol was identical, with the instruction being to touch the centre of the target with their toe. Participants also completed five rounds of target reaching towards each of the 10 targets in the right and left lower limbs.
Outcome Measures

Outcomes of Treatment Efficacy:

These outcome measures (Trail-making test, Stroop Test, Parkinson Anxiety Scale, and passive joint-angle matching) were included with the intention of verifying that the cognitive, limbic, and proprioceptive interventions were successful in accomplishing the outcomes that were expected based on previous studies (cited above).

a) Trail-making Test:

The trail-making test Part A and B were both assessed. In Part A, participants strategized a way to move a pen as quickly as possible to consecutively connect numbered targets on a page. The time taken to complete this task was recorded, and represents processing speed, visual tracking, and motor planning (Xanthopoulos et al., 2008). In Part B, participants sequentially connected numbers and letters by switching between sets (i.e. 1-A-2-B). Time taken to completion was also recorded for this task, and provided an indication of set-shifting ability and mental flexibility (Xanthopoulos et al., 2008). The time difference between time to complete Part B and Part A (B-A) was calculated, and provided a score which accounts for movement speed.

b) Stroop Test:

This test was completed in three parts. Participants were given 45 seconds in each part to read/name as many items as possible, and the number of correctly identified items were recorded for each part. The first part of the test involved participants reading out loud the words “RED”, “GREEN”, and “BLUE” which were printed in black ink. In the second part, participants were instructed to name the colour of X’s printed in various coloured ink (e.g. XXXX, XXXX, XXXX). The third part involved the words RED, GREEN, and BLUE printed in incongruent ink
colours (e.g. RED, GREEN, BLUE), in which participants were instructed to name the colour of the ink, ignoring the word itself.

c) Parkinson Anxiety Scale (PAS):

This self-report questionnaire, which has demonstrated good concurrent validity in individuals with PD against other existing anxiety scales, was used to assess anxiety levels (Leentjens et al., 2014). A score out of 48 was summed at the end, where higher scores were indicative of greater anxiety symptoms.

d) Passive Upper Limb Joint-angle Matching:

This procedure was conducted similar to the method presented by Goble (2010). Participants were seated beside the apparatus with both arms pronated, and with the elbows and shoulders at 90°. The participant’s forearms were strapped to the moveable forearm support attached to a rotating apparatus, allowing for smooth flexion and extension of the elbow joint. Participants were blindfolded and equipped with noise-cancelling headphones in order to prevent use of visual or auditory information. The protocol began with the experimenter extending the participant’s elbow to 10, 30, or 60 degrees away from the starting position (target limb). The experimenter then began slowly extending the contralateral elbow until the participant signaled once they felt that their limb matched the same angle as the target limb (initially moved).

e) UPDRS-III (Motor Subsection):

Research has shown that FOG is associated with greater disease severity (Contreras & Grandas, 2012; Giladi et al., 2001; Macht et al., 2007; Nutt et al., 2011). Therefore, an assessment of motor symptom severity using the UPDRS-III was included. This assessment evaluated individuals’ motor symptom severity on a scale of 0-108 (Fahn & Elton, 1987), where
higher scores indicated a greater severity of motor symptoms. A blinded movement disorders specialist (QJA) performed the appraisal.

*Freezing of Gait Outcomes:*

a) Gait Assessment:

This paradigm aimed to evaluate the effects of challenging cognitive, limbic, and proprioceptive processing on gait and FOG measures. Participants walked across a walkway measuring approximately 9.75 metres (length) x 0.3 metres (width) which was marked by lines on the floor. To ensure that postural control changes were not simply due to differences in constraints of the environment, the dimensions of this walkway were kept consistent for each trial. Participants were equipped with active infrared light emitting diodes (IREDs) on the following locations: xiphoid process, bilateral lateral malleoli, and bilateral 5th metatarsals to allow recording of kinematic data with eight Optotrak® cameras (Northern Digital, NDI, Waterloo, Ontario) at a frequency of 100 Hz. The primary outcome measures were the frequency and total duration of FOG episodes in each trial. The total duration of FOG during each trial was also recorded. However, since realistically it is difficult to elicit FOG events in an experimental setting, it is important to also investigate changes in gait that do not result in FOG episodes. Thus, spatiotemporal aspects of gait excluding FOG episodes [gait velocity, step length, step length variability (CV), step time, and step time variability (CV), percentage of time in double support, and percentage of double support time variability (CV)] were also analyzed. These parameters have been demonstrated to be associated with FOG, and typically become more pronounced in the periods prior to a FOG episode (Hausdorff et al., 2003; Nanhoe-Mahabier et al., 2011; Nieuwboer et al., 2001).
Gait assessments involved three conditions which aimed to challenge the cognitive, sensorimotor, and limbic domains independently, in addition to a single-task (baseline) condition. Three blocks of the four randomized conditions were completed for a total of 12 trials. These conditions are outlined below.

**Single-task (BL):** Participants were instructed to walk across the walkway at a self-selected pace with no manipulations to the gait task. These trials served as a baseline for comparison with performance during the other conditions (cognitive, proprioceptive, and limbic challenge).

**Cognitive challenge (COG):** An auditory digit monitoring dual-task condition was used to challenge cognitive processing by diverting attention from walking. A 12-second audio track played a stream of numbers ranging from 1-9 presented in random order in each trial. The inter-stimulus interval between each announced number ranged from 100-1000 ms and was also randomized in order to prevent gait synchronization with the audio track. Participants were instructed to walk at a comfortable pace while mentally counting the number of times that 2 previously specified numbers (e.g. 2’s and 4’s, or 3’s and 4’s) were announced among the stream of numbers. At the end of each trial, participants responded with the number of times they heard the target numbers. If the audio track ended before the participant reached the end of the walkway, they were instructed to retain their response until the walking task was complete. No feedback on performance of the secondary task was given to the participant at any time. This method was previously employed by Pieruccini-Faria and colleagues (2014) and has been verified to interfere with cognitive processing. This type of secondary task was selected since it does not include any motor components, thus allowing for the dual-task to be isolated to the cognitive domain (Pieruccini-Faria et al., 2014).
Limbic challenge (LIM): This condition aimed to induce anxiety while walking by increasing the level of postural threat. Participants walked across an elevated walkway (similar to a balance beam) measuring 9 metres (length) x 0.3 metres (width) x 0.6 metres (height). This height has also been used in previous studies to increase postural threat in healthy older adults (Brown, Doan, Whishaw, & Suchowersky, 2007; Gage et al., 2003). The width of the walkway was consistent with the other conditions in order to ensure that the environmental constraints were not the cause of differences in postural control.

Proprioceptive challenge (PROP): This condition aimed to increase the reliance on proprioceptive feedback in the absence of vision while walking, thus challenging the sensorimotor domain (Ehgoetz Martens et al., 2013). Participants were instructed to walk at a comfortable pace through a completely darkened room. The room was free of immediate obstacles in order to prevent collision or the fear of a potential collision from interfering with the proprioceptive manipulation. After completion of each trial, the lights were turned on to allow participants to safely return to the starting position, as well as to prevent participants’ eyes from acclimating to the darkness.

b) New Freezing of gait Questionnaire (NFOGQ):

This questionnaire provided a self-reported measure of frequency and duration of FOG episodes. This tool has been validated and proven to be highly reliable in individuals with PD, as well as assessing treatment interventions for FOG (Nieuwboer et al., 2009).

Data and Statistical Analysis

Statistical analyses were completed using Statistica version 8.0 (StatSoft Inc., Tulsa, OK, USA). Since the Stroop test, Trail-making test, Parkinson Anxiety Scale, and passive joint-angle
matching were intended to confirm efficacy of each intervention, only the outcome measures relevant to the specific intervention were analyzed. Thus, the Stroop test and Trail-making test were only analyzed prior to and following the completion of cognitive training, the passive joint-angle matching task was only analyzed when the proprioceptive training occurred, and the Parkinson Anxiety Scale was only analyzed when the Cognitive Behavioural Therapy occurred. However, for the FOG outcomes (i.e. gait measures, New Freezing of Gait Questionnaire) and UPDRS-III scores, analyses included the three interventions as categorical predictors in order to examine differences between the three types of interventions. Shapiro-Wilk tests were used on all data to confirm normality, and Mauchly’s test was used to confirm sphericity when necessary. Data that violated these assumptions were analyzed using the appropriate non-parametric tests. Alpha level was set at 0.05 for all statistical analyses in this study.

a) Trail-making Test, Stroop Test, Parkinson Anxiety Scale, and Passive Joint-angle Matching

The Trail-making test and Stroop Test were administered in order to determine whether the Computerized Cognitive Training intervention was effective. Thus, related samples t-tests were conducted for each measure at the timepoints before and after the Computerized Cognitive Training took place. The Parkinson Anxiety Scale was used to investigate whether Cognitive Behavioural Therapy (CBT) effectively reduced anxiety, therefore, a related samples t-test was used to compare this measure before and after CBT took place. Total scores, and scores of each subsection (i.e. Persistent Anxiety, Episodic Anxiety, and Avoidance Behaviour) were analyzed between pre and post-test. The passive upper limb joint-angle matching task was performed to verify the efficacy of the Proprioceptive Training. Each angle (10, 30, and 60 degrees) was analyzed separately, and on the most affected limb only (unilateral disease progression). The
most affected side was determined using the calculation provided by Foster et al. (2011). A two-way repeated measures ANOVA was used to analyze constant and absolute error outcomes. As variable error does not involve a comparison between trials, this was analyzed with a Wilcoxon Signed-Rank test (since Shapiro-Wilk tests confirmed non-normal distributions).

Since it has been previously shown that cognitive status can affect cognitive outcomes in PD (Silveira, 2016), a further analysis was conducted for the cognitive outcome measures by categorizing participants into HIGH and LOW cognitive status subgroups. This was achieved by using a median split on the baseline Montreal Cognitive Assessment scores evaluated as a demographic measure prior to starting the study. A mixed repeated measures ANOVA (2 subgroups x 2 times of assessment) was conducted on the Trail-making test and Stroop test scores pre and post Computerized Cognitive Training. In order to remain consistent, the same analysis was also done on the Parkinson Anxiety Scale and Passive Joint-angle Matching outcomes. A median split was conducted using the baseline PAS scores, and average constant error at 60 degrees (since this was the condition demonstrating the greatest constant, absolute, and variable error) was used to categorize participants into HIGH and LOW subgroups. A mixed repeated measures ANOVA was also used to statistically analyze these outcomes pre and post CBT and Proprioceptive Training, respectively. It is important to note that these subgroups were not included in the analysis of FOG and gait measures, since the subgroups for each of these outcome measure domains (i.e. cognitive, anxiety, and proprioception outcome measures) were incongruent due to differences in group medians for each measure. That is, the individuals in the HIGH cognitive status group were not identical to those in the HIGH anxiety and HIGH proprioceptive error groups, and individuals in the LOW cognitive status group were not congruent with the LOW anxiety and LOW proprioceptive error groups.
b) FOG Measures:

All gait data (FOG and spatiotemporal parameters) were analyzed in Matlab 9.2 (MathWorks Inc.). Missing data due to marker occlusion were handled in several ways, depending on the duration of the occlusion. Short occlusions (≤ 25 frames) were filled in by cubic-spline interpolation. For occlusions of moderate length (31-60 frames), the centre of the missing section was replaced by the nearest-neighbor match, based on the 20 frames on either side of the occlusion, and then 10 frames at each end were filled with cubic-spline interpolation. These moderate-length occlusions were only filled if there was a close match (Pearson correlation r>0.95). Longer occlusions (≥61 frames) were not filled in, and the corresponding steps were excluded from the analysis. Each trial was considered to start and end with the participant’s gait onset and offset, identified by the onset and offset of the first and last peaks (respectively) in fifth-metatarsal marker anteroposterior (AP) velocity of at least 25% of the trial maximum. Signals outside this time range were not analyzed. Except where noted, signals were smoothed with a 7Hz low-pass, 4th-order, zero-lag Butterworth filter.

Freezing was identified from velocity of the xiphoid process. First, the participant’s normal velocity was calculated by averaging over the participant’s trials at each time of assessment, beginning when the velocity first reached 50% of maximum on each trial, and ending when it last dropped below 50% of maximum. Then, similar to Cowie et al. (2012), FOG episodes were identified when the velocity dropped below 10% of normal. Velocity often transiently increased during freezes (e.g. due to slight motions of the trunk) so FOG offset was marked only when velocity rose above 25% of normal. This allowed for the inclusion of periods of festination, in which “full blown” akinetic FOG episodes did not occur. This analysis did not include any initiation FOG (i.e. FOG episodes that occurred when the participant attempted to initiate
walking). Since FOG episodes did not occur in every trial, the total number of FOG episodes that occurred across three trials, and mean duration across the three trials was analyzed (rather than each trial separately). Friedman’s ANOVA was used to statistically analyze differences across all conditions (COG, LIM, and PROP) and assessment times (pre- and post-test) as a single (one-way) factor, since comparison with multiple factors was not possible using this test. Significant outcomes were further analyzed using Wilcoxon Signed Rank tests. Since Friedman’s ANOVA did not allow for an analysis between interventions, each intervention was analyzed separately.

c) Spatiotemporal measures:

Spatiotemporal gait measures were calculated from the lateral malleolus marker, including step length, step length variability, step time, step time variability and percent of time in double support. Heel strike (HS) and toe-off (TO) times were estimated from the lateral malleolus marker, using the method of O’Connor et al. (2007). However, the gait events of some participants were not consistently captured by this method (due to the large degree of variability in steps especially in PD), leading to excessive omission of steps from the analysis in some trials. To check whether the details of this method affected the results, the data were re-analyzed with an alternative method. Specifically, the AP malleolus position was low-pass filtered (zero-lag, 4th-order Butterworth), and the points of greatest acceleration and deceleration were taken as TO and HS, respectively. This matched qualitative impressions of gait events based on visual inspection of the marker data. After inspecting the data, it was determined that the AP method accurately detected a greater number of steps in each trial and would provide more reliable results, therefore, this method was used for all gait parameter calculations.

The first two steps were omitted, as were steps that contained unfilled marker occlusions or FOG events, and atypical steps that did not have alternating HS and TO events (e.g. two TO
events in a row). For each included step, the step length was calculated as the peak AP distance between the malleolus markers. Step duration was calculated as the time from HS of one foot to the next HS time of the other foot. Percent double-support was calculated as 100 times the period from HS to TO of the other foot, divided by the step duration. Variability of step length and step time were calculated using the coefficient of variation (CV) of each.

Each gait parameter was statistically analyzed using a four-factor mixed repeated measures ANOVA (3 interventions x 2 assessment times x 4 conditions x 3 trials), where each intervention was included as a separate categorical factor. Tukey’s HSD post hoc analyses were conducted when necessary. In order to determine if participants prioritized the secondary (i.e. counting) task during the cognitive dual task condition, the absolute error of the counting task was averaged across the three COG trials during the gait assessment and the trials performed when seated quietly (i.e. single task counting) at pre-test and post-test (Beck et al., 2015; Pieruccini-Faria et al., 2014). This was analyzed with a three-way mixed repeated measures ANOVA (3 interventions x 2 assessment times x 2 conditions).

d) New Freezing of Gait Questionnaire and UPDRS-III

To investigate whether there were changes in subjective FOG ratings (NFOGQ) and motor symptom severity (UPDRS-III) before and after each intervention, separate analyses for each intervention were conducted. A subsequent analysis was conducted to examine whether there were differences between intervention types using a two-factor Repeated Measures ANOVA (3 groups x 2 assessment times). Post hoc analyses were performed using Tukey’s HSD.
CHAPTER 3

Results

Seventeen individuals with Parkinson’s disease who were confirmed as freezers by a movement disorders specialist completed pre-assessment and were block randomized into six orders of receiving intervention. Following randomization, two individuals believed they were unable to meet the necessary time commitment and withdrew from the study. After commencement of the study, two individuals withdrew for reasons which are outlined in Figure 1. These individuals were kept in the final analyses, abiding by the intention to treat analysis. Participant demographics are presented in Table 1.

Table 1. Participant demographics presented as group means (standard deviation in brackets)

| Number (M/F) | Age   | Disease Duration | UPDRS-III | MoCA  | LED     | Attendance (%) |
|--------------|-------|------------------|-----------|-------|---------|----------------|
|              |       |                  |           |       |         | Cognitive Training | CBT | Proprioceptive Training |
| 15 (11/4)    | 74.22 | 10.78            | 24.9      | 24.66 | 1456.58 | 96.43          | 97.5 | 97.11 |
|              | 6.22  | 6.89             | 7.18      | 3.37  | 1010.17 | 7.64           | 5.17 | 5.48 |

Outcomes of Treatment Efficacy:

i) Trail-making test

No significant differences were found for the Trail-making test B-A score from pre-test (M=87.26 s, SD=62.27) to post-test (M=72.57 s, SD=52.34) (t(13)=1.2, p=0.25) during the Cognitive Training period. When comparing between HIGH and LOW cognitive status groups, only a main effect of cognitive status was present (F(1,12)=12.35, p=0.004), indicating that the
HIGH group performed significantly better than the LOW group, irrespective of time of assessment.

ii) Stroop Test

No significant differences were found for the Stroop test interference score from pre-test (M=27.29, SD=9.49) to post-test (M=28.36, SD=11.63) (t(13)=-0.59, p=0.56) of the Cognitive Training intervention. A comparison between HIGH and LOW cognitive status groups also revealed only a main effect of cognitive status (F(1,12)=10.4, p=0.007), in that the HIGH group had performed better than the LOW group regardless of assessment time.

iii) Parkinson Anxiety Scale

No significant differences were demonstrated for PAS scores from pre-test (M=14.33, SD=6.86) to post-test (M=13.46, SD=6.05) (t(14)=1.45, p=0.17). When comparing between HIGH and LOW anxiety groups, only a main effect of group (F(1,13)=37.52, p<0.0001) was demonstrated, indicating the HIGH group had significantly high PAS scores (reported more anxiety) than the LOW group, regardless of time. When analyzing within each subsection of the scale (Persistent Anxiety, Episodic Anxiety, and Avoidance Behaviour), no main effects or interactions were demonstrated in any of the three parts.

iv) Passive Upper Limb Joint-Angle Matching

No main effects or interactions were present for constant and absolute error outcomes at 10, 30, and 60 degrees. With respect to variable error, no significant differences were found at the 10 and 30 degree conditions, however, there was a significant improvement found at 60 degrees (Z=2.35, p=0.019) in which participants demonstrated less variable error at post-test (after completing proprioceptive training) compared to pre-test.
When comparing between HIGH and LOW groups of proprioceptive error, no significant main effects or interactions were demonstrated for constant error at 10 degrees. A time x group interaction was demonstrated for constant error at the 30-degree condition (F(1,10)=7.23, p=0.023). Tukey HSD post hoc analysis revealed that the HIGH and LOW groups were significantly different only at pre-test, but not different at post-test (Figure 2). Visual inspection of this interaction effect appeared to demonstrate that, on average, the HIGH error group undershot the target (i.e. positive constant error) at pre-test, whereas the LOW error group overshot the target (i.e. negative constant error). However, at post-test, both groups were close to the target (i.e. close to zero), suggesting that both groups improved (although no main effect of time was demonstrated). A marginally significant time x group interaction effect was also demonstrated for constant error at 60 degrees (F(1,10)=4.96, p=0.050005). Tukey HSD post hoc revealed that the HIGH and LOW groups were also significantly different only at pre-test, but not at post-test (Figure 2). However, visual inspection showed that the HIGH error group began with a lower degree of constant error (i.e. closer to zero) at pre-test, but undershot the target (i.e. negative constant error) at post-test, indicating a decline in performance. Conversely, the LOW error group began with a larger negative constant error (undershooting the target) at pre-test, but demonstrated less negative constant error at post-test, therefore showing an improvement. There were no significant group or time main effects or interactions for absolute error at any of the conditions. In regards to variable error, there were no significant interactions or main effects or interactions in the 10-degree condition. A time x group significant interaction effect was demonstrated at 30 degrees (F(1,10)=5.66, p=0.039) (Figure 2). Tukey’s post hoc was conducted, however, no significant differences were revealed. Therefore, Fisher’s LSD post hoc was conducted and revealed that the HIGH and LOW groups were significantly different only at
pre-test. Additionally, a significant improvement (lower variable error) from pre- to post-test was demonstrated by the LOW error group only. At 60 degrees, only a main effect of time was demonstrated (F(1,10)=9.44, p=0.011), in which an improvement from pre- to post-test (lower variable error) was demonstrated by all participants, irrespective of proprioceptive error group.

v) Unified Parkinson’s Disease Rating Scale (Motor Subsection)

There were no significant effects or interactions for UPDRS-III scores. However, upon visual inspection, it appeared that the only intervention which decreased scores at post-test (i.e. improved) was the proprioceptive training group (pre-test M=23.3, SD=9.73; post-test M=21.3, SD=9.1), although it should be noted that a minimum change of five points is required to be considered clinically significant (Schrag et al., 2006). The cognitive training group appeared to increase scores (pre-test M=21.5, SD=8.5; post-test M=24.6, SD=8.7), while the CBT group did not appear to change (pre-test M=21.9, SD=6.6; post-test M=22.5, SD=9.2).

vi) Dual-task Secondary Task Error

No significant main effects or interactions were detected for absolute error on the secondary (i.e. counting) task.
Figure 2. Significant results of passive upper limb joint-angle matching task in HIGH and LOW proprioceptive error groups. Time (pre and post) x group (HIGH and LOW) interactions are shown for constant error (top) in the 30-degree condition (left) and 60-degree condition (right). A time x group interaction is shown for variable error in the 30-degree condition (bottom). * represents significant differences (p<0.05).
FOG Outcome Measures

i) **FOG Severity**

When comparing pre- and post-assessment within the cognitive treatment, a significant difference was detected for the frequency of FOG episodes ($\chi^2(7)=18.06$, $p=0.011$) (Figure 3) and total duration of FOG ($\chi^2(7)=18.25$, $p=0.01$) (Figure 3). Wilcoxon signed-rank tests revealed that the frequency ($Z=2.02$, $p=0.043$) and duration ($Z=2.02$, $p=0.043$) of FOG episodes in the COG gait assessment condition at post-test was significantly less than the PROP assessment condition at pre-test. However, there was a greater frequency ($Z=2.36$, $p=0.017$) and duration ($Z=2.36$, $p=0.017$) of FOG episodes in the PROP assessment at post-test compared to the LIM assessment condition at pre-test.

Within the cognitive-behavioural therapy (CBT) group, a significant difference was found for FOG frequency ($\chi^2(7)=24.43$, $p=0.0009$) (Figure 4) and duration of FOG episodes ($\chi^2(7)=22.26$, $p=0.002$) (Figure 4). Regarding FOG frequency, Wilcoxon signed-rank tests revealed that the PROP assessment condition at post-test demonstrated a significantly greater frequency of FOG episodes compared to the BL ($Z=2.37$, $p=0.18$), COG ($Z=2.37$, $p=0.018$), and LIM ($Z=2.38$, $p=0.017$) assessment conditions at pre-test, but not at post-test. This might suggest that in the BL, COG, and LIM assessment conditions after the CBT treatment, FOG frequency increased (i.e. worsened). With respect to FOG duration, a similar trend was present, in that FOG duration became worse only in the BL and COG assessment conditions at post-test.

Within the proprioceptive training group, a significant difference was demonstrated for FOG frequency ($\chi^2(7)=19.29$, $p=0.007$) (Figure 5), and FOG duration ($\chi^2(7)=21.63$, $p=0.003$) (Figure 5). With respect to FOG frequency, Wilcoxon signed-rank tests demonstrated that the PROP assessment condition at pre-test evoked a significantly greater number of FOG episodes
compared to the BL (Z=2.37, p=0.018), COG (Z=2.2, p=0.027), and LIM (Z=2.37, p=0.018) assessment conditions at post-test, thus FOG frequency decreased in the BL, COG, and LIM assessment conditions. A similar trend was shown for FOG duration, where only the BL (Z=2.37, p=0.018) and LIM (Z=2.37, p=0.018) assessment conditions demonstrated a reduction in FOG duration at post-test.
Figure 3. Total frequency (left) and duration (right) of FOG episodes in all gait assessment conditions at pre and post after Cognitive Training intervention. *, ** represents significant differences (p<0.05).

Figure 4. Total frequency (left) and duration (right) of FOG episodes in all gait assessment conditions at pre and post after the Cognitive Behavioural Therapy (CBT) intervention. *, ** represents significant differences (p<0.05).
Figure 5. Total frequency (left) and duration (right) of FOG episodes in all gait assessment conditions at pre and post after the Proprioceptive Training intervention. *, ** represents significant differences (p<0.05).
ii) *Spatiotemporal Measures*

**Velocity:**

A marginally significant time by condition by trial interaction was also demonstrated (Greenhouse-Geisser correction: $F(3.4, 78.3)=2.53, p=0.056$) (Figure 6). Tukey’s post hoc analysis revealed that within pre-test, in all trials of the BL and COG assessment conditions, participants walked with a greater velocity compared to all trials of the PROP and LIM assessment conditions. The same trend was present within post-test as well. At post-test, all trials of the BL and COG assessment conditions also had a significantly greater velocity than the PROP and LIM assessment conditions at pre-test. The third LIM trial at post-test demonstrated a significantly greater velocity than the first two LIM and PROP trials. No main effects or interactions involving group were demonstrated, indicating that there were no differences between the three types of interventions.

Effects of condition were also investigated to confirm whether the COG, LIM, and PROP challenges of the gait assessment influenced velocity. A main effect of condition (Greenhouse-Geisser correction: $F(1.64, 37.82)=46.41, p<0.0001$) was present, where Tukey’s HSD post hoc analysis revealed that participants walked significantly slower in the PROP and LIM assessment conditions compared to the BL and COG assessment conditions. A main effect of trial was also demonstrated ($F(2,46)=4.73, p=0.013$), where Tukey’s post hoc analysis showed that velocity was lower in the first trial compared to only the third trial. A condition by trial interaction was also present (Greenhouse-Geisser correction: $F(4.1,93.6)=5.9, p=0.0002$). Tukey’s post hoc analysis showed that participants walked slower in the third trial of the COG assessment condition compared to all trials of the BL assessment condition. In the PROP assessment
condition, participants walked faster in the third trial compared to the first two trials, and in the LIM condition, the third trial was faster than only the first trial.

Figure 6. Graphical illustration of a time (pre and post) by condition (BL, COG, LIM, and PROP) by trial interaction for gait velocity. Letters represent significant differences (p<0.05).

Step Length:

There were no interactions or main effects involving time (i.e. pre and post) or group (i.e. cognitive, limbic, and proprioceptive interventions) for step length. An effect of condition was also investigated to determine whether the COG, LIM, and PROP challenges in the gait assessment affected step length. A significant main effect of condition was demonstrated (Greenhouse-Geisser correction: F(1.43,27.21)=23.13, p<0.0001), where Tukey’s post hoc showed that participants walked with shorter steps in the PROP and LIM assessment conditions compared to both the BL and COG assessment conditions. A main effect of trial was also present (Greenhouse-Geisser correction: F(1.42,26.93)=4.01, p=0.04), which also showed that
participants walked with smaller step lengths in the first trial only compared to the third trial. A condition by trial interaction was also demonstrated (F(6,114)=2.44, p=0.029). Tukey’s post hoc revealed that in all trials of the PROP and LIM assessment conditions, participants had smaller step lengths compared to all trials of the BL and COG assessment conditions. Participants also walked with longer step lengths in the third trial compared to the first trial in both the PROP and LIM assessment conditions.

**Step Length Variability (CV):**

A four-way interaction involving group, time, condition, and trial was present (Greenhouse-Geisser correction: F(8.33,74.99)=2.54, p=0.015) (Figure 7). Tukey’s post hoc analysis was conducted and showed that in the cognitive training intervention, step length variability demonstrated in the PROP assessment condition decreased at post-test. With respect to the CBT intervention, step length variability in the PROP assessment condition was reduced at post-test only in the first trial. In the proprioceptive training intervention, step length variability increased in the second trial of the BL and LIM assessment conditions at post-test. No differences between intervention types were demonstrated. Effects of condition were analyzed to determine whether the COG, LIM, and PROP gait assessment conditions influenced step length variability. A significant main effect of condition (Greenhouse-Geisser correction: F(1.45,26.17)=17.08, p<0.0001) demonstrated that the PROP assessment condition had a significantly greater variability in step length compared to all other conditions.
Figure 7. Graphical illustration of an interaction in step length variability (CV) involving group [cognitive training (top), CBT (centre), and proprioceptive training (bottom)], time (pre and post), condition (BL, COG, LIM, PROP), and trial. Letters represent significant differences (p<0.05).
Step Time:

A time by condition by group interaction also approached significance for step time (Greenhouse-Geisser correction: F(4.44,48.89)=2.38, p=0.058) (Figure 8). Tukey’s post hoc analysis was conducted and revealed that in the cognitive training group, step time in the LIM assessment condition was significantly greater at post-test. In the CBT group, at both pre- and post-test, participants demonstrated significantly greater step times in the LIM assessment condition compared to the BL and COG assessment conditions. Step time also significantly decreased in the BL, COG, and PROP assessment conditions at post-test. In the proprioceptive training group, step time in the LIM assessment condition decreased at post-test, however, also increased in the BL and COG assessment conditions at post. A significant time by trial by group interaction was also demonstrated (Greenhouse-Geisser correction: F(2.85,31.34)=3.66, p=0.024) (Figure 8), where Tukey’s post hoc revealed that the only significant difference was in the cognitive training group. Participants demonstrated significantly lower step times in the third trial at pre-test compared to the first trial at pre-test and the first two trials at post-test, irrespective of condition. Effects of condition were also investigated to determine whether the COG, LIM, and PROP challenges in the gait assessment influenced step time. A main effect of condition was demonstrated (Greenhouse-Geisser correction: F(1.64,36.0)=7.67, p=0.003), which showed that participants walked with significantly greater step time in the LIM assessment condition compared to only the BL and COG assessment conditions. A main effect of trial (Greenhouse-Geisser correction: F(1.24,27.39)=6.16, p=0.014) revealed that step time was significantly longer in the first trial only compared to the third trial.
Figure 8. For step time, a significant interaction involving group (cognitive training, CBT, and proprioceptive training), time (pre and post), and trial is shown (top). An interaction involving group (cognitive training, CBT, and proprioceptive training), condition (BL, COG, LIM, PROP), and time (pre and post) is also shown (bottom). * represents significant differences (p<0.05).
Step Time Variability (CV):

There were no effects or interactions involving time (pre to post) or group (cognitive, limbic, or proprioceptive interventions) for step time variability. Effects of condition were investigated in order to confirm that the COG, LIM, and PROP challenges in the gait assessment influenced step time variability. A main effect of condition was present for step time variability (Greenhouse-Geisser correction: F(1.22,20.75)=5.2, p=0.027). Tukey’s post hoc analysis revealed that the PROP assessment condition demonstrated significantly greater variability in step time compared to only the BL and COG assessment conditions.

Percentage of Double Support Time:

No effects or interactions involving time (pre to post) or group (cognitive, limbic, or proprioceptive interventions) were demonstrated. The effects of condition were also investigated to confirm that the gait assessment challenge conditions influenced percentage of double support time. A main effect of condition (Greenhouse-Geisser correction: F(1.98,43.49)=15.86, p<0.0001) revealed that the PROP and LIM assessment conditions demonstrated a significantly greater percentage of double support time compared to both the BL and COG assessment conditions. A main effect of trial was also present (Greenhouse-Geisser correction: F(1.5,33.03)=5.69, p=0.013), which showed that the first trial had significantly greater percentage of double support time compared to only the third trial.
Percentage of Double Support Time Variability (CV):

There were no effects or interactions of time (pre to post) or group (cognitive, limbic, or proprioceptive interventions). Effects of condition were investigated to confirm that the gait assessment challenge conditions influenced percentage of double support time variability. Only a main effect of condition was present ($F(3,54)=6.44$, $p=0.00082$), in which the PROP assessment condition demonstrated a significantly greater variability in double support time compared to only the BL and COG assessment conditions.

iii) New Freezing of Gait Questionnaire

There were no significant effects or interactions for NFOGQ scores. However, by visual inspection of the data, it appeared that in the CBT group, there was no change in NFOGQ score from pre-test ($M=13.1$, $SD=8.3$) to post-test ($M=12.9$, $SD=9.3$). The cognitive training (pre-test $M=12.8$, $SD=8.1$; post-test $M=14.9$, $SD=8.7$) and proprioceptive training (pre-test $M=13.6$, $SD=8.7$; post-test $M=14.5$, $SD=9.7$) groups, however, appeared to increase scores at post-test, which might indicate that FOG severity worsened after these interventions.

Investigating Potential Additive Effects of Interventions for FOG

The comparison of results of individual treatment groups demonstrated that proprioceptive training appeared to lead to the greatest benefit to outcome measures of gait and FOG. However, it is still unknown whether any improvements demonstrated after receiving a treatment were augmented as a result of effects from having received multiple treatments leading to additive benefits. Thus, further analyses were conducted to investigate various combinations of interventions with proprioceptive training to determine whether combining treatments with proprioceptive training would produce additional benefits to gait. Specifically, velocity, step
length variability, and step time were investigated since these parameters were shown to be most relevant from the initial analysis of results demonstrated above.

First, proprioceptive training combined with either cognitive training or CBT was investigated. There were four combinations of counterbalanced intervention orders which included proprioceptive training combined with either cognitive training or CBT sequentially (i.e. before or after) (see Figure 1). The four combinations were: i) Proprioceptive training completed before CBT; ii) CBT completed before proprioceptive training; iii) proprioceptive training completed before cognitive training; iv) cognitive training completed before proprioceptive training. To achieve this analysis, since gait trials were missing from some participants, the median of the three trials for each assessment condition was compiled so that these participants would not be excluded from the analysis. Thus, a three-way repeated measures ANOVA (2 intervention groups x 2 assessment times x 4 walking assessment conditions) was conducted for this analysis.

Second, combinations of all three interventions were investigated to determine whether the benefits of the three treatments were simply additive, thus adding more interventions would augment further improvements to gait regardless of what the treatment was. The six combinations of intervention orders (presented in Figure 1) were compared also using a three-way repeated measures ANOVA (3 intervention groups x 2 assessment times x 4 walking assessment conditions).

1) Velocity (Two Treatments Combined)

When proprioceptive training was completed before CBT, there were no main effects or interactions between intervention groups in this combination. When CBT was completed before
proprioceptive training, there were no main effects or interactions between groups in this combination.

When proprioceptive training was completed before cognitive training, there was a significant interaction between intervention group and time of assessment (group x time) (F(1,4)=19.95, p=0.011) (Figure 9). Tukey’s post hoc analysis revealed that participants walked faster at the pre-assessment of cognitive training only compared to the pre-assessment of proprioceptive training (p=0.038). By visual inspection, it appears that there was an improvement in velocity from pre to post with proprioceptive training, but velocity worsened from pre to post with cognitive training. This might suggest that the improvements to gait from proprioceptive training were carried through until the cognitive training commenced, however, cognitive training caused decrements to gait which resulted in worsening of velocity. It could also be argued that cognitive training had no effects, and that any existing improvements present from proprioceptive training were “washed out” after cognitive training was complete.

When cognitive training was completed before proprioceptive training, a significant interaction involving group (cognitive and proprioceptive training), time, and condition of walking assessment was demonstrated (F(3,12)=3.62, p=0.045). However, post hoc analyses revealed that there were no significant differences between the two interventions within each walking assessment condition. Therefore, it is likely that this interaction was driven by an effect of assessment condition. This could also indicate that adding cognitive training prior to proprioceptive training did not augment treatment effects.
Figure 9. Graphical illustration of a significant group (proprioceptive and cognitive training) by time (pre and post) interaction for gait velocity.

2) Step Length Variability and Step Time (Two Treatments Combined)

There were no main effects or interactions in any of the four combinations of groups for step length variability or step time.

3) Velocity, Step Length Variability, and Step Time (Three Treatments Combined)

There were no main effects or interactions demonstrated in any of the six intervention orders, for velocity, step length variability, and step time.

Taken together, these findings help rule out the possibility of an additive effect of having completed multiple interventions which might have influenced the interpretations and conclusions made from the initial analysis. The only effects shown were when proprioceptive training was completed prior to cognitive training. However, it was demonstrated that improvements from proprioceptive training did not result in augmented improvements with cognitive training. In fact, participants appeared to become worse after the second intervention
was added. Since there were no added improvements when combinations of two or three interventions were completed, this also confirms that employing proprioceptive training independently would have the greatest benefit to gait behaviour. Proprioceptive training alone was enough to produce these gait improvements, and combining it with cognitive or limbic interventions would not yield any additional benefits.

**Practice and Washout Effects**

A further analysis was conducted in order to rule out the influence of any potential practice effects, therefore providing further support for gait improvements resulting from improvements in proprioception. To investigate this, a one-way repeated measures ANOVA was used to analyze across all gait trials in the order that each trial was completed through each time of assessment during the study. If practice effects were present, one might expect to see a gradual improvement across time. There were no relevant changes as a result of practice in velocity (Figure 12). Similar findings were demonstrated for step length, step length variability, step time, and step time variability as well, therefore confirming that practice effects did not influence these findings.

![Figure 10. Velocities plotted across all gait assessment trials completed in the study period](image-url)
Washout effects were also analyzed during the two washout periods in this study in order to investigate whether carryover effects could have affected the results. To analyze the washout periods, performance in the gait trials were compared from the post-test assessment after the first intervention to the pre-test assessment before beginning the second intervention. If the washout period was effective, one might expect that performance should worsen. As shown above in the analysis of potential additive effects, there was no change demonstrated across washout timepoints for any of the combinations of interventions. This might suggest that any effects from the initial intervention may not have fully washed out before beginning the next intervention. However, the above analysis showed that there were no additional benefits with the different combinations of interventions, which suggests that there were no significant carryover effects.
CHAPTER 4

Discussion

The aim of the current study was to investigate and compare three types of interventions for the remediation of FOG in individuals with PD. To our knowledge, this is the first study to investigate therapies that target the potential underlying mechanism of FOG in individuals with FOG. Overall, the results appear to demonstrate that each intervention did improve some aspects of the underlying cognitive, limbic, and proprioceptive contributions to gait deficits and FOG. These findings are elaborated below.

First, it is important to confirm that the interventions did result in the expected changes (cognitive training to improve cognitive function, CBT to improve anxiety, proprioceptive training to improve proprioception), before conclusions about improvements to FOG are evaluated. Contrary to our expectation, participants did not significantly improve on any of the outcome measures of cognitive function (i.e. Trail making test and Stroop test) after the cognitive training intervention. These results also conflict with previous findings which used the same software in individuals with PD and demonstrated improvements in several cognitive measures including the Trail making test and Stroop test (París et al., 2011). It is important to note that the timing of sessions and total duration of training employed by Paris and colleagues was different than that of the current study. The total duration of the intervention was greater in the Paris study (9 hours using Smartbrain plus cognitive homework exercises) compared to the current study (8 hours using Smartbrain). However, since the aim of the current study was to keep the duration of all interventions equal and comparable, the homework exercise were not included. It is possible that increasing the total duration of training may result in the improvements demonstrated in the previous study. Additionally, there were no significant
improvements in the Parkinson Anxiety Scale after completion of CBT, which might suggest that lacked efficacy in the current study. The current study matched the guidelines for the minimum time required for a CBT intervention in individuals with PD to be effective (Egan et al., 2015), yet improvements were not significant. One possible reason why improvements were not consistent with previous studies using CBT in PD could be that the outcome measures selected in previous studies have not validated in a PD population, and may lack the sensitivity or specificity to accurately evaluate changes in anxiety. The outcome measure selected for the current study (PAS) has been validated in PD (Leentjens et al., 2014), however, sensitivity to change has not yet been evaluated. Therefore, it is also possible that the PAS was not sensitive enough to detect a change from the intervention. Participants significantly improved on the passive joint-angle matching task after completion of proprioceptive training, thus indicating that this intervention was effective in improving proprioception. This also provided clearer evidence that benefits to FOG were potentially due to improvements in proprioception.

The objective FOG measures from the gait assessment revealed that the cognitive training improved FOG severity only in the gait assessment condition which challenged the cognitive domain, however, worsened in the proprioceptive challenge condition. With respect to CBT, FOG severity appeared to worsen over all gait assessment conditions except in the proprioceptive challenge. Surprisingly, CBT was the only intervention demonstrating a worsening of FOG severity. One possible explanation for this could be that CBT allowed participants to become more aware of their gait deficits and FOG, which consequently could have triggered more FOG behaviour. Conversely, with proprioceptive training, FOG severity appeared to improve overall, except in the proprioceptive challenge condition. The lack of change in FOG severity in the proprioceptive walking assessment condition may be attributed to
the fact that it was the most challenging condition, and may require more vigorous therapy or training in order to observe a significant improvement. Overall, the severity of FOG appeared to improve across the greatest number conditions with the proprioceptive training. This type of intervention may also be the most pertinent to freezers, given that manipulations of the sensorimotor domain have been demonstrated to evoke the greatest severity of FOG episodes.

With respect to velocity, an interaction of time irrespective of intervention groups may be argued to be a practice effect, since this effect was obtained across all participants. However, as shown in the previous chapter, it was determined that there were no effects of practice. Step length variability appeared to improve with cognitive training, but only revealed in proprioceptive assessment conditions. Previous studies have demonstrated that gait variability is related to cognitive dual-task interference on gait (Hausdorff, Balash, & Giladi, 2003; Yoge et al., 2005). Furthermore, increases specifically in step length variability has been shown to be associated with poorer executive function and dementia (Brach, Studenski, Perera, VanSwearingen, & Newman, 2008; R. Morris et al., 2017; Nakamura, Meguro, & Sasaki, 1996; Pieruccini-Faria et al., 2014), and has been correlated with gray matter integrity particularly in the hippocampus and anterior cingulate gyrus [which are involved memory in executive functioning, respectively (Bush, Luu, & Posner, 2000; Olton & Papas, 1979)] in older adults (Rosso et al., 2014). Thus, the improvement in variability of step length following cognitive training may reflect an improvement in the cognitive control of gait, and potentially an improvement in the gray matter integrity of these regions. Since there was no change in performance in the secondary task, it is likely that participants were prioritizing the gait task more at post-test, hence improvements were revealed only in gait parameters. Interestingly, previous research has demonstrated that reducing sensory information available during
locomotion (i.e. challenging the sensorimotor domain) in individuals with PD causes an increase in demands on cognitive processing (Pieruccini-Faria et al., 2014). Therefore, since the improvement in step length variability was only demonstrated during the proprioceptive challenge condition, it is possible that cognitive training improvements mitigated the additional cognitive demands produced when proprioceptive processing is challenged. In contrast, step time became worse after cognitive training, but only appeared in assessment conditions where the limbic domain is challenged. Since temporal modifications of gait have been demonstrated to be influenced by sensorimotor feedback demands (Almeida et al., 2005), this deterioration in step time might be expected since cognitive training likely did not affect sensorimotor processing. Collectively, improvements from cognitive training appear to mainly affect parameters related to cognitive function, which suggests that these results fit with the objective of cognitive training.

After completion of CBT, there appeared to be an improvement in step length variability only in the first trial of the proprioceptive walking assessment condition. A previous study demonstrated that heightened anxiety caused an increase in step to step variability (Ehgoetz Martens et al., 2014; Plotnik et al., 2009; Yogev et al., 2005), therefore, the improvement in variability of step length may be an indication that anxiety was reduced as a result of CBT. Interestingly, anxiety has been shown to interfere with sensorimotor processing while walking in individuals with PD (Ehgoetz Martens et al., 2015b), which might explain why this improvement was demonstrated in the proprioceptive challenge condition. Reducing anxiety levels effectively lowered the interference on proprioceptive processing. Alternatively, this might also suggest that the effects of the proprioceptive challenge utilized in the current study (i.e. walking in complete darkness) was not influencing only the sensorimotor domain, but potentially compounded by anxiety (possibly from fear of postural instability). This has also been suggested in a previous
study using a similar manipulation (Ehgoetz Martens et al., 2013). However, it is still unclear whether anxiety is simply a consequence of an inability to use sensory feedback for postural control (Ehgoetz Martens et al., 2013). Step time also appeared to improve after CBT, which was demonstrated in the limbic assessment condition. Importantly, previous research has suggested that individuals with PD attempt to modify temporal aspects of gait (e.g. step time) in order to increase proprioceptive feedback to adapt to inaccurate basal ganglia processing (Almeida et al., 2005). Furthermore, a previous study demonstrated that when postural threat is greater (i.e. increasing anxiety), individuals with PD adapt by increasing stride time to reduce the risk of instability (Caetano et al., 2009), which could be argued to be an attempt to increase proprioceptive feedback when anxiety is overloading basal ganglia processing (since temporal modulation may be due to sensory feedback demands). In fact, anxiety has been shown to interfere with the processing of sensory feedback while walking in individuals with PD (Ehgoetz Martens et al., 2015b). Therefore, this improvement following CBT may represent an enhanced ability to use sensory feedback when the limbic domain is challenged. Since anxiety may hinder sensorimotor processing (Ehgoetz Martens et al., 2015), decreasing anxiety levels as a result of CBT may have lessened the need to increase sensory feedback while walking (e.g. by modulating temporal gait parameters) (Almeida et al., 2005).

After completion of proprioceptive training, step length variability appeared to worsen in the baseline and limbic challenge conditions of the gait assessment. As previously suggested, greater step length variability is associated with greater cognitive decline (Brach et al., 2008; R. Morris et al., 2017; Nakamura et al., 1996; Pieruccini-Faria et al., 2014), hence a deterioration in this parameter might be expected since proprioceptive training would not be influencing the cognitive domain. In contrast, step time seemed to improve when the limbic domain was
challenged, but worsened in the baseline and in the cognitive challenge conditions. Similar to the improvement in step time demonstrated after the CBT intervention in the current study, an improvement in step time may be an indication of an enhanced ability of the basal ganglia to process proprioceptive inputs as a result of proprioceptive training. As previously alluded to, heightened anxiety levels have been demonstrated to interfere with sensorimotor processing (Ehgoetz Martens et al., 2015b). Therefore, this improvement in step time, specifically in the limbic challenge condition, might suggest that improving proprioceptive functioning modulated the effect of the heightened anxiety or “limbic load” induced when walking in this gait assessment condition. One possible explanation for the decline in step time in the baseline and cognitive challenge conditions at post-test could be that proprioceptive improvements (as a result of proprioceptive training) were not utilized when the cognitive domain was challenged, which might suggest that a cognitive challenge relies on processing from other domains.

No significant changes were found for the subjective assessment of FOG severity (NFOGQ). Interestingly, visual inspection of the means showed that there was an increase in scores (i.e. worsening of FOG severity) after cognitive and proprioceptive training (although not significantly), but scores remained the same after CBT. There were also no statistically or clinically significant changes in UPDRS-III scores in any of the three interventions. It is worth noting, however, that proprioceptive training was the only intervention in which scores lowered, indicating an improvement (although not significantly). This slight improvement would be expected after a proprioceptive intervention, since this assessment evaluates motor symptom severity.

These findings may also offer insight into the underlying mechanism of FOG. Overall, results seem to correspond with the cross-talk model (Lewis & Barker, 2009). In brief, this
model theorizes that FOG episodes are caused by competing demands of the cognitive, limbic, and sensorimotor circuits, which overloads and transiently depletes processing resources required for locomotion (Lewis & Barker, 2009). The limited output nuclei in each of these domains creates an element of cross-talk, wherein the processing output of each domain conflicts with one another. It is believed that these cortical domains connect downstream onto a common neural pathway, and it is conflict within this pathway that may trigger FOG (Lewis & Shine, 2014). Since improvements found by each intervention were demonstrated in incongruent domains, this might suggest that each intervention was able to reduce the conflict in processing between domains. For example, cognitive training showed an improvement in gait in the condition which challenged the sensorimotor domain. This might denote an enhanced ability to process proprioceptive challenges when cognitive processing improves, which could suggest that the processing conflict between the sensorimotor and cognitive domain was resolved due to the intervention. Likewise, the improvement in gait in the proprioceptive challenge condition following CBT might indicate that this intervention decreased the processing conflict between the limbic and sensorimotor domains. Furthermore, the improvement demonstrated in the limbic challenge condition, as a result of proprioceptive training, could also be indicative of improvements in processing conflict between the sensorimotor and limbic domains. Therefore, since a reduction in the processing conflict between domains could potentially explain these improvements in gait, this provides further support for the cross-talk model as the underlying mechanism of FOG.

Although the cross-talk model highlights the contribution of three domains to the underlying mechanism, it was previously demonstrated that a challenge to proprioceptive processing caused the greatest decrement to gait and severity of FOG episodes (Chow &
Based on findings from this particular study, an alternative hypothesis for the mechanism underlying FOG could be that a proprioceptive impairment lies central to the impairments of the cognitive and limbic domains. That is, gait decrements demonstrated when the cognitive or limbic domains are challenged only because the additional cognitive or limbic demands consume processing resources away from effective proprioceptive processing, which is also impaired. Thus, a deprivation of processing resources from the impaired sensorimotor domain could potentially be underpinning impairments in all gait conditions. If this were the case, then a proprioceptive treatment should decrease the gait impairments demonstrated in the cognitive and limbic domains. Indeed, after proprioceptive training FOG severity did improve in the cognitive and limbic challenge conditions (although ironically not in the proprioceptive walking assessment condition). This could be an indication that improving the underlying proprioceptive impairments resulted in less detriments to gait when processing resources are depleted by cognitive or limbic challenges. Furthermore, after the cognitive and limbic interventions, improvements to gait in the proprioceptive walking condition were exhibited. In support of this hypothesis, an explanation for this could be that improving upon cognitive and limbic processing deficits led to a reduction in processing resources required by the cognitive and limbic domains, therefore leaving more resources available for proprioceptive processing.

While this is a compelling argument, this hypothesis does not fully explain all the results. For example, participants appeared to worsen in the limbic challenge condition (with respect to step length variability) and in the cognitive challenge condition (with respect to step time) following the proprioceptive intervention. If proprioceptive impairments were underlying cognitive and limbic deficits, then improvements in the cognitive and limbic conditions should have been demonstrated. Furthermore, FOG severity worsened in the proprioceptive challenge
condition after the cognitive intervention. Similarly, if the cognitive domain was depriving the sensorimotor domain from processing resources, then improving upon cognitive function should have also reduced FOG severity in the proprioceptive challenge condition. Therefore, it remains unclear whether proprioceptive impairments are the sole underlying cause of FOG.

The findings from this thesis provide preliminary evidence for the therapeutic benefits of novel treatments for FOG. These findings may guide future research and clinicians in the development of treatment strategies for freezers. In summary, all three treatments improved in some aspects of FOG. Based on the collective evidence presented in this thesis, it could be suggested that proprioceptive training would offer the best outcomes for individuals with FOG, since it provided the most benefit and least detriment to objective gait measures compared to the cognitive and limbic interventions. Furthermore, proprioceptive training could be easily implemented and practiced by PD patients since it was the most cost-effective intervention and could be done with minimal supervision. Therefore, proprioceptive training would be the most efficient intervention to be employed in a clinical setting or in the community.

**Thesis Limitations**

There are several considerations that need to be carefully contemplated in this thesis. First, as stated previously, the secondary outcome measures which were intended to confirm the efficacy of each treatment indicated no significant changes from the cognitive training or CBT treatments. It could be suggested that these interventions were either not effective given the limited time frame of this study, or the outcome measures selected were not sensitive enough to detect changes as a result of treatment. A previous study using the same cognitive training software in individuals with PD demonstrated cognitive improvements after completing nine
hours of training (París et al., 2011). With respect to CBT, a previous study in individuals with PD showed improvements to anxiety levels with 16 hours of group CBT (Lakkhina Troeung et al., 2014). Although neither of these studies investigated changes to gait as a result of treatment, it may be postulated that improvements to gait could occur only after these specific time frames of treatment. The lack of significant outcomes in cognitive function and anxiety in the present study creates difficulty in inferring that the demonstrated changes in gait or FOG demonstrated are truly due to the effects of the intervention. However, it could be argued that objective spatiotemporal measures of gait are more sensitive to changes in cognitive function, since evidence has shown that gait impairments precede cognitive decline (Montero-Odasso et al., 2014; Montero-Odasso, Verghese, Beauchet, & Hausdorff, 2012; Montero-Odasso & Hachinski, 2014; R. Morris et al., 2017). Thus, the gait changes demonstrated could validly represent intervention effects that were merely not captured by the outcome measures selected. Other approaches to treatment, such as pharmacological interventions for cognitive and anxiety problems may provide greater benefits, since the non-pharmacological interventions employed in the current study were not efficacious.

Second, the sample size included in this study was quite small despite the fact that the maximum number of available freezers was included. Since dementia was a criterion for exclusion in this study, this further limited the number of eligible participants, as cognitive decline tends to be worse in individuals with FOG (Amboni et al., 2008; Giladi et al., 2007; Shine, Naismith, & Lewis, 2013). Furthermore, this might also limit the external validity of the findings of the study since these treatments were not assessed in freezers with dementia. However, in order to overcome the limitation in sample size, a cross-over design was employed in this study which allowed all participants to undergo all interventions.
Third, due to the inherent nature of a crossover design, participants were required to undergo outcome measure assessments at two additional time points. This could have introduced practice effects which may influence the results. The reason for utilizing a crossover design was to maximize the number of participants completing each intervention since the sample of available participants was limited. The counterbalanced order of interventions may have moderated any practice effects that might have occurred. The potential influence of practice effects was investigated, and demonstrated that there were no differences across time in gait outcome measures.

Fourth, another inherent limitation of using a crossover design is the potential for carryover effects from the interventions completed previously to combine with effects of interventions completed later. However, as demonstrated in Chapter 3, there were no additional benefits shown with different combinations of interventions added to proprioceptive training. Therefore, it could be argued that carryover effects did not influence results.

Finally, the method used for the gait analysis in the current study employs a novel technique which utilized anteroposterior (AP) acceleration to automatically mark gait events, rather than vertical acceleration which has been applied in previous studies. Although this AP method has not been validated, it appeared to be better than the vertical method at accurately capturing gait events. The reason for this discrepancy may be because the vertical method was only validated in healthy individuals (O’Connor et al., 2007). However, due to the large degree of gait variability in individuals with PD, which are exacerbated in freezers, the resulting signals were highly inconsistent causing the vertical algorithm to omit several steps in every trial. This might suggest that the vertical method is not appropriate for analysis of gait in populations with
movement disorders, and that the AP method should be used as the standard instead. However, it is recommended that future studies should first validate this method in this population.

**Conclusion**

In summary, evidence from this pilot investigation suggests that all three types of therapies were able to improve aspects of FOG behaviour either directly (e.g. severity of FOG episodes) or indirectly (e.g. gait parameters related to FOG). Therefore, each intervention could be employed as a viable treatment option for FOG. Individual treatment approaches might also be beneficial. For example, individuals with greater cognitive impairment may benefit from cognitive treatment, and individuals with anxiety may benefit from an anxiety treatment. However, overall, proprioceptive training demonstrated the most improvement to direct objective measures of FOG severity. This might suggest that interventions targeting proprioceptive processing could provide the most relevant improvement to individuals with FOG. Furthermore, results demonstrated by each type of intervention may also provide some insight into the underlying mechanism of gait impairments and FOG episodes.

**Future Directions**

Given that this was an exploratory study, future studies should investigate these treatments in a larger sample of freezers, and employ a more stringent study design, such as a randomized controlled trial (gold-standard). The inclusion of a control group could confirm that any improvements seen are due to the interventions. Studies could also investigate whether combining all three treatments could augment benefits to FOG. Additionally, neuroimaging techniques could be used to explore functional and/or structural neural changes in cortical...
networks that may be involved in the underlying mechanism of FOG (i.e. the cognitive, limbic, and sensorimotor domains). This might provide insight into the mechanisms by which each intervention could improve FOG behaviour, which could also allow for amendments to interventions to be made in order to maximize benefits to FOG. Furthermore, the pragmatics of each of these interventions could be assessed in order to determine whether these interventions would be suitable for implementing in a clinic or in the community, and could provide feedback to make interventions more enjoyable and fulfilling for participants.
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