# Understanding the influence of anxiety on gait in Parkinson's disease

by

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## AUTHOR'S DECLARATION

This thesis consists of material all of which I authored or co-authored: see Statement of Contributions included in the thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

# STATEMENT OF CONTRIBUTIONS

I have made substantial contributions to all work presented in this thesis, including the conception and design of the research experiments. I performed all data acquisition, analysis and interpretations for this work. Finally, I drafted all manuscripts and actively took part in the revision process.

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## Abstract

Anxiety is a prevalent non-motor symptom of Parkinson's disease (PD) and has been linked to motor impairments in PD, yet there is a huge gap in the understanding of whether anxiety affects movement, namely gait, in those with PD. Thus, the main objective of the current thesis was to understand *if* and *how* anxiety influences gait in PD and whether dopaminergic replacement therapy mediates this relationship. Three studies were conducted to achieve this objective by using a virtual reality setup where participants were asked to walk in virtual environments with and without threat (i.e. across an ELEVATED plank versus across a plank located on the GROUND). Throughout all of the studies all participants (PD and healthy age-matched controls) had greater levels of anxiety in the ELEVATED condition and walked with a slower velocity, smaller steps and greater step-to-step variability compared to the GROUND condition. These results confirmed that the experimental manipulation was effective in every study. The most interesting results in this thesis found that the ELEVATED condition provoked a greater number of freezing of gait (FOG) episodes in PD Freezers (study 1) and significantly more variable gait specifically in Freezers compared to Non-freezers (study 1) and in those with PD who had high trait anxiety compared to those with PD who had low trait anxiety and healthy control participants (study 2). Highly trait anxious PD also appeared to be less able to use visual feedback about their lower limbs when it was provided (study 3) to improve gait especially in the ELEVATED condition. Notably, the frequency of FOG in Freezers (study 1) and step-to-step variability (among other gait parameters) in highly trait

anxious PD (study 2 and 3) were improved with dopaminergic replacement therapy. Furthermore, dopaminergic medication also improved step time variability in highly trait anxious PD when visual feedback about their lower limbs was available (study 3). Taken together, this thesis provides strong evidence to suggest that anxiety influences gait in PD, possibly by demanding shared processing resources at the level of the basal ganglia, which may interfere with other processes (such as processing sensory information) necessary to control gait. Dopaminergic replacement therapy might improve information processing within the basal ganglia and thus alleviate some of the interference due to the competition for shared resources. In conclusion, this thesis has (i) provided evidence that suggests anxiety does have an important impact on gait in PD; (ii) provided a mechanistic explanation for *how* anxiety exacerbates gait impairments in PD; and (iii) elucidated the role of dopamine in mediating anxiety's influence on gait in PD. Therefore, this thesis has extended the current understanding of anxiety's influence on movement in PD which has important implications for better management of anxiety and gait impairments in PD.

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# Dedication

This dissertation is dedicated to my loving husband, Brett Meadows. Without his continual encouragement, motivation, love and selflessness, I would not have been able to achieve the accomplishments I have throughout these past five years. He inspires me to pursue my dreams, celebrates any success I achieve, and keeps me grounded and focused on our future goals. I am forever grateful to have a companion that is so deeply committed to my success and happiness.

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# Chapter 1

# INTRODUCTION

## 1.1 Parkinson's Disease

Parkinson' disease (PD) is one of the most common neurodegenerative disorders, affecting nearly 100,000 Canadians with an overall prevalence rate between 1-2% of the population. It is characterized by dopaminergic depletion in the nigrostriatal pathway because of extensive loss of dopamine-producing pigmented cells in the basal ganglia, specifically the substantia nigra (Agid et al., 1989). The basal ganglia (including the caudate, putamen, nucleus accumbens, globus pallidus, subthalamic nuclei, and substantia nigra) are important components of complex neural networks serving sensorimotor, cognitive and limbic functions, and process an array of information delivered from these segregated BG-thalamo-cortical circuits. Researchers have noted that during the first decade of neurodegeneration there is a rapid rate of dopaminergic neuronal loss (40-50%) that impacts many of these circuits early in the disease progression (Braak, Ghebremedhin, Rüb, Bratzke, & Del Tredici, 2004; Fearnley & Lees, 1991), and manifest most of the motor and non-motor symptoms of PD.

Bradykinesia (slowness of movement), rigidity (stiffness), tremor and postural instability are common motor symptoms of PD and their severity are typically evaluated by using the Unified Parkinson's Disease Rating Scale motor subsection (UPDRS-III). Gait is also affected in those with PD often appearing as slow and small "shuffled" steps that are

arrhythmic. Gait disturbance is often referred to as the most debilitating motor symptom, since it limits one's mobility and independence. Furthermore, mild gait impairments can eventually progress to a more severe phenomenon known as freezing of gait which is one of the leading causes of falls (Paul et al., 2014) and hospitalization in PD. Ambulatory quantitative assessment has become one of the most useful tools for measuring these gait impairments in PD (Maetzler, Liepelt, & Berg, 2009) in order to better understand the origins and phenotype of gait deficits and begin to quantify and analyze severe gait disturbances like freezing so that therapies can be developed to overcome them. Even though gait impairments contribute greatly to independence and quality of life in those with PD, their origin, progression, and management still remain largely unknown.

It is likely that PD gait impairments are multifactorial in origin, but there is strong evidence to suggest that impaired integration of sensory feedback from vestibular, visual and proprioceptive sensory systems are major contributors (Patel, Jankovic, & Hallett, 2014). In fact, the BG have been thought of as a gate-keeper for sensory inputs at various levels of the central nervous system (Abbruzzese & Berardelli, 2003; Kaji & Murase, 2001) since they indirectly process sensory information and feedback that is critical for movement control. Although gait is typically considered an automatic motor skill requiring very little attention or resources in order to carry it out, gait automaticity is reduced in those with PD, likely as a result of impaired sensory integration. It has been noted by many researchers that PD patients rely heavily on vision (both of their limbs and optic flow) to maintain and coordinate gait as a

compensatory process (Azulay, Mesure, Amblard, & Pouget, 2002; Davidsdottir, Wagenaar, Young, & Cronin-Golomb, 2008; Ehgoetz Martens, Ellard, & Almeida, 2015b; Martens & Almeida, 2012). Since those with PD are required to cognitively control their walking in order to compensate for their gait deficits (Iansek, Danoudis, & Bradfield, 2013; Lord et al., 2014), gait becomes highly sensitive and susceptible to interference from secondary tasks and possibly other non-motor symptoms of PD.

A number of non-motor symptoms also accompany PD such as sensory abnormalities, cognitive impairments (Caballol, Martí, & Tolosa, 2007; Locascio, Corkin, & Growdon, 2003), autonomic dysfunction (Korchounov, Kessler, Yakhno, Damulin, & Schipper, 2005; Thorner, 1975), and mood disorders (for complete review see (Chaudhuri, Healy, & Schapira, 2006)). Many of these symptoms often go undiagnosed and undertreated despite being present in the majority of patients (Chaudhuri, Yates, & Martinez-Martin, 2005; Sullivan, Ward, Hauser, & Zesiewicz, 2007). Importantly, PD patients rank non-motor symptoms amongst the top symptoms that influence quality of life (Schrag, Jahanshahi, & Quinn, 2000; Witjas et al., 2002). Research has shown that anxiety and depression have more than twice the impact of motor symptoms on health status in PD (Hinnell, Hurt, Landau, Brown, & Samuel, 2012), yet very little research has focused on non-motor symptoms. Non-motor symptoms overall are poorly understood in PD and even less is known about whether they interact and possibly contribute to motor impairments such as gait in PD.

### 1.1.1 Responsiveness of Motor and Non-motor Symptoms to Dopaminergic Therapy

To date, the most effective treatment for PD aims to restore nigrostriatal dopaminergic transmission by supplying dopaminergic replacement therapy (i.e. levodopa or dopaminergic agonists). The majority of motor symptoms improve with dopaminergic treatment however there are some notable exceptions, such as balance control and gait rhythmicity (Almeida, Frank, Roy, Patla, & Jog, 2007; Lord, Baker, Nieuwboer, Burn, & Rochester, 2011; Yogev et al., 2005). Overall, the extent of dopaminergic improvements for non-motor symptoms largely remains unclear. Research has shown inconsistent findings with respect to the influence of dopamine on sensory processing, mainly proprioceptive deficits in PD (Ehgoetz Martens, Ellard, & Almeida, 2013; Mongeon, Blanchet, & Messier, 2009; Suilleabhain, Bullard, Dewey, & Hines, 2001). Additionally, dopaminergic treatment can also selectively improve cognition (Kehagia, Barker, & Robbins, 2010) and mood fluctuations in PD (Czernecki et al., 2002; Menza, Sage, Marshall, Cody, & Duvoisin, 1990). For example, levodopa treatment has been found to alleviate depression in PD (Barone, 2010; Czernecki et al., 2002) perhaps since dopaminergic innervation of the ventral striatum is involved in Parkinsonian depression. A few small studies have also demonstrated a relationship between anxiety and levodopa treatment (Black, Hershey, Hartlein, Carl, & Perlmutter, 2005; Maricle, Nutt, Valentine, & Carter, 1995), suggesting these symptoms may also be linked to a dopaminergic deficit. However, anxiety is

still one of the most under-studied non-motor symptoms of PD and further research is needed to fully understand whether it is truly responsive to dopaminergic medication.

### 1.2 Anxiety in PD

Research on anxiety in PD has largely been neglected, irrespective of its prevalence in up to 50% of people with PD (Marinus, Leentjens, Visser, Stiggelbout, & Van Hilten, 2002) and its impact on quality of life (Hanna & Cronin-Golomb, 2012). Furthermore, research has shown that anxiety in PD affects quality of life more than depression, overall cognitive status, and even their motor deficits (Hanna & Cronin-Golomb, 2012). It is important to note that anxiety is much more common in PD than in age-matched healthy older adults (Bogdanova & Cronin-Golomb, 2012; Bolluk, Ozel-Kizil, Akbostanci, & Atbasoqlu, 2010; Picillo et al., 2013) which has prompted psychological explanations for the origins of anxiety in PD. Some researchers have postulated that anxiety may be a reaction to the diagnosis of PD, and is further amplified from debilitating, unpredictable and uncontrollable motor symptoms (e.g. freezing of gait) (Burn et al., 2012). Although these explanations hold true, anxiety in PD cannot be fully explained by a psychological response since anxiety is more prevalent in PD compared to other populations with similar chronic diseases (Menza, Robertson-Hoffman, & Bonapace, 1993) and often precedes motor symptom onset in those with PD (Jacob, Gatto, Thompson, Bordelon, & Ritz, 2010). Importantly, anxiety and motor symptoms in PD share a common pathophysiology, thus neurobiological mechanisms also likely play a significant role in their origins (Dissanayaka et al., 2014; Péron, Dondaine, Le Jeune, Grandjean, & Vérin, 2012).

Although it has been speculated that the etiology of anxiety in PD is multifactorial, the exact pathophysiology remains unknown. Many researchers have postulated that anxiety in PD may result from dysfunctional dopaminergic systems, which has been supported by evidence from PET studies showing a relationship between severity of anxiety and striatal dopamine transporter (DAT) availability in the basal ganglia (Ceravolo et al., 2013; Moriyama et al., 2011; Weintraub et al., 2005) and even *de novo* PD patients with anxiety show severe reductions of striatal DAT density compared to those without anxiety (Erro et al., 2012). Dopaminergic degeneration in PD is known to influence the mesolimbic and mesocortical pathways projecting from the BG (ventral striatum aka nucleus accumbens) to emotional centers such as the amygdala and prefrontal areas (Heimer et al., 1997; Mogenson, Jones, & Yim, 1980) which are critical for emotional processing (LeDoux, 2000; Phan, Wager, Taylor, & Liberzon, 2002) and regulation of anxiety (LeDoux, 2000). Research has shown that individuals with PD have up to a 20% reduction in volume in the amygdala (Harding, Stimson, Henderson, & Halliday, 2002), and PET and fMRI studies also revealed metabolic abnormalities and reduced activation in the limbic system including the amygdala in PD (Harding et al., 2002; Ouchi et al., 1999; Tessitore et al., 2002). Thus, dopaminergic depletion in the basal ganglia-limbic circuits is one possible mechanism involved in PD anxiety. In support of this theory, studies have shown that dopaminergic replacement therapy can improve anxiety (Maricle, Nutt, Valentine, et al., 1995), and furthermore that anxiety fluctuates with dopamine independent of motor fluctuations (Leentjens et al., 2012; Maricle, Nutt, & Carter,

1995). Such findings are controversial. Some have asserted that there is no improvement following levodopa (Dissanayaka et al., 2010; Kummer, Cardoso, & Teixeira, 2010; Menza et al., 1993; Pontone et al., 2009). In fact some evidence even suggested that levodopa may even exacerbate anxiety (Singh, Althoff, Martineau, & Jacobson, 2005). There is also a growing body of research that demonstrates emotional dysfunction in PD may not be limited to dopaminergic dysfunction but other neurotransmitter alterations as well.

While widespread dopaminergic loss is a main feature of PD, other neurotransmitter systems also degenerate or are impacted by the degeneration process such as noradrenergic and serotonergic systems (Halliday et al., 1990). According to the neuropathological staging of PD proposed by Braak and colleagues, amygdala dysfunction first appears in the presymptomatic stage 3 (total of 6 stages) (Braak et al., 2006, 2004). The amygdala connects with locus coeruleus and receives noradrenergic and dopaminergic innervation (Fallon, Koziell, & Moore, 1978; Fudge & Emiliano, 2003) which is reduced in PD (Moore, 2003) adding to the damage within the limbic system. Additionally, negative correlations between locus coeruleus binding potential and severity of anxiety in PD (Remy, Doder, Lees, Turjanski, & Brooks, 2005) supports a direct role for noradrenaline in the pathophysiology of anxiety in PD. Evidence also shows that anxiety symptoms in PD improve with the selective serotonin reuptake inhibitor, citalopram (Menza, Marin, Kaufman, Mark, & Lauritano, 2004), possibly suggesting a serotonergic origin as well. Therefore, it is evident that anxiety in PD is

multifactorial, and further research is needed in order to fully understand both the dopaminergic and non-dopaminergic contributions to anxiety in PD.

In addition to the unknown pathophysiology of anxiety, the overall influence that anxiety has on other PD symptoms is a mystery. Research has identified symptoms that are associated with anxiety in PD such as more severe motor problems (Siemers, Shekhar, Quaid, & Dickson, 1993), gait problems and dyskinesias (Vazquez, Jimenez-Jimenez, Garcia-Ruiz, & Garcia-Urra, 1993) and an incredibly debilitating phenomenon called freezing of gait (Lieberman, 2006), suggesting that anxiety may have implications on movement in PD, especially gait. Considering that gait in PD is highly susceptible to interference since it demands conscious control due to the loss of automaticity (Iansek et al., 2013), it seems plausible that anxiety may have an extraordinary influence over gait in those PD who have greater amounts of anxiety. Bearing in mind the limited amount of research on anxiety in PD to date, there are even fewer studies that have directly investigated whether anxiety influences movement in PD, let alone gait impairments. Most of the existing research has focused primarily on quantifying the influence of anxiety on postural stability in healthy adults during static balance (i.e. standing on a platform) or using a standing rise to toes task (Adkin, Frank, Carpenter, & Peysar, 2000, 2002; Brown, Polych, & Doan, 2006; Brown, Sleik, Polych, & Gage, 2002; Carpenter, Frank, & Silcher, 1999; Carpenter, Frank, Silcher, & Peysar, 2001). Their findings suggest that increased postural threat (typically a height manipulation) causes both young and older adults to tighten their control over their body and minimize their

variability of sway, leading to a tighter regulation of their center of mass and a reduced risk of losing their balance. A few studies have extended this paradigm to evaluate the effects of anxiety on static balance control in PD. However, results showed that PD and healthy older adults were similarly affected by anxiety (Pasman, Murnaghan, Bloem, & Carpenter, 2011), and dopaminergic medication in PD also did not influence postural response to threat (Brown, Doan, Whishaw, & Suchowersky, 2007). It was concluded in both of these studies that upright standing may not be challenging enough, and more dynamic tasks such as walking may be necessary to detect measurable differences. Two studies have investigated gait differences in PD in response to postural threat or emotional stimuli. However, both studies also found that those with PD employed similar strategies of accommodation to postural threat as those of healthy older adults (Caetano, Gobbi, Sánchez-Arias, Stella, & Gobbi, 2009; Naugle, Hass, Bowers, & Janelle, 2012). Thus, to date, there has been very little evidence that anxiety influences gait in PD differently than in healthy older adults, even though there is a strong theoretical framework that might suggest an intricate and important relationship between the two. It is important to note however, that many studies with these null results have acknowledged the importance for future research to consider: 1) including a broader spectrum of PD patients with anxiety and with different levels of severity of motor impairments; 2) tasks that are focused on more dynamic balance measures; and 3) clarifying the influence on dopaminergic replacement therapy, since most studies only investigate PD patients when they are on rather than off their dopaminergic medication.

### 1.3 Theoretical Basis for How Anxiety may Influence Gait in PD

Emotion has been known to have widespread influences on cognitive processing, physiological activation, motor behavior and subjective feeling state, and can present as both a temporary state and/or a chronic emotional arousal although both affect cognitive processing (Eysenck, Macleod, & Mathews, 1987; Mogg, Bradley, De Bono, & Painter, 1997; Mogg, Bradley, & Williams, 1995; Mogg & Bradley, 1998; Williams, Watts, Macleod, & Mathews, 1988). From a cognitive perspective, emotional disorders, such as anxiety, often result from a breakdown in the complex information processing system within the brain. Research suggests that anxiety reduces processing capacity and impairs processing efficiency especially in the central executive and attentional systems of working memory in the healthy population (Eysenck & Derakshan, 2011; Eysenck et al., 1987). Thus, anxiety in PD may act in a similar way, but have more profound consequences on movement since there are greater demands placed on resources especially during walking.

#### 1.3.1 Resource Management and Processing Capacity

Within the brain, it is commonly believed that there are a limited number of resources that are used to process information and perform mental functions. Many mental functions (such as movement control, emotional regulations, sensory processing, perception, etc.) share from a common resource pool limited by its capacity to process information (i.e. resource capacity) (Baddeley, 1992). Given the limited capacity of these mental resources, if one component (user) takes/demands resources, then fewer resources are available for the other

components or processes, so there is often competition for resources. Thus, processes that make relatively small demands upon the resource pool proceed simultaneously but whenever the overall requirements exceed the capacity of the resource pool, then breakdowns in information processing occur (Williams et al., 1988). Automatic processes are operations that can be carried out regardless of the availability of resources, since they are rarely constrained by capacity limitations, whereas a controlled process is a temporary sequence of operations activated under control of and maintained through processing resources, and therefore are tightly constrained by capacity limitations, and susceptible to interference (Williams et al., 1988). Therefore, processes such as gait which are normally automatic in the regular population become controlled processes in PD (due to their disease), and may therefore be particularly susceptible to the influence of anxiety.

Interestingly, emotion-evoking stimuli (especially threatening and fear inducing stimuli) receive privileged access to these resources (Fox, Russo, Bowles, & Dutton, 2007; Pessoa, 2010). The amygdala can allocate these resources through attention (i.e. ventral attentional network in the brain dealing with salience) to prioritize processing of relevant information to the threat (Holland & Gallagher, 1999). For example, if one were to see a snake, the amygdala would be activated in response to the threat, and would take the central resources and allocate them to visual processing in order to enhance the perception and awareness of the snake and to control subsequent behaviors accordingly (Egner & Hirsch, 2005; Pessoa, 2010). However, if emotions are too intense then behavior and performance can severely suffer, since

the emotional response might be consuming the majority of resources. Thus, emotional responses can take processing resources away from other cognitive tasks, such as processing sensory information about other aspects of the environment (Blair et al., 2012) or processing sensory information about their own movement, all of which are needed in order to control walking and navigate complex environments.

Within the theoretical framework of information processing and resource capacity, it is also highlighted that capacity limitations can exist within the working memory system (central executive) which serves as a temporary store for intermediate processing (Baddeley, 1992), and capacity limitations can also be present within specific structures that are necessary for information processing and performance (Williams et al., 1988). For example, tasks that draw on a single pool of resources cannot easily be performed at the same time without some cost, whereas those which draw upon different pools can proceed simultaneously. Thus, the efficiency with which tasks can be performed may depend on the amount of resources within a given pool, and the number of tasks that draw upon a given pool. I postulate that the basal ganglia may have a finite capacity of resources which must be allocated to process concurrent inputs.

### 1.3.2 Specificity of the Basal Ganglia

Since the basal ganglia are important structures for processing cognitive, sensorimotor and limbic inputs, competition for resources is inevitable. Furthermore, the amount of resources in this pool may be markedly reduced if the basal ganglia are damaged as they are in

Parkinson's disease. Integrated processing across different basal ganglia circuits has been suggested to be modulated by striatal dopamine (Lewis & Barker, 2009a, 2009b), such that when dopamine levels are critically low (e.g. when PD patients are off their dopaminergic medication) there may be only sufficient resources to accomplish limited tasks. Therefore, the capacity of the BG and the limited resources available might impair one's ability to effectively process various types of incoming information (i.e. sensory, emotional, cognitive) and ultimately affect movement output (Lewis & Barker, 2009a). More specifically, the interconnections between the limbic and motor circuits within the basal ganglia (nucleus accumbens) provide the theoretical means for anxiety to influence motor outputs (Nakano, 2000), like gait, especially in stressful situations.

Given that the basal ganglia is broken in PD and cannot sufficiently perform what is supposed to be automatic processing of information that the cortex depends on, the broken basal ganglia may also require central resources in order to compensate for the damage (Wu & Hallett, 2005). Thus, anxiety likely influences information processing at the cortical central executive level (e.g. the working memory system), as well as at the structural level of the basal ganglia. Additionally, anxiety may also influence the interaction between these two levels such that it might affect the amount of resources the damaged basal ganglia demand from the central executive to compensate in order to process threat-related information as well.

## 1.4 The Problem

Currently it is well established that anxiety is a common and prominent non-motor symptom of Parkinson's disease (Marinus et al., 2002; Prediger, Matheus, Schwarzbold, Lima, & Vital, 2012) that has a major impact on movement symptoms, specifically gait impairments (supported by correlations, (Burn et al., 2012; Dissanayaka et al., 2014; Lieberman, 2006)), and is a major contributor to quality of life (Hanna & Cronin-Golomb, 2012). Research has shown that anxiety demands resources and attention (Eysenck et al., 1987; Mogg, Mathews, & Eysenck, 1992) and can influence postural control and balance in healthy individuals (Adkin et al., 2000, 2002; Brown et al., 2006; Carpenter et al., 2001; Gage, Sleik, Polych, McKenzie, & Brown, 2003). However, currently, there is a gap in the understanding of whether anxiety affects movement, namely gait, in a population with basal ganglia damage such as those with Parkinson's disease. It is even less clear whether anxiety demands additional resources in PD than in normal, older adults, and if the resources are required at the level of the basal ganglia level and modulated by the level of dopamine in the system.

In the current thesis, anxiety will be defined as feelings of worry, fear, threat, and panic and will be measured and manipulated at both the state level, defined as a temporary period of emotional arousal (e.g. induced by walking through a threatening environment), and trait level, defined as a chronic level of emotional arousal (e.g. comparing groups with different levels of trait anxiety). Both state and trait levels of anxiety have been shown to influence cognitive processing in previous work (Eysenck et al., 1987; Mogg et al., 1997, 1995; Mogg & Bradley,

1998; Williams et al., 1988). Although there are a number of methods that could be employed to investigate the role of anxiety on gait in PD, the bulk of the literature has used a manipulation of postural threat by raising participants off of the ground and/or constraining the width of the pathway (Adkin et al., 2000, 2002; Brown et al., 2007, 2006, 2002; Caetano et al., 2009; Carpenter et al., 1999, 2001; Gage et al., 2003; Pasman et al., 2011). Thus, across all of the studies in this thesis, a similar manipulation was carried out, where participants were asked to stand or walk across a plank that was located on the ground, or high above a deep pit. This was conducted using virtual reality in order to maximize safety, and was verified in each experiment to be an effective tool to manipulate anxiety using measures of self-reported levels of anxiety, skin conductance and observations of common gait adaptations observed from previous studies on healthy older adults. Additionally, in order to evaluate the role of dopamine and its influence on anxiety and gait, a comparison between ON and OFF dopaminergic states was made within those with PD.

## 1.5 Overall Thesis Aims

The overall goal of the present thesis was to examine whether anxiety influences gait in Parkinson's disease, and gain a better understanding of whether this relationship is mediated by dopaminergic replacement therapy. Since the topic of anxiety and walking was largely motivated by anecdotal reports from patients who experience freezing of gait (FOG), the first study aimed to evaluate whether anxiety influences FOG and whether dopaminergic replacement therapy influences FOG in anxiety-provoking situations. In order to fully

understand how anxiety might influence FOG, it is also necessary to understand how anxiety effects walking in PD who do not freeze, but do have basal ganglia damage with a broad spectrum of anxiety profiles. Thus, the second study in this thesis aimed to investigate whether anxiety effects gait in regular PD and also if dopaminergic medication modulates the effect anxiety has on gait. Based on the theoretical framework stated above, I had postulated the implications of high levels of anxiety in PD on resource management and processing capacity especially within the basal ganglia, and conducted the third study to evaluate whether there is an information overload at the level of the basal ganglia that interferes with processing of these important types information, and thus impairs walking. Therefore, the third study in this thesis aims to examine whether anxiety interferes with processing of aspects of the environment or using sensory feedback, and whether dopaminergic treatment improves resource management and subsequently information processing.

# Chapter 2

# DOES ANXIETY CAUSE FREEZING OF GAIT IN PARKINSON'S DISEASE?

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## 2.1 Abstract

Individuals with Parkinson's disease (PD) commonly experience freezing of gait under time constraints, in narrow spaces, and in the dark. One commonality between these different situations is that they may all provoke anxiety, yet anxiety has never been directly examined as a cause of FOG. In this study, virtual reality was used to induce anxiety and evaluate whether it directly causes FOG. Fourteen patients with PD and freezing of gait (Freezers) and 17 PD patients without freezing of gait (Non-Freezers) were instructed to walk in two virtual environments: (i) across a plank that was located on the ground (GROUND), (ii) across a plank above a deep pit (ELEVATED). Multiple synchronized motion capture cameras updated participants' movement through the virtual environment in real-time, while their gait was recorded. Anxiety levels were evaluated after each trial using self-assessment manikins. Freezers performed the experiment on two separate occasions (in their ON and OFF state). Freezers reported higher levels of anxiety compared to Non-Freezers ($p<0.001$) and all patients reported greater levels of anxiety when walking across the ELEVATED plank compared to the GROUND plank ($p<0.001$). Freezers experienced significantly more freezing of gait episodes ($p=0.013$) and spent a significantly greater percentage of each trial frozen ($p=0.005$) when crossing the ELEVATED plank. This finding was even more pronounced when comparing Freezers in their OFF state. Freezers also had greater step length variability in the ELEVATED compared to the GROUND condition, while the step length variability in Non-Freezers did not change. In conclusion, this was the first study to directly compare freezing of gait in anxious

and non-anxious situations. These results present strong evidence that anxiety is an important mechanism underlying freezing of gait and supports the notion that the limbic system may have a profound contribution to freezing in PD.

## 2.2 Introduction

Freezing of gait (FOG) is arguably the most debilitating symptom of Parkinson's disease (PD) and commonly occurs in confined spaces (such as doorways, and corridors) (Almeida & Lebold, 2010; Schaafsma et al., 2003), under time constraints (such as entering an elevator, or rushing to answer a phone) (Bloem, Hausdorff, Visser, & Giladi, 2004; Moreau et al., 2008; Schaafsma et al., 2003) and in the dark (Ehgoetz Martens, Pieruccini-Faria, & Almeida, 2013). Interestingly, one link between these very different situations is that they all may provoke anxiety. It has been speculated that anxiety might trigger freezing of gait (Bloem et al., 2004; Lieberman, 2006; Maidan et al., 2011; Schaafsma et al., 2003). In fact a recent study showed that significantly greater amounts of freezing were found when participants walked in complete darkness toward a doorframe compared to complete darkness into open space (Ehgoetz Martens, Pieruccini-Faria, & Almeida, 2013). Based on these findings, it was hypothesized that anxiety might play an important role in triggering freezing behavior; however, no study to date has gone beyond correlational analyses to test directly whether anxiety might be a cause of freezing.

Anxiety is a not only a common non-motor symptom of Parkinson's disease (affecting up to 69% of patients (Prediger et al., 2012; Richard, 2005)), but it is also one of the most influential predictors of quality of life in those with PD (Hanna & Cronin-Golomb, 2012; Quelhas & Costa, 2009). Several studies have shown that anxiety is associated with more severe gait disturbance in PD (PIGD subtype) (Burn et al., 2012; Vazquez et al., 1993).

Interestingly, a higher prevalence of anxiety and other mood disorders have been reported amongst the specific subgroup of patients that experience freezing of gait (Burn et al., 2012). Moreover, panic attacks have been reported prior to and during freezing of gait episodes (Lieberman, 2006). Physiological measures such as heart rate support this association between anxiety and freezing, since heart rate increases have been reported just prior to and during a freezing episode (Maidan et al., 2011). Taken together, there are several lines of research that suggest stress and anxiety are not only related, but might play a key role in the underlying mechanism of freezing of gait.

Although the pathophysiology of freezing of gait remains unclear, increasing evidence suggests that non-motor systems are likely involved in its underlying mechanism (Giladi & Hausdorff, 2006; Maidan et al., 2011). Of all the recent hypotheses attempting to explain freezing of gait (for complete review see (Nieuwboer & Giladi, 2013)), one specific model (cross-talk model) has emphasized the potential role of the limbic system. According to the model, striatal dopaminergic loss in Parkinsonian conditions can be compounded by competing inputs from the cognitive, limbic and motor loops, which in certain situations can overload the striatum's processing capacity, thereby leading to freezing of gait (Lewis & Barker, 2009a). Based on this hypothesis, one might expect that in anxious situations, the increased "limbic load" could in fact elicit freezing of gait.

The cross talk model not only suggests that the limbic system might play an important role in freezing of gait but also emphasizes the role of striatal dopamine in integrative basal

ganglia processes, such that insufficient levels may result in a functional deficit (Lewis & Barker, 2009a). Interestingly, a growing body of evidence suggests that freezing of gait is more severe in the OFF state and improves with dopaminergic medication (Cowie, Limousin, Peters, Hariz, & Day, 2012; Fietzek, Zwosta, Schroeteler, Ziegler, & Ceballos-Baumann, 2013; Gilat et al., 2013). However, there is little consensus as to how dopamine contributes to the underlying mechanism of freezing and how it may act to ameliorate freezing severity and behavior. Many patients report greater levels of anxiety during their off-period, and some researchers have suggested that this may represent a dopaminergic "mood-off" phenomenon (Burn et al., 2012; Jankovic, 2005). However, this has also been debated since other researchers have shown that levodopa exacerbates anxiety symptoms (Damásio, Lobo-Antunes, & Macedo, 1971; Richard, Schiffer, & Kurlan, 1996; Vazquez et al., 1993). The nucleus accumbens is central to processing and integrating emotional (limbic) information in the basal ganglia and is mediated by dopaminergic input (Lewis, Slabosz, Robbins, Barker, & Owen, 2005). Therefore, freezing of gait might be expected to be greater in the OFF state, especially when walking in an anxiety-provoking environment since this situation would create an overload of information to be processed by a "dopamine depleted" basal ganglia. However, with dopaminergic replacement therapy (ON state), there may be more integrated processing across the basal ganglia resulting in less freezing of gait compared to the OFF state.

The current study is the first to utilize virtual reality to induce anxiety and directly measure freezing of gait while walking, in order to establish whether anxiety causes freezing

of gait in Parkinson's disease. Virtual reality has been shown to be an effective tool to immerse participants in specific situations in order to induce freezing-like behavior, as well as the typically associated step-to-step variability changes (Gilat et al., 2013; Shine, Matar, Bolitho, et al., 2013) that have been identified in real-life gait studies of freezing. The secondary aim of this study was to investigate whether dopaminergic medication influences freezing of gait in anxious situations. To achieve these aims, we asked participants who experience freezing of gait to perform the experimental protocol on two separate occasions: once ON and once OFF regular dopaminergic medication to determine whether the lack of dopamine exacerbated freezing of gait in anxious environments.

## 2.3 Materials and Methods

### 2.3.1 Participants

Thirty-one participants with Parkinson's disease were tested in this study. Table 1 shows the demographic characteristics and clinical details of participants. All participants were recruited through the Sun Life Financial Movement Disorder Research and Rehabilitation Centre database at Wilfrid Laurier University in Waterloo, Canada. Fourteen patients were confirmed to experience freezing of gait using the previously established criteria: (i) previous diagnosis of idiopathic Parkinson's disease by a neurologist and a history of freezing of gait; (ii) patients self-reported freezing of gait using UPDRS-II; (iii) a movement disorder specialist confirmed the presence of FOG during assessment prior to participation in the study (see (Almeida & Lebold, 2010; Knobl, Kielstra, & Almeida, 2012) for full procedure). Participants

were excluded if they could not walk 10m unassisted, had vertigo, motion sickness, severe kyphosis, other neurological disorders, severe head tremor or dyskinesias (since it would make the virtual environment appear to be shaking, increasing the difficulty and likelihood of motion sickness). Patient files were also carefully screened for co-morbid conditions (i.e. history of stroke, visual impairments, hearing loss, peripheral neuropathies, or diabetes). The Unified Parkinson's Disease Rating Scale motor section (UPDRS-III) (Goetz et al., 2007) was administered by a certified clinician and assessed disease severity, while the Modified Mini Mental State Exam (3MS) (Teng & Chui, 1987) screened for dementia. Additionally, all participants completed the State and Trait Anxiety Inventory (Spielberger, 1987) assessing baseline levels of anxiety prior to completing the experiment; Geriatric Depression Scale (Yesavage et al., 1983); and the SCOPA-AUT questionnaire which has been shown to assess the integrity of the autonomic nervous system (Visser, Marinus, Stiggelbout, & Van Hilten, 2004). Finally, a simulator sickness questionnaire was completed once before the experiment and then again after the experimental walking trials to quantify any adverse effects as a result of the virtual reality protocol.

**Table 1. Demographic characteristics and clinical details of participants**

| | **Freezers** | **Non-freezers** | **P-value** |
|---|---|---|---|
| Number | 14 | 17 | |
| Age | 71 (7.8) | 66 (8.7) | p=0.13 |
| Gender | 3 F | 3 F | |
| Symptom Severity (UPDRS-III) | 34 (10.1)* | 20 (10.4)* | **p=0.0009 |
| 3MS | 95 (7) | 96 (4.5) | p=0.53 |
| LDE | 204.1 (62.7) | 223.1 (98.9) | p=0.54 |
| STAI-Trait | 33 (6.9) | 32 (6.6) | p=0.74 |
| STAI-State | 34 (8.7) | 30 (5.9) | p=0.19 |
| GDS | 7 (3.4) | 7 (5) | p=0.82 |
| SCOPA-AUT | 16 (5.6) | 16 (4.4) | p=0.89 |
| Pre-SSQ | 6 (4.7) | 9 (7.1) | p=0.47 |
| Post-SSQ | 9 (7.4) | 8 (5.5) | p=0.97 |
| | **'OFF' Freezers** | **'ON' Freezers** | **P-value** |
| UPDRS-III | 39 (10.6)* | 32 (11.3)* | **p=0.0001 |
| STAI-Trait | 35 (8.9) | 33 (5.8) | p=0.37 |
| STAI-State | 37 (10.8) | 31 (8.9) | p=0.20 |

3MS: Modified Mini Mental State Exam; STAI: State-Trait Anxiety Inventory; GDS: Geriatric Depression Scale; SSQ: Simulator Sickness Questionnaire; LDE: Levodopa Dose Equivalence; SCOPA-AUT: Scales for Outcomes in Parkinson's disease-Autonomic; UPDRS-III: Unified Parkinson's Disease Rating Scale – motor subsection

### 2.3.2 Design and Procedure

#### 2.3.2.1 Apparatus

Participants were outfitted in a completely wireless virtual reality (VR) head mounted display (HMD) system that was tracked in real-time using three infrared light emitting diodes attached to a rigid body which was secured to the virtual reality helmet. The viewpoint in the virtual environment was controlled by the position and movement of the rigid body captured by seven OPTOTRAK Certus cameras (NDI Principles Inc., Waterloo, Canada). This

synchronized the participants' position and movements, allowing the viewpoint to update in real-time, creating an immersive virtual setting.

The virtual environment used in this study was constructed using virtual reality software, *Vizard* (Worldviz L.L.C., Santa Barbara, USA). The testing environment was delivered using a high definition, low latency wireless link to a zSight head mounted display (HMD) (Sensics Inc., Columbia, USA) that featured a 60-degree field-of-view with 100% binocular overlap and a 1280 x 1024 full-color pixels per eye resolution. The HMD also had a light-blocking cover that was pressed firmly to the participants' face, which prevented participants from seeing the real-world environment around them and allowed them to focus only on the virtual environment. In order to make the virtual environments as immersive as possible, the experiment was completed in a dark room which prevented participants from seeing the floor, their own feet, or the spotters' feet walking beside them in the "real-world". The visual focus and eye width settings were adjusted for each participant at the beginning of the study and confirmed to display a clear stereoscopic 3-D image. Participants were positioned at the end of the laboratory room and a GAITRite carpet (over 8m in length) was located on the floor in front of them lengthwise. The GAITRite carpet (CIR systems Inc., Sparta, USA) was used to capture spatiotemporal aspects of gait during each walking trial.

#### 2.3.2.2 Experimental Protocol

All participants completed a total of 10 randomized walking trials in two different conditions. To begin, they stood on the edge of a GAITRite carpet which was calibrated to

visually display the starting platform in virtual reality. To complete the task, participants were required to walk across a plank (6m in length x 1m in width) to the opposite platform in one of two 3-D virtual environments (*Vizard*, Worldviz L.L.P., Santa Barbara, USA) (see Figure 1). In the GROUND condition, all participants were required to walk across a plank that was located on the floor of the virtual environment (Figure 1A). In contrast, during the ELEVATED condition, all participants viewed the floor surrounding the platform as it descended creating a deep pit below. Participants were required to walk across the plank which appeared to be approximately 8m above the deep pit (Figure 1B). After walking across the plank to the opposite platform in each trial, a 9 point self-assessment manikin scale (Bradley & Lang, 1994) would be displayed and patients were asked to rate their feelings of stress and anxiety using the self-assessment manikins. Once an anxiety rating was given, the head mounted display would present a black screen and a research volunteer would guide the patient back to the start position for the next trial. A standing rest period of 30 seconds was given after each trial to prevent carry-over effects from anxiety on the previous trial.

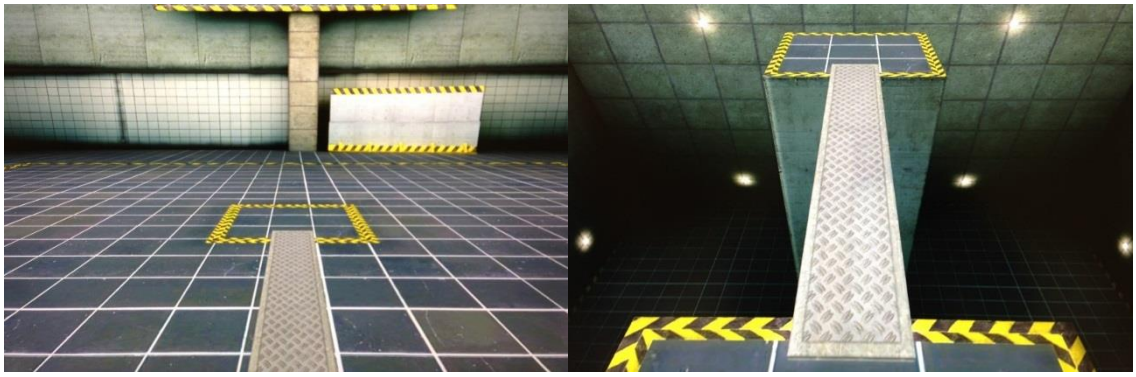

**Figure 1. The experimental paradigm. Patients walked across the virtual plank in two environments: A) while the plank was located on the ground (GROUND); B) participants viewed the floor descend, and then walked across the elevated plank (ELEVATED).**

Our primary research question was whether anxiety influences freezing of gait. Thus, it was most ecologically valid to test all of the participants in the ON state since this is typically their medication state during their daily activities (Ehgoetz Martens, Pieruccini-Faria, & Almeida, 2013). All patients were tested approximately one hour after taking their regular dosage of anti-Parkinsonian medication. However, since there has been debate as to whether dopaminergic medication reduces or exacerbates anxiety in Parkinson's disease, and furthermore it is controversial whether freezing of gait is dopa-responsive, all patients with freezing of gait were invited to be tested in both medication states on two separate occasions (counterbalanced across participants). Of the fourteen Freezers, ten gave consent to complete this study twice (once OFF and once ON their regular dopaminergic medication), however one patient was unable to complete any walking trials in the ELEVATED condition due to severe akinetic freezing in the OFF state, and another two patients dropped out after completing the study once in their ON state, convinced that they would not be able to perform any trials in

their OFF state. Thus, seven patients with freezing completed this study once after at least a 12 hour withdrawal from dopaminergic medication overnight (this withdrawal was increased to 24 hours for dopamine agonists) and again approximately one hour after their regular dosage. Ethical approval was obtained by both the Research Ethics Board at Wilfrid Laurier University as well as the Office of Research Ethics at the University of Waterloo. Written informed consent was obtained from all participants before participating according to the Declaration of Helsinki.

### 2.3.3 Data Analysis

The primary outcome measure was the percent of each trial spent frozen since it is known to be the most reliable measure of freezing of gait (Morris et al., 2012). The number of freezing of gait episodes was also recorded and compared. A freezing of gait episode was defined both objectively and subjectively as suggested in previous research (Cowie et al., 2012; Ehgoetz Martens, Pieruccini-Faria, & Almeida, 2013). First, trials with freezing of gait were visually identified through video playback of steps recorded on the GAITRite carpet using PKMAS software (Protokinetics, Havertown, USA). If freezing of gait was observed, each step during the trial was exported and analyzed. A freezing of gait episode was defined as any period where the stride velocity dropped between zero (i.e. completely stopped) and one standard deviation above zero of their regular velocity on that trial. Previous studies have used this criterion (Ehgoetz Martens, Pieruccini-Faria, & Almeida, 2013; Ehgoetz Martens, Pieruccini-Faria, Silveira, & Almeida, 2013) since it is a stringent, objective measure of FOG.

This procedure allowed us to quantify the number of freezing of gait episodes, the duration of each freezing episode and calculate the percent of each trial spent frozen.

Previous research has found that spatial and temporal aspects of gait, such as step-to-step variability, can be indicative of an upcoming FOG occurrence (Blin, Ferrandez, & Serratrice, 1990; Hausdorff et al., 2003; Plotnik & Hausdorff, 2008). Furthermore, since freezing of gait is difficult to evoke in experimental settings, it is also important to understand changes in gait behavior that may not result in a full blown freezing episode in response to the experimental manipulations. For these reasons, we chose to also analyze participants' gait characteristics such as velocity (cm/s), mean step length (cm), step length variability (Coefficient of Variation – CV), mean step width (cm), step width variability (CV), step time (s) and step time variability (CV), which tend to be indicative of cautious walking in response to anxiety. It should be noted that any freezing of gait episodes detected were removed from the secondary gait analysis to avoid bias comparison between groups and conditions. The dependent gait variables were analyzed using PKMAS software.

#### 2.3.3.1 Statistical Methods

Baseline demographic variables were compared between groups and also within the Freezer subgroup between medication states using independent and dependent t-tests. Assumptions were assessed and when necessary (i.e. Mauchly's test of sphericity was violated) then the degrees of freedom were corrected using Greenhouse-Geisser estimate of sphericity and reported. A mixed repeated measures ANOVA (group x condition x trial) was used to

evaluate changes in the anxiety self-assessment ratings and gait variables across all participants. The frequency of FOG episodes, the total duration of time spent frozen, and the percent of each trial spent frozen were analyzed using a repeated measures ANOVA with 2 factors of repeated measures (i.e. condition and trial), allowing for a comparison of the FOG variables between the two conditions specifically within the freezer group. In all cases, Tukey's HSD post hoc procedure was used to further investigate significant differences.

Since very few participants were able to complete the study both ON and OFF their dopaminergic medication, and FOG did not occur in any individuals during the GROUND condition while ON their dopaminergic medication (causing a lack of variance); none of the freezing of gait variables were statistically compared between medication states. These variables were still calculated and reported (see Table 2). In order to evaluate dopaminergic influences on anxiety, repeated measures ANOVA (medication x condition x trial) were used to compare anxiety ratings.

**Table 2. Summary of freezing of gait measures for all Freezer participants during walking in virtual reality**

| | **Freezers (ON N=14)** | | |
|---|---|---|---|
| | **GROUND** | **ELEVATED** | **p-value** |
| Percent of Trial Spent Frozen | 11.03 | 23.1 | *p=0.005 |
| Total Number of Freezing Episodes | 88 | 231 | *p=0.013 |
| Average Number of Freezing Episodes per trial | 1.3 | 3.3 | *p=0.013 |
| Average Duration of Each Freezing Episode (sec) | 1.31 | 3.04 | p=0.14 |

**Table 3. Summary of freezing of gait measures for a subset of Freezer participants that completed both ON and OFF dopaminergic testing**

| | Freezers (OFF N=7) | | Freezers (ON N=7) | |
|---|---|---|---|---|
| | **GROUND** | **ELEVATED** | **GROUND** | **ELEVATED** |
| Percent of Trial Spent Frozen | 2.09 | 81.6 | 0 | 51.88 |
| Total Number of Freezing Episodes | 3 | 111 | 0 | 26 |
| Average Number of Freezing Episodes per trial | 0.4 | 15.9 | 0 | 3.8 |
| Average Duration of Each Freezing Episode (sec) | 0.58 | 7.5 | 0 | 7.91 |

## 2.4 Results

### 2.4.1 Baseline Data

Results showed that Freezers had significantly higher motor symptom severity (UPDRS-III) compared to the Non-Freezers ($t(29)=3.71$, $p=0.0009$). Importantly, these groups were not statistically different at baseline on the following demographic measures (See Table 1); age ($t(29)=1.54$, $p=0.13$), levels of Trait anxiety ($t(29)=0.34$, $p=0.74$), State anxiety ($t(29)=1.35$, $p=0.19$), Depression ($t(28)=0.23$, $p=0.82$), SCOPA-AUT ($t(27)=0.14$, $p=0.88$), pre-simulator sickness ($t(28)=0.73$, $p=0.47$), and post-simulator sickness questionnaire ($t(29)=0.04$, $p=0.97$). It is important to note however that the Freezers had a lower cognitive status compared to Non-Freezers ($t(28)=0.64$, $p=0.053$), although this was not quite significant.

### 2.4.2 Anxiety Ratings

A main effect of group ($F(1,29)=16.96$, $p=0.0003$) showed that Freezers reported higher levels of anxiety during the experiment compared to Non-freezers. A main effect of condition ($F(1,29)=29.83$, $p<0.0001$) revealed that all participants reported higher levels of anxiety during the ELEVATED condition compared to the LOW (Figure 2). Finally, a main effect of trial (Greenhouse-Geisser correction: $F(2.3, 67.9)=8.88$, $p<0.0001$) demonstrated that participants reported the greatest amount of anxiety on the first trial in each condition.

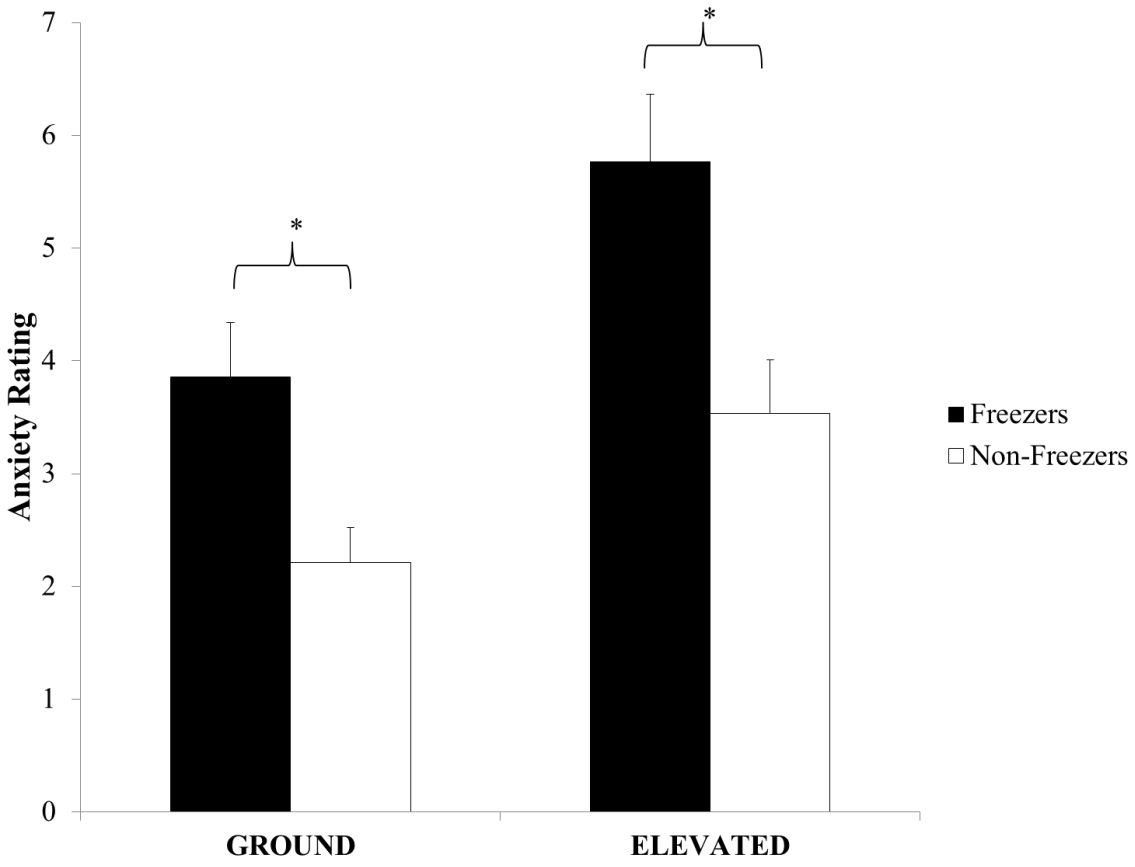


**Figure 2. Comparison of anxiety ratings after participants walked across the plank. Error bars represent standard error of the mean. * illustrates significant differences between groups ($p<0.05$)**

### 2.4.2.1 Influence of Medication State on Anxiety Ratings

Symptom severity was significantly greater when Freezers were tested in their OFF state compared to ON their regular dopaminergic medication ($t(6)=8.48$, $p=0.0001$). Results also showed that baseline levels of anxiety (both trait and state) prior to the experiment did not change significantly between medication states ($t(6)=0.97$, $p=0.36$; $t(6)=1.44$, $p=0.20$) (Table

1). Finally, there was no main effect of medication state on anxiety ratings during the walking trials ($F(1,6)=0.12$, $p=0.92$).

### 2.4.3 Freezing of Gait Measures

#### 2.4.3.1 Percent of Trial Spent Frozen

Freezers spent a significantly greater percent of each trial frozen during the ELEVATED condition compared to the GROUND ($F(1,13)=11.35$, $p=0.005$) (see Figure 3A). There was no main effect of trial found ($F(4,52)=0.49$, $p=0.74$).

#### 2.4.3.2 Frequency of Freezing of Gait

Freezers experienced significantly greater number of freezing episodes during the ELEVATED condition compared to the GROUND ($F(1,13)=8.29$, $p=0.013$) (see Figure 3B). There was no main effect of trial found ($F(4,52)=0.53$, $p=0.72$).

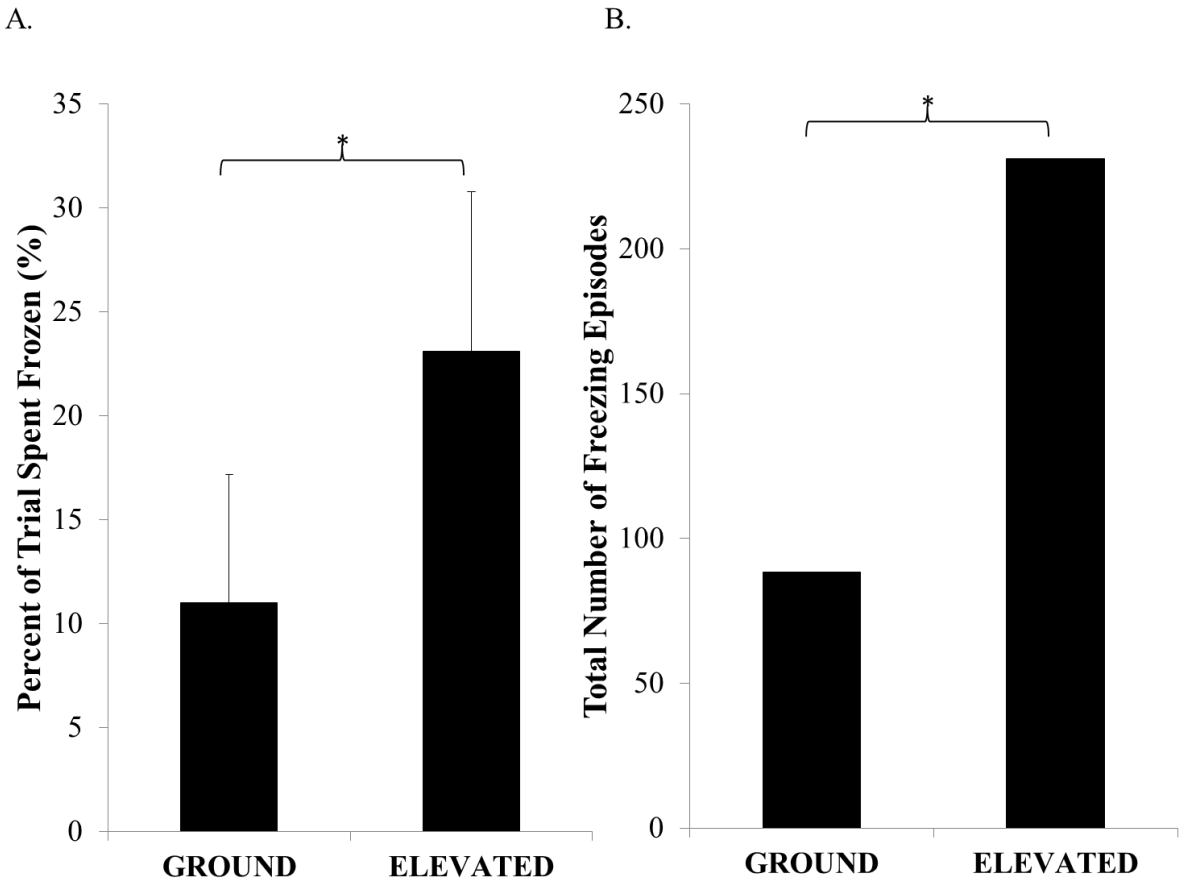


**Figure 3. Comparison of ON state freezing of gait between ELEVATED and GROUND conditions within the Freezer group only. Error bars represent standard error of the mean. * illustrates a significant difference between conditions within Freezers ($p<0.05$).**

### 2.4.3.3 Duration of Freezing of Gait

There were no significant main effects found for either condition ($F(1,13)=2.48$, $p=0.14$) or trial ($F(4,52)=2.11$, $p=0.09$), suggesting that the duration of each freezing episodes was similar regardless of anxiety condition or trial.

### 2.4.4 Gait Parameters

#### 2.4.4.1 Velocity

Overall, Freezers walked significantly slower than Non-Freezers ($F(1,29)=25.31$, $p<0.0001$) (See Table 4), although all participants walked significantly slower during the ELEVATED condition compared to the GROUND ($F(1,29)=53.54$, $p<0.0001$). A significant condition by trial interaction (Greenhouse-Geisser estimate: $F(2.6, 76)=3.36$, $p=0.028$) showed that all participants reduced their velocity more during the first trial of the ELEVATED condition compared to the GROUND, although as the trials progressed the participants' increased their velocity in both conditions.

#### 2.4.4.2 Step Length

Overall, Freezers walked with a significantly shorter step length ($F(1,29)=43.05$, $p<0.0001$) compared to Non-Freezers. Moreover, during the ELEVATED condition, all participants walked with a reduced step length compared to the GROUND condition (Greenhouse-Geisser estimate: $F(2.6, 75.5)=31.55$, $p<0.0001$). A group by trial interaction ($F(4,116)=3.7$, $p=0.007$) revealed that Freezers had significantly shorter steps during the first trial (regardless of condition) compared to the third trial, whereas Non-Freezers increased their step length significantly by the second trial (compared to the first) and had even greater step length by the final trial (compared to the second). A significant interaction between condition and trial (Greenhouse-Geisser estimate: $F(3,85.6)=6.52$, $p<0.0001$) showed that all participants

had a greater reduction in step length during the first trial of the ELEVATED condition compared to the GROUND. In both conditions, participants' step length improved as the trials progressed.

#### 2.4.4.3 Step Time

There were no significant main effects of group ($F(1,29)=0.22$, $p=0.65$), condition ($F(1,29)=0.96$, $p=0.33$), or trial ($F(1.2, 35.7)=2.61$, $p=0.1$) for step time.

#### 2.4.4.4 Step Width

Overall, Freezers walked with a significantly smaller step width compared to Non-Freezers regardless of condition ($F(1,29)=4.32$, $p=0.047$). There were no significant effects of condition ($F(1,29)=1.16$, $p=0.29$) or trial ($F(4,116)=1.76$, $p=0.14$).

#### 2.4.4.5 Step Length Variability

Freezers had higher step length variability compared to Non-Freezers ($F(1,29)=11.62$, $p=0.002$), although all participants walked with a higher step length variability during the ELEVATED condition compared to the GROUND ($F(1,29)=12.8$, $p=0.001$). Interestingly, there was a near significant interaction between group and condition ($F(1,29)=3.88$, $p=0.058$). Tukey's post hoc showed that Freezers had similar step length variability during the GROUND condition as Non-Freezers, however Freezers had significantly greater variability during the ELEVATED condition compared to Non-Freezers ($p=0.002$) (see Figure 4A).

#### 2.4.4.6 Step Time Variability

Freezers had higher step time variability compared to Non-Freezers ($F(1,29)=7.79$, $p=0.009$), although all participants walked with a higher step time variability during the ELEVATED condition compared to the GROUND ($F(1,29)=13.9$, $p=0.0008$) (see Figure 4B).

#### 2.4.4.7 Step Width Variability

Overall, Freezers walked with a significantly lower step width variability compared to Non-Freezers regardless of condition ($F(1,29)=7.04$, $p=0.013$). There were no significant effects of condition ($F(1,29)=0.43$, $p=0.52$) or trial ($F(4,116)=0.32$, $p=0.86$).

**Table 4. Comparison of overall spatiotemporal aspects of gait between Freezers and Non-freezers**

| Spatiotemporal variables | Freezers (N=14) | Non-Freezers (N=17) | p-value |
|---|---|---|---|
| Velocity (cm/s) | 35.6 (22.2) | 74.5 (26.4) | **p<0.0001 |
| Step length (cm) | 18.3 (11.3) | 44.1 (14) | **p<0.0001 |
| Step time (s) | 0.63 (0.4) | 0.6 (0.1) | p=0.65 |
| Step Width (cm) | 13.6 (3.3) | 10.9 (4.2) | *p=0.047 |
| Step length CV (%) | 58 (65.1) | 15 (9.6) | *p=0.002 |
| Step time CV (%) | 26.4 (29.4) | 10.5 (7.6) | *p=0.009 |
| Step width CV (%) | 14.4 (7.6) | 26.7 (24.7) | *p=0.013 |

CV: Coefficient of variation

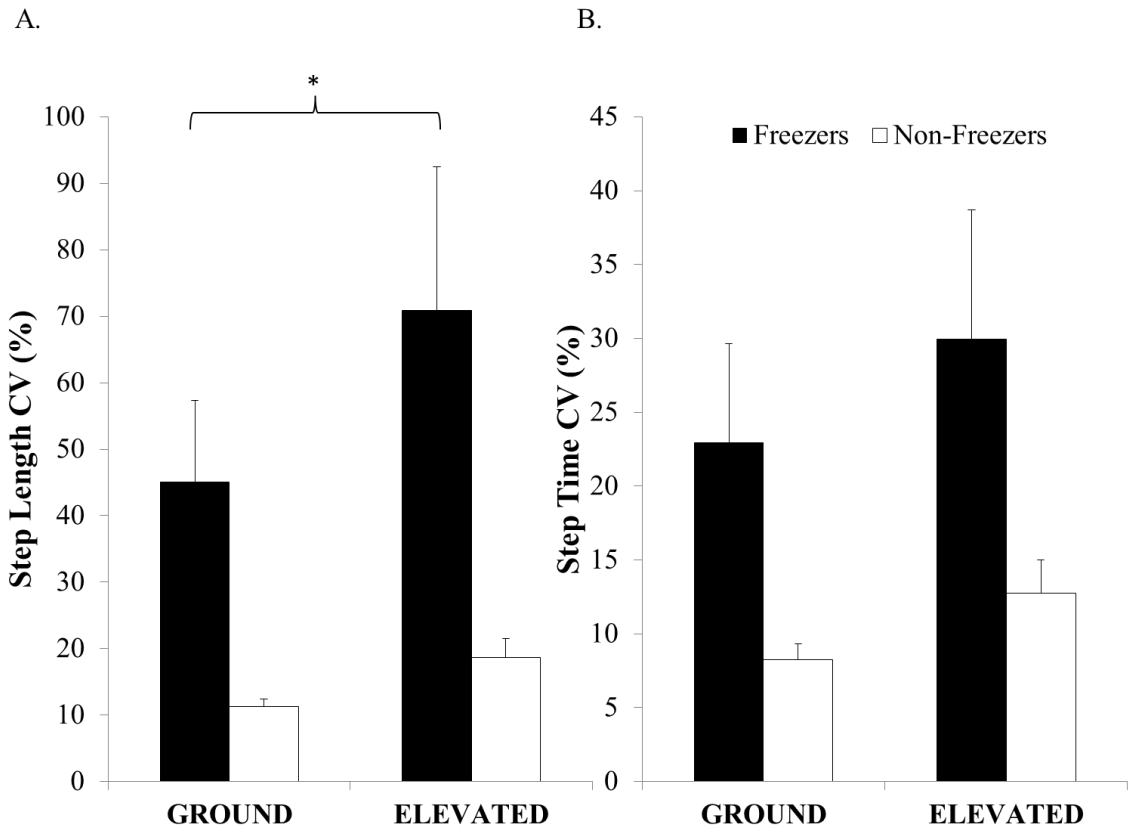


**Figure 4. Comparison of step-to-step variability between Freezers and Non-freezers. Error bars represent standard error of the mean. * illustrates a significant difference within Freezers between the ELEVATED and GROUND conditions ($p<0.05$).**

## 2.5 Discussion

To our knowledge this study was the first to directly compare freezing of gait in anxiety-provoking situations. The primary objective was to use virtual reality to induce anxiety and directly evaluate its influence on freezing of gait in Parkinson's disease. As previously discussed, freezing of gait has been deemed difficult to elicit in experimental settings. Yet, the current experiment led to freezing of gait in 85.7% percent of the freezing population studied and a remarkable 300+ freezing episodes were elicited within this group. To date, this

frequency of freezing drawn out in an experimental setting is well beyond the frequency reported in any other freeze-provoking paradigms. Overall, this study provides strong evidence that anxiety can play a causal role in freezing of gait. Freezers spent a significantly greater percentage of each trial frozen when walking across a plank that appeared to be high above a pit (ELEVATED) compared to walking across the plank located on the ground (GROUND). Furthermore, Freezers experienced a significantly greater number of freezing of gait episodes in the ELEVATED condition compared to the GROUND, and also had significantly higher step length variability and step time variability when walking across the ELEVATED plank. Thus, it is evident from this study that anxiety is an important trigger that may underlie freezing of gait.

It is important to highlight that the anxiety-inducing protocol used in this study effectively manipulated anxiety in all participants. Results showed that all participants reported higher levels of anxiety (using the self-assessment manikins) after walking across the plank high above a deep pit compared to walking across the plank on the ground. In addition, all participants showed more cautious gait (e.g. significantly reduced their velocity, step length and increased their step time variability) when walking across the ELEVATED plank compared to the GROUND plank. This cautious gait adaptation has been shown in older adults when walking across an elevated plank in a "real world" setting (Caetano et al., 2009; Gage et al., 2003) and demonstrates that both groups in the current study found the virtual environments immersive and realistic enough to elicit more cautious gait and provoke freezing

of gait episodes. This provides additional evidence that virtual reality is a very powerful tool for eliciting and studying freezing behavior in Parkinson's disease in order to better understand the mechanism underlying this phenomenon (Gilat et al., 2013; Shine, Matar, Bolitho, et al., 2013).

### 2.5.1 Does anxiety cause freezing of gait?

Although baseline levels of anxiety (i.e. state and trait levels) were not different between groups, anxiety induced during the walking paradigm was significantly amplified in Freezers beyond the level of Non-freezers. This would suggest that in Freezers, goal-oriented movement has the potential to induce greater anxiety, leading to a cautious and potentially maladaptive movement response such as freezing of gait. Thus, in other circumstances such as walking in darkness, or approaching doorways and narrow spaces, the anxiety-driven need for cautious movement might explain the occurrence of freezing in these situations. One might question whether freezing precedes anxiety or if anxiety does in fact lead to a freeze episode. Panic attacks (Lieberman, 2006) and heart rate increases have been identified (Maidan et al., 2011) prior to and during a freezing episode. However, inferring a causal relationship would be difficult since there was no manipulation of anxiety-inducing conditions. Rather, associations make it ambiguous as to whether panic attacks and autonomic responses provoke freezing of gait or are a reactive response. The current findings support and extend this research, demonstrating that anxiety is in fact a cause of freezing of gait rather than simply a response, since manipulations of anxiety (ELEVATED and GROUND) directly influenced the

amount of freezing of gait participants experienced. Spatiotemporal gait changes (i.e. increases in step-to-step variability), which have been previously linked with freezing behavior, were also increased when anxiety was heightened.

### 2.5.2 How does anxiety cause freezing of gait?

Interestingly, increased step-to-step variability also occurs in Non-freezing Parkinson's patients when asked to perform a cognitive dual-task (Plotnik, Giladi, & Hausdorff, 2009; Yogev et al., 2005). Thus, it is plausible that increasing limbic "load" may be analogous to a cognitive load in non-freezing Parkinson's participants, in that both overload the capacity for the basal ganglia to process competing inputs. Although there are many models trying to further elucidate the mechanisms behind freezing behavior (Nutt et al., 2011), the current results fit very well with the cross-talk model, which emphasizes that competing inputs from cognitive, motor and limbic loops all get processed in the striatum, and in instances where there is insufficient dopamine and an overload of information to be processed (e.g. anxiety), freezing of gait occurs (Lewis & Barker, 2009a). Although there has been support for this model from a cognitive perspective (Matar, Shine, Naismith, & Lewis, 2014; Shine, Matar, Ward, Bolitho, Gilat, et al., 2013; Shine, Matar, Ward, Bolitho, Pearson, et al., 2013; Shine, Matar, Ward, Frank, et al., 2013), there has been no study that has tested whether "limbic overload" could produce freezing of gait. The current study effectively demonstrated that "limbic overload" does trigger greater amounts freezing of gait and produces higher step-to-step variability that has been suggested to be conducive to freezing. The cross-talk model also

suggests that integrated information processing (i.e. cognitive, motor and limbic) across the basal ganglia circuits is modulated by striatal dopamine; thus when dopamine levels are critically reduced (ex. OFF state) there may be insufficient processing of all information, which result in freezing of gait. In the current study, freezing was quadrupled when participants walked across the ELEVATED plank in the OFF state, supporting the cross-talk theory. However, anxiety levels did not change with medication at baseline nor during the experimental conditions. In accordance with the cross-talk model, this would suggest that dopaminergic medication increased the capability of the basal ganglia to process the limbic input, rather than reducing the limbic overload in itself (Balaban & Thayer, 2001).

Recently, imaging studies have begun to identify neural correlates associated with freezing behavior. Although these studies did not focus on inducing anxiety to provoke freezing of gait, it is interesting that decreases in activation were found in the medial prefrontal cortex, left anterior insula and left ventral striatum during motor arrests compared to walking (Shine, Matar, Ward, Bolitho, Gilat, et al., 2013). Although these regions are involved in an array of functions such as the cognitive control network (suggested by the authors), these areas also have a well-established role in emotional processing (Phan et al., 2002). A recent review highlighted that nearly 60% of emotional induction studies reported activation of the insula (Phan et al., 2002), and furthermore the insula has been suggested to participate in evaluation of distressing thoughts and interoceptive emotional responses (Reiman et al., 1997). Imaging results have also shown that Freezers have significantly less BOLD signal in the bilateral

anterior insula and bilateral ventral striatum compared to Non-Freezers during simulated walking in virtual reality with increased cognitive load (Shine, Matar, Ward, Bolitho, Pearson, et al., 2013). Taken together, these results align with the current findings and theoretical framework suggesting that dysfunctional processing of emotional information in the ventral striatum might be one explanation of the current results showing that anxiety increased freezing of gait.

### 2.5.3 How do these findings fit within existing models of freezing of gait?

It is important to consider how some models of freezing of gait describe a downstream effect, without addressing the upstream cause. This might be why other models are not able to explain how anxiety or other processes might overload the basal ganglia, leading to increased freezing of gait. For example, the threshold model predicts that a motor deficit can accumulate to the point that reaches a threshold and freezing occurs (Plotnik, Giladi, & Hausdorff, 2012). This model does not identify a root cause of the initial motor deficit. According to the current results, anxiety might be the key factor that initiates the motor deficit in the first place, and thus this model would be incomplete without the upstream cause having been identified. Similarly, the decoupling model does not identify the initial upstream event that leads to decoupling between preprogrammed and intended motor responses (Jacobs, Nutt, Carlson-Kuhta, Stephens, & Horak, 2009). Thus, in both cases identifying the upstream cause can elucidate why freezing of gait is the resultant behavior.

In contrast, the cognitive model suggests that freezing of gait is an outcome of a conflict-resolution deficit, specifically exacerbated in situations where response selection and inhibition of unwanted responses are necessary (Vandenbossche et al., 2012). This model also emphasizes that executive dysfunction might enhance freezing behaviors in these situations. The results from this study do not directly support this model, since response selections were not made during the walking trials. However, one could argue that conflicting signals could arise from limbic or sensory input, and a limited amount of resources (possibly executive dysfunction) might restrict one's ability to resolve this conflict resulting in a freezing episode. If this were the case, this model describes a very similar mechanism as the cross-talk model. A recent cohort study highlighted that persons with PD are unable to modulate step width variability in order to adapt to threatened stability and also ineffectively increase their step width under dual task conditions compared to healthy control participants (Rochester, Galna, Lord, & Burn, 2014). In the current study, both groups did not modulate their step width or step width variability when walking across the ELEVATED plank compared to the GROUND plank, suggesting that cognitive interference may have limited their ability to adapt to threatened stability. Furthermore, Freezers had a smaller step width and reduced step width variability compared to the Non-freezers. Thus, it may be the case that Freezers experienced greater cognitive interference while walking in virtual reality, but since step width and step width variability did not differ between conditions, especially in the Freezers, cognitive

interference cannot fully account for the significant increases in freezing of gait when walking across the ELEVATED plank.

### 2.5.4 Limitations and Considerations

One limitation of this study was the small number of participants that were able to complete this study OFF their dopaminergic medication. Since our sample was limited, and there were no freezing episodes in the ON state GROUND condition, statistical analyses were not performed on the freezing of gait variables between the ON and OFF state. Future research should investigate and confirm our observations of reduced freezing specifically during waking in the anxious environment (ELEVATED) in the ON state compared to the OFF state. It should also be noted that the participants that were able to complete the study both in ON and OFF states, were much less severe with mild freezing, rather than severe freezing of gait. Therefore, the reported change from OFF to ON in freezing is likely conservative considering these individuals were much higher functioning. Additionally, all participants were unable to see their limbs or body in the virtual environment (since it was dark). Research has suggested that sensory processing is an important contributor to freezing of gait (Ehgoetz Martens, Pieruccini-Faria, & Almeida, 2013) and freezing might be increased when visual feedback about body position is not available. Although this rationale might explain the occurrence of freezing of gait while walking across the plank on the ground (GROUND), it cannot explain the massive increases in freezing behavior experienced when Freezers walked across the plank above the

pit, since in both ELEVATED and GROUND conditions visual feedback about body position would have been absent.

## 2.6 Conclusion

This was the first study to directly compare freezing of gait in anxious and non-anxious situations and showed that virtual reality is a very effective means of inducing anxiety and causing freezing of gait. It was found that Freezers reported significantly higher levels of anxiety compared to Non-freezers. Additionally, over 230 freezing of gait episodes were elicited (in a sample of only 14 Freezers) when walking in the anxious environment (over double that of over ground walking in virtual reality). This study provides strong evidence that anxiety is an important mechanism underlying freezing of gait and suggests that increasing limbic "load" (i.e. anxiety) leads to increased freezing of gait and step-to-step variability. Future studies should investigate whether effectively treating anxiety might reduce the occurrence of freezing of gait and potentially other severe symptoms of Parkinson's disease.

# Chapter 3

# ANXIETY PROVOKED GAIT CHANGES ARE SELECTIVELY DOPA-RESPONSIVE IN PARKINSON'S DISEASE

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## 3.1 Abstract

In order to understand how dopamine modulates the effect of anxiety on gait, the goal of this study was to use virtual reality to provoke anxiety in PD (in both the ON and OFF state) and quantify its effect on gait. Seventeen PD and 20 HC were instructed to walk in a virtual environment in two anxiety-provoking conditions: (i) across a plank that was located on the ground (GROUND); (ii) across a plank above a deep pit (ELEVATED). All PD participants completed this in both the ON and OFF states, and then were striated into low and high trait anxious groups for further analyses. Anxiety (skin conductance and self-report) and spatiotemporal aspects of gait were measured. Overall, the ELEVATED condition resulted in greater skin conductance levels and self-reported anxiety levels. Additionally, all participants demonstrated slower gait with increased step-to-step variability when crossing the ELEVATED plank compared to the plank on the GROUNG. Results showed that dopaminergic treatment selectively improved gait in only the highly anxious PD group, by significantly improving velocity, step length, step time and step-to-step variability specifically when walking across the ELEVATED plank (ON versus OFF comparison). In conclusion, only highly trait anxious PD benefitted from dopaminergic treatment, specifically when walking in the anxiety-provoking environment. Improvements to gait during anxious walking might be a result of dopaminergic medication acting in two ways: 1) improving the basal ganglia's capacity to process information and 2) by reducing the load from anxiety and subsequently making more resources available to effectively process other competing inputs.

## 3.2 Introduction

Anxiety is a common non-motor symptom of Parkinson's disease (PD). In fact, between 23-38% of patients are diagnosed with clinical anxiety disorders (Richard, 2005) and non-clinical anxiety has been found in up to 69% of individuals with PD (Prediger et al., 2012). Although anxiety fluctuations have been shown to be related to levodopa dose (Maricle, Nutt, & Carter, 1995; Maricle, Nutt, Valentine, et al., 1995), non-dopaminergic systems (such as the serotonergic and noradrenergic systems) have also been suggested to play a role in the pathophysiology of anxiety in PD (Prediger et al., 2012). Given that the ventral striatum receives direct input from limbic centers that control emotion (de la Fuente-Fernández, 2013), one simple way to determine the role of the dopaminergic system in anxiety driven behaviors would be to test individuals with Parkinson's disease ON and OFF their dopaminergic treatment.

Anecdotally, patients with PD often report: 1) that their dopaminergic medications appear to wear off more quickly in anxious settings, and 2) greater movement impairments during stressful situations. Associations have been found in PD between anxiety and increased motor symptoms, more severe gait impairments such as freezing of gait (Ehgoetz Martens, Ellard, & Almeida, 2014b). In fact, research recently showed that PD patients who experience freezing of gait (FOG) demonstrate greater step-to-step variability and experience more FOG episodes when walking in a threatening situation (Ehgoetz Martens et al., 2014b). However, limited research has investigated how anxiety influences movement control in PD. Studies of

both gait and balance did not identify any unique relationship between anxiety and movement behaviors in PD (when compared to healthy controls), but it is important to recognize that PD participants were only tested in their ON state and excluded PD participants who experienced high levels of anxiety (Caetano et al., 2009; Pasman et al., 2011). Given that dopaminergic replacement ameliorates basal ganglia associated deficits, one might expect that testing PD patients in the OFF state might reveal a different pattern of behavior in response to anxious stimuli. Further, considering anxious PD patients were excluded from these previous studies, it may be important to evaluate a greater spectrum of PD patients. For example, those who experience high levels of anxiety and those who do not.

Thus, the objective of the study was to more carefully investigate how anxiety influences gait control in PD by comparing PD in the OFF state to healthy age-matched controls. Further, to evaluate how dopaminergic replacement therapy influences the effect of anxiety on gait, OFF and ON states in PD were also compared in PD patients categorized into groups of low and high anxiety.

## 3.3 Materials and Methods

### 3.3.1 Participants

Seventeen individuals with idiopathic PD and twenty healthy control participants were recruited through the Sun Life Financial Movement Disorders Research and Rehabilitation Centre participant database (see Table 1 for participant demographics). Participants were excluded if they could not walk 10m unassisted, had severe kyphosis, or other neurological

disorders. Patient files were also carefully screened for co-morbid conditions (i.e. history of stroke, visual impairments, hearing loss, peripheral neuropathies, or diabetes). The Unified Parkinson's Disease Rating Scale motor section (UPDRS-III) (Goetz et al., 2007) was administered by a certified clinician to assess disease severity. Additionally, all participants completed the Modified Mini Mental State Exam (Teng & Chui, 1987), State and Trait Anxiety Inventory (Spielberger, 1987) assessing baseline levels of anxiety, Geriatric Depression Scale (Yesavage et al., 1983), the SCOPA-AUT questionnaire (Visser et al., 2004), and the modified clinical test of sensory interaction on balance (m-CTSIB). Ethical approval was obtained by both the Research Ethics Board at Wilfrid Laurier University as well as the Office of Research Ethics at the University of Waterloo. Written informed consent was obtained from all participants before participating according to the Declaration of Helsinki.

**Table 1. Baseline clinical and demographic information**

| | HC (N=20) | LA-PD (N=9) | HA-PD (N=8) | p-value |
|---|---|---|---|---|
| Age | 68 (9.5) | 65.9 (9.9) | 66 (7.7) | p=0.5 (n.s.) |
| Sex | 6F | 2F | 1F | |
| UPDRS-III (OFF) | --- | 28.7 (10.9) | 25.4 (8.7) | p=0.9 (n.s.); p<0.01 [d,e] |
| UPDRS-III (ON) | --- | 22.9 (11.2) | 17.6 (9.4) | p=0.5 (n.s.) |
| LDE | --- | 179.4 (99.0) | 272.3 (77.1) | p=0.05** |
| STAI-Trait (OFF) | 30.6 (5.7) | 29.8 (4.6) | 42.5 (5.5) | p=0.001[b,c]; p= 0.001[e] |
| STAI-Trait (ON) | --- | 28.7 (5.3) | 36.9 (5.2) | p=0.03[c] |
| STAI-State (OFF) | 27.9 (6.7) | 30.8 (6.6) | 38.9 (10.2) | p<0.001[b,c]; p=0.049[e] |
| STAI-State (ON) | --- | 27.6 (5.2) | 32.6 (5.8) | p=0.005[c] |
| 3MS | 98.1 (2.7) | 96 (3.6) | 96.3 (5.5) | p=.11 (n.s.) |
| GDS | 3.3 (2.9) | 3.9 (3.9) | 10.5 (3.7) | p<0.001[b,c]** |
| SCOPA-AUT | 7.7 (4.9) | 15.6 (5.3) | 15.8 (3.6) | p<0.01[a,b] |
| Pre-SSQ (OFF) | 2.2 (3.1) | 8 (5.0) | 11.4 (4.5) | p<0.001[a,b] |
| Pre-SSQ (ON) | --- | 8.8 (8.9) | 7.3 (7.5) | p=0.7 (n.s.) |

| | | | | |
|---|---|---|---|---|
| Post-SSQ (OFF) | 3.7 (3.0) | 6.2 (3.3) | 10.9 (7.4) | p=0.001[b] |
| Post-SSQ (ON) | --- | 8.8 (5.5) | 8 (5.9) | p=0.8 (n.s.) |
| m-CTSIB (Firm Surface, Eyes Open) | 0.72 (0.22) | 0.82 (0.24) | 0.72 (0.14) | p=0.55 (n.s.) |

**Table 1. Continued**

| | | | | |
|---|---|---|---|---|
| m-CTSIB (Firm Surface, Eyes Closed) | 1.45 (0.39) | 1.41 (0.44) | 1.31 (0.28) | p=0.69 (n.s.) |
| m-CTSIB (Foam Surface, Eyes Open) | 0.99 (0.28) | 1.12 (0.3) | 1.17 (0.38) | p=0.32 (n.s.) |
| m-CTSIB (Foam Surface, Eyes Closed) | 2.87 (0.47) | 3.57 (1.67) | 2.89 (0.59) | p=0.17 (n.s.) |
| # of Fallers | 5 | 3 | 3 | |
| # of People who Fear Heights | 7 | 5 | 4 | |

a=HC significantly different from LA-PD ($p<0.05$)
b=HC significantly different from HA-PD ($p<0.05$)
c=LA-PD significantly different from HA-PD ($p<0.05$)
d=LA-PD (within group difference): ON state significantly different from OFF state ($p<0.05$)
e=HA-PD (within group difference): ON state significantly different from OFF state ($p<0.05$)
UPDRS-III: Unified Parkinson's Disease Rating Scale motor subsection; LDE: Levodopa Dose Equivalence; STAI: State-Trait Anxiety Inventory; 3MS: Modified Mini Mental State Exam; GDS: Geriatric Depression Scale; SCOPA-AUT: Assessment of Autonomic Dysfunction in Parkinson's disease; SSQ: Simulator Sickness Questionnaire; m-CTSIB: Modified Clinical Test of Sensory Interaction on Balance.
**Note: Although depression and LED was significantly higher in the HA-PD, both of these measures did not correlate with any gait parameters.

### 3.3.2 Design and Procedure

#### 3.3.2.1 Apparatus

The virtual environment (VE) used in this study was constructed using *Vizard* (Worldviz L.L.C., Santa Barbara, USA) and delivered using a high definition, low latency

wireless link to a zSight head mounted display (HMD) (Sensics Inc., Columbia, USA) that featured a 60-degree field-of-view with 100% binocular overlap and a 1280x1024 full-colour pixels per eye resolution. In order to make the VE as immersive as possible, the experiment was completed in a dark room, which prevented participants from seeing the floor, their own feet, or the spotters' feet walking beside them. The viewpoint in the VE was controlled by seven OPTOTRAK Certus cameras (NDI Principles, Waterloo, Canada) capturing and synchronizing the participants' position and movement using a rigid body with three infrared light emitting diodes that was attached to the HMD, allowing the viewpoint to update in real-time creating an immersive virtual setting. The visual focus and eye width settings were adjusted for each participant to display a clear stereoscopic 3-D image. In order to measure electrodermal activity, Q sensor cuffs were also strapped to the participants' left hand and collected skin conductance levels as a psychophysiological marker of anxiety. The Q sensor collected electrodermal activity at a frequency of 8 Hz from the hypothenar eminence which has been suggested for ambulatory experimental paradigms (Boucsein, 2012). Synchronization of the start and end of each trial was achieved with a button press from the researcher. The m-CTSIB was collected using a BIODEX Balance System™ SD (Biodex Medical Systems, New York, USA).

#### 3.3.2.2 Experimental Protocol

All participants completed 10 randomized walking trials in a virtual environment (VE) (see Apparatus section below). They stood on the edge of a GAITRite sensor carpet, which

was calibrated to visually display the starting platform in virtual reality (VR). To complete the task, participants were required to walk across a plank (6m long x 1m wide) plank to the opposite platform in one of two conditions formed in a 3-D VE (Vizard, Worldviz) (see Figure 1). In the GROUND condition participants were required to walk across a plank that was located on the floor of the VE (Figure 1A). In contrast, during the ELEVATED condition participants viewed the floor surrounding the platform, as it descended, creating a deep pit below. Participants were required to walk across the plank, which appeared to be approximately 8m above the deep pit (Figure 1B). After walking across the plank in each trial, a 9 point self-assessment manikin scale (Bradley & Lang, 1994) was displayed and patients were asked to rate their feelings of stress and anxiety. Then, the head mounted display (HMD) would present a black screen and a research assistant would guide the participant back to the

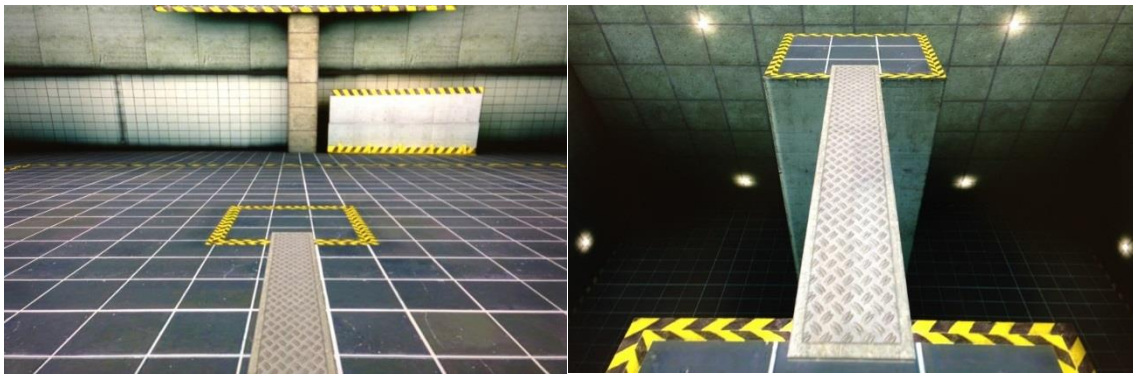

**Figure 1. The experimental paradigm. Patients walked across the virtual plank in two environments: A) GROUND: while the plank was located on the ground; B) ELEVATED: participants viewed the floor descend, and then walk across the elevated plank**

start position for the next trial. A standing rest period of 30 seconds was given after each trial to prevent carry-over effects from anxiety on the previous trial.

In order to assess how dopaminergic replacement therapy influenced anxiety and gait, participants with PD completed the full protocol on two separate occasions (approximately one week apart), once OFF their dopaminergic medication (after a minimum of 12 hours withdrawal) and ON their optimal dosage of medication (approximately one hour after their regular dosage). In order to account for practice effects, half of the patients completed the study first in their ON state while the other half completed the study first in their OFF state, thus the order was counterbalanced across PD participants.

### 3.3.3 Data Analysis

There were two different outcome measures for anxiety. The primary outcome measure was participants' self-report anxiety levels using the self-assessment manikins after each trial. Skin conductance responses (SCR) were measured between 1 and 3 seconds after the presentation of the environment. SCRs were calculated by extracting the maximum skin conductance value within that time window and subtracting the average skin conductance level during the 30 second baseline "rest" period prior to each trial (Boucsein, 2012). This subtraction was performed to normalize the data across participants and as the trials progressed. It is important to note that participants were simply viewing the environment during the SCR period, they had not commenced walking until after the 3 second period. Skin conductance levels (SCL) were also measured 5 seconds after the start of the trial and until completion of the trial. SCLs were calculated by taking the average skin conductance level

over that time period and then also normalized by subtracting the average skin conductance level during the 30 second baseline "rest" period prior to each trial (Boucsein, 2012). Spatiotemporal aspects of gait (i.e. velocity, step length, step time, step width, step length variability (CV), step time CV, step width CV) were processed using PKMAS software.

#### 3.3.3.1 Statistical Methods

In order to evaluate whether anxiety influences gait in individuals with basal ganglia damage (PD-OFF) differently than in healthy age-matched controls, a three factor mixed repeated measures ANOVA (group (HC, PD) x threat condition (GROUND, ELEVATED) x trial) was carried out.

Since the second aim was to understand whether dopamine influences the effect of anxiety on gait within PD, a subsequent analysis compared OFF and ON states (within PD participants) where the PD participants were categorized (by performing a median split-bimodal distribution was confirmed) based on their reported Trait anxiety into two subgroups of PD: Low Anxiety PD (LA-PD) and High Anxiety PD (HA-PD) (Table 1). Thus, a four factor mixed repeated measures ANOVA (group (HA-PD, LA-PD) x medication state (ON, OFF) x threat condition (GROUND, ELEVATED) x trial) was carried out. Additionally, a three factor mixed repeated measures ANOVA (group (HC, HA-PD, LA-PD) x threat condition (GROUND, ELEVATED) x trial) was performed to evaluate whether the influence of anxiety on gait differed in healthy relative to the spectrum of anxiety experienced in PD.

Baseline demographic variables were compared between groups with a one-way ANOVA and also within the PD group and between medication states using independent and dependent t-tests.

## 3.4 Results

### 3.4.1 Anxiety Measures

A main effect of condition for self-assessment anxiety (SAM) levels ($F(1,34)=34.38$, $p<0.001$) skin conductance response ($F(1,33)=5.25$, $p=0.029$) and skin conductance levels ($F(1,33)=35.09$, $p<0.001$) revealed that all participants had greater levels of anxiety during the ELEVATED condition compared to the GROUND. Finally, a main effect of trial for SAM levels ($F(4,136)=10.63$, $p<0.001$) skin conductance response ($F(4,132)=6.08$, $p<0.001$) and skin conductance levels ($F(4,132)=8.71$, $p<0.001$) showed that all participants had less anxiety as the trials progressed. An interaction between condition and trial for skin conductance levels ($F(4,132)=9.51$, $p<0.001$) showed that all participants had significantly higher SCL during the first three trials of the ELEVATED condition compared to the GROUND condition. Additionally, an interaction between group, condition and trial for skin conductance responses ($F(4,132)=2.89$, $p=0.025$) showed that PD participants displayed significantly greater response in the first trial of the ELEVATED condition compared to the first trial of the GROUND condition.

There was a significant main effect of medication state for anxiety ratings in those with PD ($F(1,15)=4.82$, $p=0.044$), which showed that all PD participants reported feeling less

anxious when they were ON compared to OFF across both conditions. There was no effect of medication on skin conductance levels.

### 3.4.2 Gait Parameters: Effects of anxiety on gait kinematics

#### 3.4.2.1 PD versus Healthy Controls

A main effect of condition revealed that PD-OFF respond to anxiety similar to healthy age-matched control participants, in that all participants displayed slower and more variable gait during the ELEVATED condition compared to the GROUND condition (for a summary of these results see Table 2).

**Table 2. Similar gait changes in response to the condition in PD and HC**

| | THREAT | | | | Main effect of Condition |
|---|---|---|---|---|---|
| | GROUND | | ELEVATED | | |
| **Gait Parameter** | **HC** | **PD** | **HC** | **PD** | **p-value** |
| **Velocity (cm/s)** | 69.7 (5.97) | 63.6 (5.56) | 42.9 (5.54) | 38.0 (4.80) | p<0.0001 |
| **Step Length (cm)** | 44.8 (3.25) | 38.7 (2.97) | 29.4 (3.08) | 23.7 (2.27) | p<0.0001 |
| **Step Time (s)** | 0.67 (0.03) | 0.62 (0.02) | 0.78 (0.07) | 0.67 (0.04) | p=0.035 |
| **Step Length CV (%)** | 13.4 (1.89) | 15.5 (1.96) | 27.6 (2.29) | 26.8 (2.8) | p<0.0001 |
| **Step Time CV (%)** | 10.1 (2.26) | 9.4 (0.79) | 15.9 (2.15) | 22.1 (4.2) | p<0.0001 |

Note: values displayed for PD in this table represent gait in the OFF dopaminergic state.

#### 3.4.2.2 Healthy Controls versus Low Anxiety and High Trait Anxiety PD subgroups

An interaction between condition and trial was found for velocity ($F(4,136)=15.78$, $p<0.001$), step length ($F(4,136)=15.82$, $p<0.001$) and step length variability ($F(4,136)=6.71$,

$p<0.001$). These results showed that all participants walked slower, with smaller steps and with greater step length variability during the ELEVATED condition compared to the GROUND, and that this effect was amplified in all participants on the first trial of the ELEVATED condition.

An interaction between group, condition and trial was found for step time ($F(8,136)=2.05$, $p=0.04$) and step time variability ($F(8,136)=2.83$, $p=0.006$). Post hoc analyses revealed that HC and HA-PD had significantly higher step time on the first trial of the ELEVATED condition compared to all other trials, whereas step time in the LA-PD group was similar across all trials. Additionally, HA-PD had significantly higher step time variability on the first trial of the ELEVATED condition compared to HC participants and nearly significantly higher than LA-PD ($p=0.077$) on the first ELEVATED trial (Figure 2A). Likewise, HA-PD had significantly higher step time variability in their first trial during the ELEVATED condition compared to all other trials. In contrast, both the LA-PD and HC groups displayed similar step time variability during ELEVATED and GROUND trials.

An interaction between group and condition for step width ($F(1,34)=4.66$, $p=0.016$) showed that healthy control participants significantly increased their step width when walking across the ELEVATED plank compared to the GROUND plank (Fisher LSD $p=0.042$), whereas the LA-PD did not change and the HA-PD significantly reduced their step width during the ELEVATED condition compared to the GROUND CONDITION (Fisher LSD $p=0.03$) (see Figure 2B). It is important to note however, that the more conservative post-hoc

measure (Tukey's post hoc) did not find significant differences between groups in either condition. There were not any significant results for step width variability.

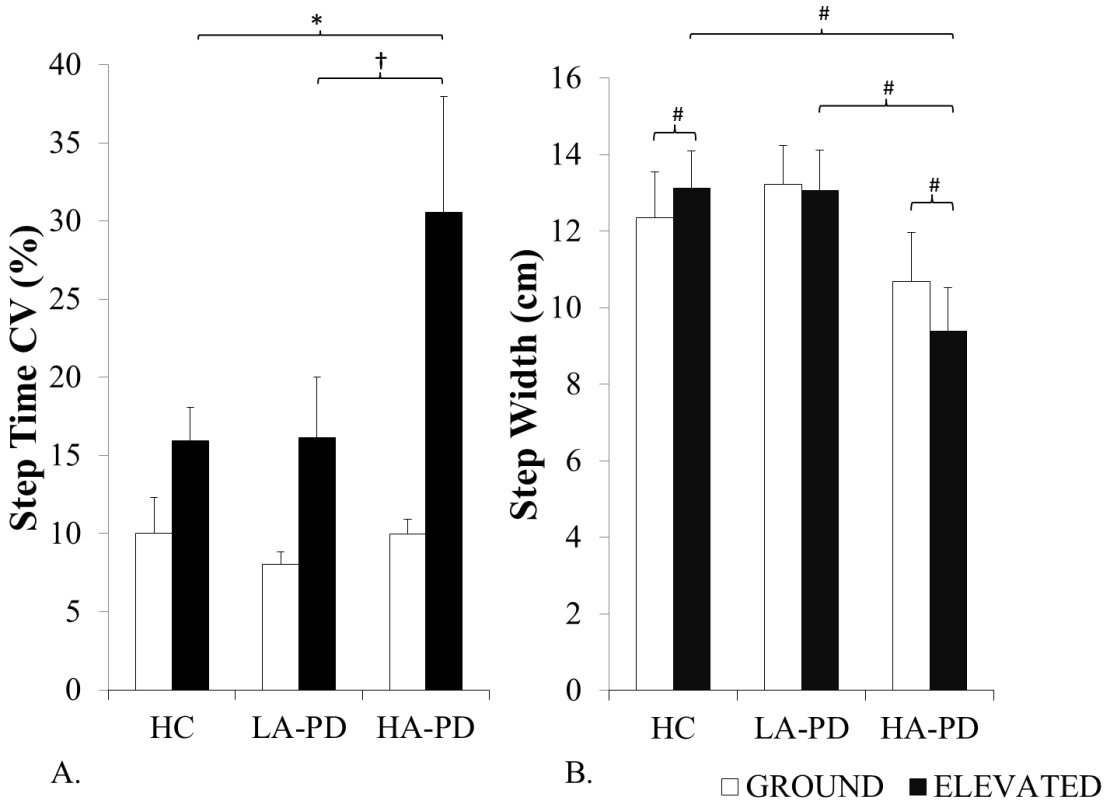


**Figure 2. Gait differences between both HA-PD and LA-PD and HC. A.) illustrates the step time variability on the first trial in order to show the group x condition x trial interaction showing that PD who are highly anxious had greater step time variability during the ELEVATED condition compared to HC and LA-PD; B.) Fisher's LSD show that HC increase their step width when walking across the ELEVATED plank compared to the LOW, whereas PD who are highly anxious reduce their step width and PD with low level of anxiety do not adjust their step width. *indicate Tukey's $p<0.05$; + indicate Tukey's $p<0.08$; #indicates a Fisher's LSD $p<0.05$; error bars display standard error of the mean.**

### 3.4.3 Gait Parameters: Effects of dopaminergic medication on gait kinematics

#### 3.4.3.1 OFF versus ON state in both Low and High Trait Anxiety PD subgroups

A significant interaction between group, medication state and condition was found for velocity ($F(1,15)=8.84$, $p=0.009$); step length ($F(1,15)=6.91$, $p=0.019$); and step length variability ($F(1,15)=6.88$, $p=0.019$). Post hoc analyses revealed that dopaminergic medication increased velocity, step length and reduced step length variability in both PD groups when walking across the plank on the GROUND. However, during the ELEVATED condition, only high anxious PD participants significantly improved velocity, step length and step length variability when they were tested in their ON state compared to OFF. Furthermore, a significant interaction between group, medication state, condition and trial was found for step time ($F(4,60)=2.77$, $p=0.035$) and step time variability ($F(4,60)=4.19$, $p=0.005$). These results showed that dopaminergic medication (ON-state) selectively improved gait only in the HA-PD group (compared to OFF-state), specifically while walking across the ELEVATED plank (see Figure 3).

Finally, an interaction between group, medication and condition ($F(1,15)=7.41$, $p=0.016$) for step width showed that HA-PD significantly reduced their step width during the ELEVATED condition compared to the GROUND condition specifically during their OFF state. There was also a main effect of group ($F(1,15)=5.00$, $p=0.041$) and medication ($F(1,15)=8.41$, $p=0.011$) for step width CV which demonstrated that HA-PD had greater step width CV than LA-PD, and dopaminergic medication amplified their step width CV.

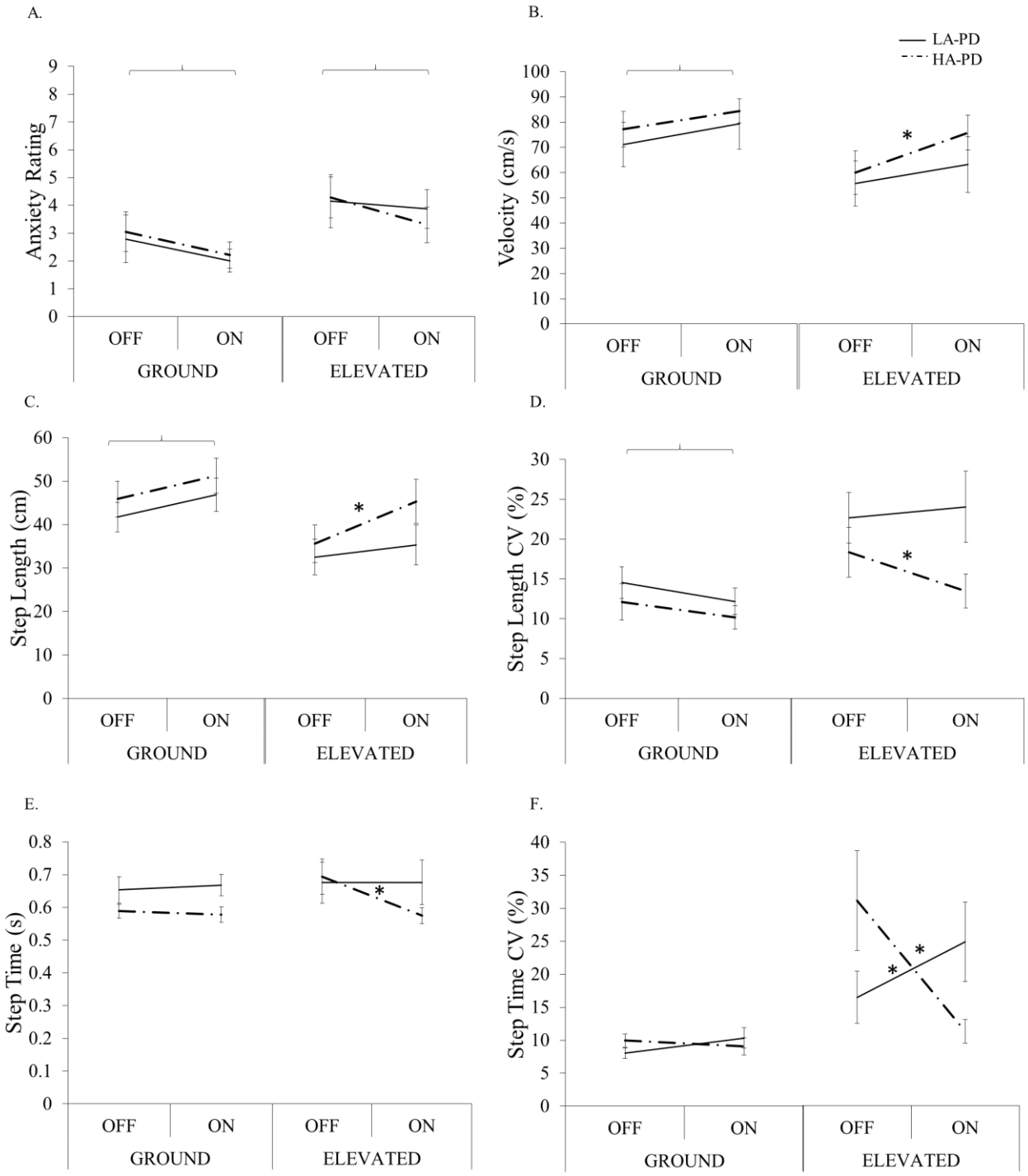


**Figure 3. Highly trait anxious PD are indicated with the dotted line and low trait anxious PD are indicated with the solid line. A) illustrates that a main effect of medication state**

**and condition whereby both LA-PD and HA-PD reported significantly less anxiety when they were tested in their ON state compared to their OFF state and significantly greater levels of anxiety when crossing the ELEVATED plank compared to the GROUND CONDITION; B) shows that only HA-PD walked with a significantly faster velocity during the ELEVATED condition when tested ON compared to OFF; C) illustrates that only HA-PD had significantly longer step length during the ELEVATED condition when tested in their ON state compared to OFF; D) shows that only HA-PD significantly reduced their step length variability when crossing the ELEVATED plank in their ON state compared to their OFF state; E) illustrates the first trial only. HA-PD significantly reduced their step time when crossing the ELEVATED plank in their ON state compared to their OFF state specifically on the first trial; F) illustrates the first trial only. HA-PD significantly reduced their step time variability when crossing the ELEVATED plank in their ON state compared to their OFF stare specifically on the first trial, whereas LA-PD significantly increased their step time variability in their ON state compared to their OFF state when crossing the ELEVATED plank. *indicates Tukey's $p<0.05$.**

## 3.5 Discussion

To our knowledge this study was the first to identify that anxiety induced gait disturbances and their responsiveness to dopaminergic medication are dependent on the anxiety profile of the PD patient. These aims were achieved by comparing subgroups of PD with high and low levels of anxiety while ON and OFF their dopaminergic treatment during walking in two different VEs. It is important to highlight that the protocol used in this study effectively manipulated anxiety in all participants (PD and HC), since all participants reported higher levels of anxiety and had greater skin conductance levels after walking across the plank above a deep pit compared to walking across the plank on the ground. Additionally, all participants significantly reduced their velocity and step length and took longer step times while walking across the ELEVATED plank. This cautious gait adaptation has been demonstrated previously in older adults when walking across an elevated plank in a "real

world" setting (Caetano et al., 2009; Gage et al., 2003) and confirms that both groups in the current study found the VE immersive and realistic enough to elicit more cautious gait patterns.

An important question that had not yet been addressed in previous research is whether dopaminergic replacement therapy influences anxiety and gait independently, or if these factors interact. **First, it is important to point out that medication state was confirmed to be effectively manipulated since all PD participants' had significantly worse motor symptoms in their OFF dopaminergic state compared to their ON state (measured with a clinical motor assessment using the UPDRS-III).**

If we now focus on anxiety alone, it should be noted that only PD participants who were highly anxious at baseline (i.e. reported high levels of trait anxiety) demonstrated a reduction in state and trait levels of anxiety with dopaminergic medication. One possible reason that the low anxiety PD group did not significantly reduce their reported levels of trait anxiety was because many of them were already at the very low end of the scale, thus there was little room for improvement from dopaminergic treatment. In addition, dopaminergic treatment improved anxiety ratings after each VR walking condition across all PD participants (using the self-assessment manikins). These results support the notion that dopaminergic medication independently influences anxiety in PD (Burn et al., 2012; Maricle, Nutt, & Carter, 1995; Maricle, Nutt, Valentine, et al., 1995), particularly in those with higher levels of anxiety.

If we were to focus on the independent effects of dopamine on gait, the current results reveal that the typical improvements in gait from dopaminergic medication (i.e. greater

velocity and increased step length) were found in PD when tested in the ON state compared to the OFF when walking in the GROUND condition. The most interesting result was that dopaminergic medication selectively improved gait in only the highly anxious PD participants, by improving velocity, step length, step time, and even step-to-step variability (which is not usually dopa-responsive) and only when walking across the ELEVATED plank in their ON state (compared to OFF). These findings are similar to recent results which showed that dopaminergic medication reduced the number of FOG episodes in PD patients by a clinically significant amount, however these reductions in FOG were specifically seen when participants walking across an elevated plank (Ehgoetz Martens et al., 2014b). Overall, these gait improvements may be a result of dopaminergic medication acting in two ways: (i) it may improve the basal ganglia's capacity to process incoming information (emotional, sensory, etc.), and/or (ii) it may also reduce the "load" of anxiety, subsequently making more resources available to effectively process other competing inputs, thus allowing participants to employ tighter control (less gait variability) and produce less cautious gait (increased velocity, step length, and decreased step time). Therefore, this is the first study to demonstrate a robust link between anxiety and gait that is modulated by dopaminergic replacement therapy, and emphasizes the importance of examining different anxiety profiles in PD in order to identify different responses to dopaminergic medication.

It may be important to consider why the low anxiety PD group lost the typical benefits of dopamine treatment on gait when faced with the threat of the ELEVATED plank, even

though their gait improved with dopaminergic medication when walking across the plank on the GROUND. This finding is similar to Brown et al (2007), which showed that regardless of medication state, PD participants did not adjust standing postural control in situations of high postural threat (i.e. standing on an elevated platform). These authors suggest that dopamine uptake in PD participants might be restricted depending on the context (Brown et al., 2007), although this was an anecdotal suggestion by participants that could not be confirmed experimentally. A more likely alternative explanation based on our results, might be that the typical PD patient with low levels of anxiety might adopt a more cautious gait pattern, regardless of whether they are medicated or not, in order to ensure safe walking in threatening situations, possibly to compensate for sensory impairments that help guide movements accurately. It appears that highly anxious PD patients do not adopt a similar strategy.

Notably, the current study was able to separate the effects of dopamine on gait from its effects on anxiety by demonstrating that dopamine influenced gait separately from anxiety and vice versa, but most importantly the interaction highlights that the effect of dopamine on gait in threatening situations is dependent on PD participants' baseline trait anxiety level. Future research should consider comparing dopaminergic and anxiolytic treatments in order to evaluate which is more effective at reducing anxiety symptoms in PD and further clarifying whether reducing anxiety in PD leads to gait improvements or if this is specifically an outcome of dopaminergic treatment.

The current results also support previous findings that have shown that individuals with PD adapt their gait similarly to HC participants (i.e. velocity, step length and step time) even when tested in the OFF state. However, it is important to highlight that since our study was able to capture participants' gait over a much longer area than all previous studies (Caetano et al., 2009), the current study identified significant increases in step-to-step variability when all participants crossed the ELEVATED plank. It was expected that if anxiety led to tighter control of gait then participants should reduce their degrees of freedom and decrease variability (Adkin et al., 2000, 2002). Although participants adopted a more cautious gait pattern during walking in anxious environments, increases in step-to-step variability suggest that anxiety reduces gait control in all participants. One possible explanation may be that walking in anxious environments may demand greater voluntary control, and as a result demand more central resources similar to a dual-task invoking a cognitive load (Iansek et al., 2013; Lord et al., 2014; Rochester et al., 2014; Yogev et al., 2005; Yogev, Plotnik, Peretz, Giladi, & Hausdorff, 2007). Yogev and colleagues demonstrated that as cognitive demand increased, swing time variability also increased in PD. Furthermore, a recent cohort study identified that reductions in step width and step width variability were the most sensitive gait variables reflecting dual task interference (Rochester et al., 2014). The current findings also demonstrate that highly anxious PD had significantly greater step time variability (on the first trial) and reduced step width while walking across the ELEVATED plank compared to the GROUND plank and compared to the other two groups. These findings suggest that anxiety might act similar to dual-task

interference, especially in the more anxious group of PD, reducing their ability to adapt to the environment. Interestingly, in both situations (dual-tasking or anxiety-provoking) PD patients who experience FOG also demonstrate greater step variability which often precede full-blown FOG episodes. Thus, future research should consider whether those PD who are highly anxious might be more likely to develop FOG in the later stages of their disease when they become completely unable to adapt to their environment. Taken together, these results suggest that greater anxiety leads to worse control and more cautious gait. Additionally, this study proposes that anxiety may be sharing common resources, limiting the remaining capacity to consciously control gait effectively (Lewis & Barker, 2009a, 2009b).

One limitation of this study is that we did not compare PD patients who are highly anxious to a healthy control group with equally high levels of anxiety. Thus, it remains unclear whether these anxiety-provoked gait deficits are a specific outcome of anxiety in PD as a result of basal ganglia damage or not. Based on the rationale presented above, we would not expect anxious healthy control participants to produce the same magnitude of gait impairments (if any) as those with PD, since their basal ganglia would not be damaged and thus competition for resources to control emotion and motor output should be minimal. However, this is purely speculative and further results is needed to clarify this relationship.

## 3.6 Conclusion

Overall, our data suggest that anxiety is an important non-motor symptom that can have a dramatic impact on motor symptoms such as gait especially in highly anxious PD, and more

importantly that these emotional responses are modulated by dopaminergic therapy. While dopamine replacement appears to have beneficial effects on these non-motor symptoms, it may be important to consider other non-dopaminergic treatments for anxiety as a potential treatment for movement symptoms in PD.

# Chapter 4

# INVESTIGATING THE ROLE OF DOPAMINE AND WHETHER ANXIETY INTERFERES WITH PROCESSING WHILE WALKING IN THREATENING ENVIRONMENTS IN PARKINSON'S DISEASE

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## 4.1 Abstract

Research evidence has suggested that anxiety influences gait in PD, with an identified dopa-sensitive gait response in highly anxious PD. It has been well-established that accurate perception of the environment and sensory feedback is essential for gait. Arguably since sensory and perceptual deficits have been noted in PD, anxiety has the potential to exacerbate movement impairments, since one might expect that reducing resources needed to overcome or compensate for sensory-perceptual deficits may lead to even more severe gait impairments. It is possible that anxiety in threatening situations might consume more processing resources, limiting the ability to process information about the environment or one's own movement (sensory feedback) especially in highly anxious PD. Therefore, the current study aimed to (i) evaluate whether processing of threat-related aspects of the environment was influenced by anxiety, (ii) evaluate whether anxiety influences the ability to utilize sensory feedback in PD while walking in threatening situations, and (iii) further understand the role of dopaminergic medication on these processes in threatening situations in PD. Forty-eight participants (24 HC; 12 Low Anxious [LA-PD], 12 Highly Anxious [HA-PD]) completed 20 walking trials in virtual reality across a plank that was (i) GROUND: located on the ground (ii) ELEVATED: plank located above a deep pit; while provided with or without visual feedback about their lower limbs (+VF;-VF). After walking across the plank, participants were asked to judge the width of the plank they had just walked across. The plank varied in size from 60-100 cm. Both ON and OFF dopaminergic medication states were evaluated in PD. Gait parameters, judgment

error and self-reported anxiety levels were measured. Results showed that HA-PD reported greater levels of anxiety overall ($p<0.001$) compared to HC and LA-PD, and all participants reported greater anxiety during the ELEVATED condition compared to the GROUND condition ($p=0.01$). PD had similar judgment error as HC. Additionally, medication state did not significantly influence judgment error in PD. More importantly, HA-PD were the only group that did not adjust their step width when feedback was provided during the GROUND condition. However, medication facilitated a reduction in ST-CV when visual feedback was available only in the HA-PD group. Therefore, the current study provides evidence that anxiety may interfere with information processing, especially utilizing sensory feedback while walking. Dopaminergic medication appears to improve utilization of sensory feedback in stressful situations by reducing anxiety and/or improving resource allocation especially in those with PD who are highly anxious.

## 4.2 Introduction

Anxiety in Parkinson's disease (PD) is drastically understudied considering the ominous influence that anxiety has demonstrated over movement symptoms (e.g. gait behavior) and quality of life in those with PD (Ehgoetz Martens et al., 2014b; Hanna & Cronin-Golomb, 2012; Nuti et al., 2004). Although the pathophysiology of anxiety in PD remains unclear, neuroimaging research suggests that anxiety in PD is likely related to dopamine depletion within the striatum of the basal ganglia (nucleus accumbens - NAcc), and also reduced dopaminergic innervation to the amygdala (Benke, Bo, & Andree, 1998; Tessitore et al., 2002). It has been hypothesized that interconnections between the limbic and motor circuits within the basal ganglia (NAcc) provide means for anxiety to influence motor outputs (Nakano, 2000), especially in stressful situations, since integrated processing across different basal ganglia circuits has been suggested to be modulated by striatal dopamine (Balaban & Thayer, 2001; Bracs, Jackson, & Gregory, 1984; McCullough, Sokolowski, & Salamone, 1993; Valenti & Grace, 2010). Lending support to this notion, anxiety has been found to be more prevalent in the OFF dopaminergic state (Nissenbaum et al., 1987; Racette et al., 2002; Siemers et al., 1993) and dopaminergic treatment has been shown to improve anxiety and emotional processing impairments in PD (Funkiewiez et al., 2006; Maricle, Nutt, & Carter, 1995; Maricle, Nutt, Valentine, et al., 1995; Stacy, Murck, & Kroenke, 2010; Tessitore et al., 2002; Witjas et al., 2002). Interestingly, recent research has identified that anxiety profiles (high and low trait levels in PD) show different responses to medication. That is, dopaminergic

medication selectively improves gait behavior (surprisingly even step-to-step variability which is not usually dopa-responsive) when walking in anxiety-provoking environments, but only in those with PD who are highly anxious (Ehgoetz Martens, Ellard, & Almeida, 2015a). It was hypothesized that these gait improvements result from dopaminergic medication, improving the basal ganglia's capacity to process incoming information (emotional, sensory, etc.), and/or possibly reducing the "load" of anxiety.

Notably, gait changes that occur when walking in a threatening environment (in healthy older adults (HC) and PD) resemble the typical response when distracted by a dual task (i.e. slower and more variable gait) (Hausdorff et al., 2003; Rochester et al., 2014; Yogev et al., 2005). Dual-tasking has been shown to interfere with PD participants' ability to adopt a larger step width to increase stability in order to reduce their risk of falling (Rochester et al., 2014). In fact, gait impairments are exacerbated in those with PD who are highly anxious, resulting in even greater increases in their step time variability and notable *reductions* in step width (instead of increases in step width shown by HC) when walking in threatening situations (Ehgoetz Martens et al., 2015a). Thus, anxiety in PD may contribute to an overload in a similar way that a dual-task does, which might explain *how* an anxiety-provoking environment exacerbates gait impairments in PD.

Evidence from non-Parkisnonian clinical anxiety literature has shown that anxiety does influence information processing, primarily perception (Eysenck et al., 1987), since highly anxious individuals allocate greater amounts of attentional resources to threatening stimuli

and are often more sensitive to threatening content. Neuroimaging and ERP studies have both shown that levels of anxiety (most often trait anxiety) can modulate cortical and subcortical functions while patients perform attentional tasks including emotional items (Bishop, Duncan, & Lawrence, 2004; Bishop, 2007; Carretie, Mercado, Hinojosa, Martin-Loeches, & Sotillo, 2004; Etkin et al., 2004; Small et al., 2003). This abnormal distribution of attention has been investigated in detail, but has found inconsistent results. Some research suggests that anxious people orient their attention to threat during early stages of processing, but then subsequently attend away from threat (avoid) during stages of elaborated processing as a strategy to reduce affective distress (Koster, Verschuere, Crombez, & Van Damme, 2005; Mercado, Carretié, Hinojosa, & Peñacoba, 2009). However, this behavior has been argued to hinder detailed perception of their environment due to inadequate processing (Mogg et al., 1997). In contrast, other research has demonstrated that anxious individuals dedicate resources to threatening stimuli, leaving them unable to disengage attention, instead of avoiding the threat (Fox et al., 2007; Fox, Russo, & Dutton, 2008). This type of behavior has been shown to facilitate sensory processing (mainly in the visual domain) since it enhances the amount of attentional resources devoted to it.

In general, accurate processing of both the environment and self-motion are essential in order to properly navigate through an environment, especially a threatening one (Ehgoetz Martens, Ellard, & Almeida, 2014a). Compromising either of these processes could lead to impaired gait behavior that is seen when walking through anxiety-provoking environments.

Arguably since sensory and perceptual deficits have been identified in PD (Almeida & Lebold, 2010; Ehgoetz Martens et al., 2014a; Ehgoetz Martens, Ellard, et al., 2013; Johnson et al., 2004; Martens & Almeida, 2012; Patel et al., 2014), it is likely that resources are already dedicated to compensating for these impairments. Thus, the impact anxiety has on overloading information processing capacity may be greater in PD, resulting in even more severe gait impairments.

The current study aimed to investigate *how* anxiety influences walking in PD. By using virtual reality (VR), we contrasted walking along a plank in threatening and non-threatening environments while plank size and self-motion feedback was manipulated. There were three main objectives. The first one was to evaluate whether processing of threat-related aspects of the environment (plank size) was influenced by anxiety. The second objective was to evaluate whether processing of online self-motion feedback was influenced by anxiety, and the third was to further understand the role of dopaminergic medication on information processing in threatening situations in PD. It was hypothesized that if anxiety interferes with information processing (e.g. plank size or self-motion feedback) while walking, then PD participants may demonstrate inaccurate plank size judgments and visual feedback about their lower limbs may not influence gait while walking in the threatening environment. However, while walking in a non-threatening environment we might expect those with PD (especially those who are highly anxious) to demonstrate more accurate plank size judgments and improvements to spatiotemporal aspects of gait when visual feedback about their lower limbs is available.

Finally, if dopaminergic treatment reduces anxiety and facilitates more information processing, then PD participants (especially those who are highly anxious) may demonstrate improvements in judgment accuracy and utilization of sensory feedback to adapt gait when tested in their ON dopaminergic state, specifically when walking in a threatening environment.

## 4.3 Materials and Methods

### 4.3.1 Participants

Fifty-nine participants (25 HC, 34 PD) were recruited for participation in the current study, however only twenty-four healthy age-matched control participants and 24 PD participants were able to complete the full study. The Unified Parkinson's Disease Rating Scale motor section (UPDRS-III) (Goetz et al., 2007) was administered by a certified clinician and used to assess disease severity in those with PD. Additionally, all participants completed the Modified Mini Mental State Exam (Teng & Chui, 1987), State and Trait Anxiety Inventory (Spielberger, 1987) assessing baseline levels of anxiety, Geriatric Depression Scale (Yesavage et al., 1983), and the SCOPA-AUT questionnaire (Visser et al., 2004). Participants also rated their fear of heights on a 1-10 scale, and reported the number of falls they had experienced in the past year. Finally, a simulator sickness questionnaire was completed once before the experiment and then again after the experimental walking trials to quantify any adverse effects as a result of the virtual reality (VR) protocol. Table 1 shows the demographic characteristics and clinical details of participants. Previous research has demonstrated that highly anxious PD are especially impacted when walking in threatening situations, and dopaminergic treatment

selectively improves walking in only in those PD who are highly anxious. Thus, the current study split the PD group into highly anxious (HA-PD) and low anxiety (LA-PD) subgroups. These two groups were created by performing a median split on PD participants' trait anxiety in their OFF state, and then categorizing the groups into HA-PD and LA-PD. It is important to note that the median within our sample (M=35.5) was similar to previous studies who performed this method (M=35) (Broadbent & Broadbent, 1988; Ehgoetz Martens et al., 2015a).

**Table 1. Baseline clinical and demographic participant information**

| | HC | LA-PD | HA-PD | p-value |
|---|---|---|---|---|
| N | 24 | 12 | 12 | |
| Age | 70.8 (7.5) | 66.4 (7.8) | 68.8 (4.4) | p=0.2 |
| Sex | 9 F; 15 M | 3 F; 9 M | 2 F; 10 M | |
| LDE | | 931 (515.6) | 1278 (1399.6) | p=0.43 |
| UPDRS-III (OFF) | | 25.9 (8.5) | 30.6 (8.8) | p=0.21 |
| UPDRS-III (ON) | | 19 (8.4) | 19.4 (6.9) | p=0.92 |
| STAI-Trait (OFF) | 27 (6.3) | 29 (5.9) | 50 (9.5)* | p<0.001 |
| STAI-Trait (ON) | | 28 (6.0) | 48 (12.5) | p<0.001 |
| STAI-State (OFF) | 27 (8.7) | 35 (7.1) | 49 (10.8)* | p<0.001 |
| STAI-State (ON) | | 29 (5.4) | 45 (14.3) | p=0.002 |
| GDS | 2 (2.1) | 5 (3.9) | 15 (7.3)* | p<0.001 |
| SCOPA-AUT | 6 (3.6)* | 12 (4.6) | 19 (8.8) | p<0.001 |
| 3MS | 98 (3.8) | 98 (2.1) | 95 (4.7) | p=0.12 |
| # of Fallers | 5 | 4 | 6 | |
| Fear of Heights | 3 (2.1)[#] | 5 (3.1) | 7 (3.2)[#] | p=0.001 |

UPDRS-III: Unified Parkinson's Disease Rating Scale motor subsection; LDE: Levodopa Dose Equivalence; STAI: State-Trait Anxiety Inventory; 3MS: Modified Mini Mental State Exam; GDS: Geriatric Depression Scale; SCOPA-AUT: Assessment of Autonomic Dysfunction in Parkinson's disease. * indicates the group that is significantly different from the other two groups (verified with a Tukey's post-hoc analysis). [#] indicates that HC group is only significantly different from HA-PD but not LA-PD.

All participants in this study were recruited from the Sun Life Financial Movement Disorders Research and Rehabilitation Centre participant database at Wilfrid Laurier University. Participants were excluded from the study if they could not walk 10m unassisted, had vertigo, motion sickness, severe kyphosis, other neurological disorders, severe head tremor or dyskinesia (since it would make the virtual environment appear to be shaking, increasing the difficulty and likelihood of motion sickness). All PD participants had been previously diagnosed with PD by a movement disorder neurologist. Patient files were also screened for co-morbid conditions (i.e. history of stroke, visual impairments, hearing loss, or peripheral neuropathies) prior to participation. Ethical approval was obtained by both the Research Ethics Board at Wilfrid Laurier University as well as the Office of Research Ethics at the University of Waterloo. Written informed consent was obtained from all participants before participating according to the Declaration of Helsinki.

### 4.3.2 Design and Procedure

#### 4.3.2.1 Apparatus

The virtual environment (VE) used in this study was constructed using *Vizard* (Worldviz L.L.C., Santa Barbara, USA) and delivered using a high definition, low latency wireless link to a zSight head mounted display (HMD) (Sensics Inc., Columbia, USA) that featured a 60-degree field-of-view with 100% binocular overlap and a 1280x1024 full-colour pixels per eye resolution. The visual focus and eye width settings were adjusted for each participant to display a clear stereoscopic 3-D image.

The viewpoint in the VE was controlled by eight OPTOTRAK Certus cameras (NDI Principles, Waterloo, Canada) capturing and synchronizing the participants' position and movement using a rigid body with three infrared light emitting diodes (IRED) that was attached to the HMD, allowing the viewpoint to update in real-time creating an immersive virtual setting. In order for participants to be able to view their steps clearly when visual feedback about their lower limbs was provided, the viewpoint was calibrated to be angled downward 30 degrees when participants were looking straight ahead. Additionally, IRED rigid bodies were also strapped to the participants' chest, mid-thighs and mid-shanks. The OPTOTRAK camera setup also captured the participants' body and lower limb movement and synchronized it to an avatar displayed within the VE which enabled us to provide visual feedback from the lower limbs while walking through the VE in real-time (Figure 1).The experiment was completed in a dark room in effort to make the VE as immersive as possible and prevent participants from seeing the their actual feet, the real floor, or the spotters' feet walking beside them.

Participants were positioned at the end of the laboratory room and a Zeno Walkway sensor carpet (over 10 m in length) was located on the floor in front of them lengthwise. The Zeno Walkway carpet (Protokinetics, Havertown, USA) was used to capture spatiotemporal aspects of gait during each walking trial.

#### 4.3.2.2 Experimental Protocol

Before beginning the trials, participants were given 1-2 practice walking trials with visual feedback about their lower limbs while the plank was located on the ground. Participants

then completed 20 randomized experimental trials where they were instructed to walk across a plank that varied in width (60, 70, 80, 90 or 100cm) and stop once they got to the distal platform. After walking across the plank to the opposite platform in each trial, a 9 point self-assessment manikin scale (Bradley & Lang, 1994) would be displayed and participants were asked to rate their feelings of stress and anxiety using the self-assessment manikins. Once an anxiety rating was given, the experimenter would "turn out the lights" in the HMD, leaving a black screen, and a random "judgment" plank (either 50 or 110 cm wide) would appear in front of them. Participants were instructed to use the wireless mouse in their hand and adjust the plank width (by pressing the left or right buttons) to match the one they had just crossed. Left clicks increased the planks' width by 2.5 cm incrementally, while right clicks decreased the width by 2.5 cm as well. Importantly, the participants were given as much time as needed to adjust the plank, and once they had finished adjusting the plank width using the mouse, they notified the experimenter and their judgment width was recorded. This marked the end of the trial, so the screen in the HMD went completely black and a research assistant guided the participant back to the start position for the next trial.

Participants completed 5 walking trials across the virtual plank (one of each plank size: 60, 70, 80, 90, 100 cm) in each of the four conditions: (i) GROUND+VF: plank was located on the ground and visual feedback about their lower limbs was provided; (ii) GROUND-VF: plank was located on the ground but visual feedback about their lower limbs was not provided; (iii) ELEVATED+VF: plank was located above a deep pit and visual feedback about their

lower limbs was provided; (iv) ELEVATED-VF: plank was located above a deep pit but visual feedback about their lower limbs was not provided. Condition and plank size were randomized on every trial.

All PD participants included in the study completed this protocol on two separate occasions (once in their ON state and once in their OFF state). Medication state was counterbalanced, meaning that half of the participants completely the protocol OFF first (after at least a 12 hour withdrawal from their regular dopaminergic medication), whereas the other half of the participants completed the protocol ON first (approximately one hour after taking their regular dosage of dopaminergic medication).

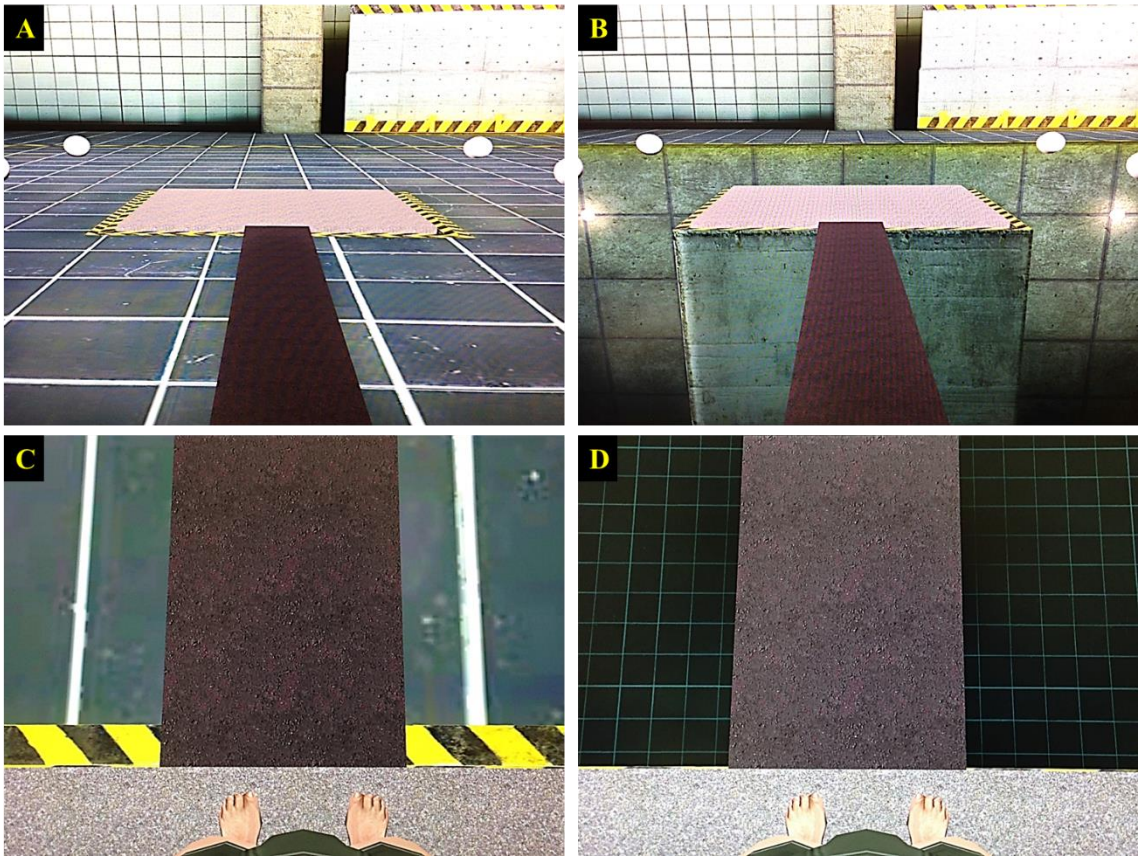


**Figure 1. Virtual environments: A) GROUND plank, B) ELEVATED plank. This figure also illustrates visual feedback conditions when it was made available to participants: C) GROUND+VF; D) ELEVATED+VF. The plank size illustrated in this figure is 60 cm.**

### 4.3.3 Data Analysis

#### 4.3.3.1 Statistical Methods

The main outcome measures for this study were self-reported anxiety, judgment error (both absolute and constant error), and spatiotemporal aspects of gait (i.e. velocity, step length,

step time, step width, step length variability (CV: coefficient of variation), step time CV, and step width CV). Gait measures were processed using PKMAS software.

Baseline measures were compared between groups (HC, LA-PD, HA-PD) using One-way ANOVAs, and independent t-tests compared ON state baseline measures between the two PD groups, while paired samples t-tests compared ON and OFF state baseline measures within the PD subgroups. Across all analyses, healthy control participants were compared to PD participants in their OFF state in order to understand the implications of basal ganglia damage in PD.

In order to verify that the experimental manipulation did in fact manipulate anxiety levels across all participants a four factor mixed repeated measures ANOVA (group (HC, LA-PD, HA-PD) x threat condition (GROUND, ELEVATED) x feedback (-VF, +VF) x size (60, 70, 80, 90, 100cm)) was conducted on participants self-reported anxiety levels on each trial.

Since the first aim of the study was to evaluate whether anxiety interferes with accurate processing of the environment, accuracy of participants' plank size estimations (i.e. judgment error) was analyzed using another four factor mixed repeated measures ANOVA for both absolute and constant error. One PD participant in the HA-PD group was removed from the judgment analysis for misunderstanding the instructions and inadequately providing magnitude estimations. A subsequent five factor mixed ANOVA (group (LA-PD, HA-PD) x medication state (OFF, ON) x threat condition (GROUND, ELEVATED) x feedback (-VF, +VF) x size) compared judgment error between medication states (OFF and ON) in both PD

subgroups. Another HA-PD participant was removed from specifically the five factor analysis for judgment error due to an equipment malfunction.

Finally, four factor ANOVAs (between HC, LA-PD and HA-PD) and five factor ANOVAs (including medication state in both PD groups) were also conducted for each of the gait measures in order address the second aim of the study, to examine whether anxiety influences one's ability to utilize self-motion feedback and whether dopaminergic medication modulates one's ability to use this information.

All significant ($p<0.05$) and near significant ($p<0.08$) interactions were followed up with Tukey's post-hoc analyses. Fisher's LSD post-hoc analyses were also employed and clearly reported in the results section with the intent of exploring patterns of data that may need to be addressed with further research.

## 4.4 Results

### 4.4.1 Baseline Data

Participant demographic, clinical and cognitive characteristics are shown in Table 1. All groups were matched for age, symptom severity (UPDRS-III), and cognitive status. Additionally, all groups had a similar number of people with a history of falling in the past year, and thus groups were matched in the number of fallers as well. Compared to healthy controls and LA-PD, the highly anxious PD participants reported higher levels of trait and state anxiety (both their ON and OFF state). Trait anxiety did not change in either PD group with dopaminergic medication, however state anxiety improved significantly with dopaminergic

medication for LA-PD. The HA-PD group scored higher on the depression scale compared to LA-PD and HC. Additionally, all PD had higher levels of autonomic dysfunction compared to HC, and further HA-PD reported greater autonomic disturbance than the LA-PD group. Finally, HA-PD reported having a greater fear of heights compared to the HC group.

### 4.4.2 Anxiety Ratings

All participants reported having greater levels of anxiety while walking across the ELEVATED plank compared to the GROUND plank as demonstrated with a main effect of condition ($F(1,45)=54.30$, $p<0.001$). An interaction between condition and feedback ($F(1,45)=7.75$, $p=0.008$) also revealed that when walking in the ELEVATED condition, all participants reported greater anxiety when they were provided visual feedback about their limbs compared to when feedback was not provided. Finally, there was also an interaction between condition and size ($F(4,180)=13.26$, $p<0.001$) which showed that the size of the plank influenced self-reported anxiety during the ELEVATED conditions. More specifically, all participants were more anxious when walking across the narrower planks (60-70cm) compared to the wider one (100 cm).

A main effect of group ($F(2,45)=13.51$, $p<0.001$) was found for self-reported levels of anxiety, with Tukey's post-hoc analysis revealing that HA-PD reported significantly higher levels of anxiety overall compared to all other groups. A medication x group interaction was also found for self-reported anxiety within the PD groups ($F(1,22)=7.30$, $p=0.013$). Dopaminergic medication reduced anxiety levels in HA-PD to be similar to that of LA-PD (see

Figure 2). This findings has additional support from an interaction between medication state, condition, feedback, size and group which neared significance (F(4,88)=2.28, p=0.067).

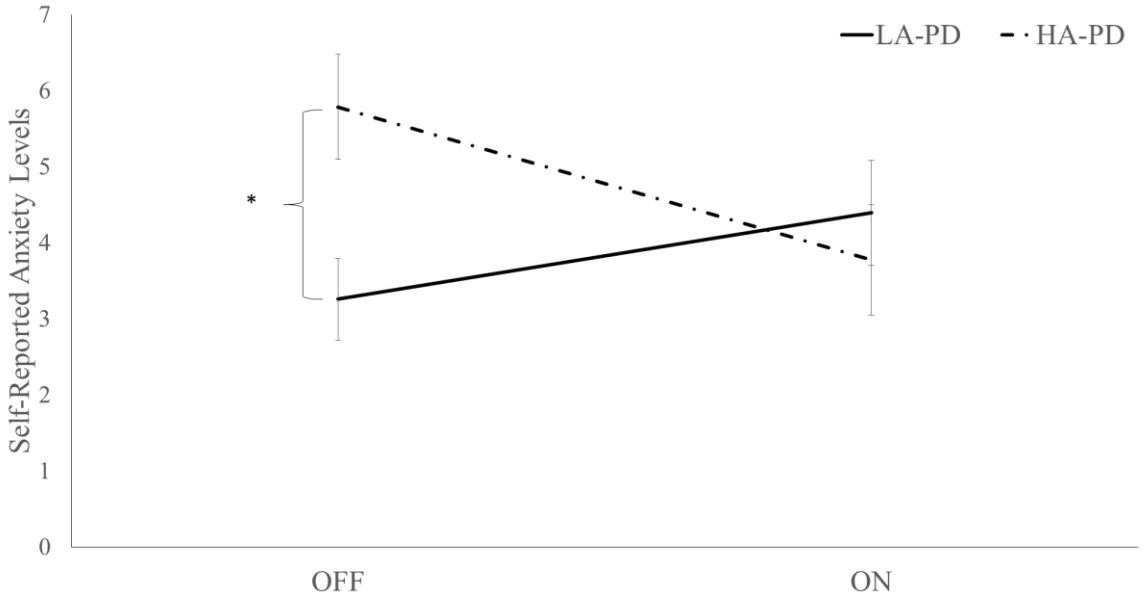


**Figure 2. Self-reported anxiety levels were significantly greater in HA-PD when tested in their OFF state compared to LA-PD, however in their ON state LA-PD and HA-PD reported similar levels of anxiety. *indicates Tukey's p<0.05.**

### 4.4.3 Judgment Accuracy: Effects of anxiety on judgment error

There were no main effects of group, condition or feedback for absolute or constant error. A main effect of size (CE: F(4,176)=45.53, p<0.001) revealed that participants made greater judgment errors at the extreme sizes of the plank (i.e. participants underestimated the narrow planks, and overestimated the wider planks). There was a significant interaction between feedback, size, and group for absolute error (AE: F(8,176)=2.09, p=0.039). Tukey's post-hoc revealed that HA-PD had worse judgments on the wider planks when visual feedback was not available compared to HC. When feedback was provided, judgment error did not

change significantly across all groups. However, Fisher's LSD showed that HA-PD increased judgment error specifically for the 70cm plank when feedback was provided compared to no feedback.

#### 4.4.3.1 Dopaminergic effects on judgment error

There was no effect of medication state for absolute nor constant error in judgment. However, within the PD group there was a significant main effect of condition for constant error (CE: $F(1,20)=10.24$, $p=0.004$) which revealed that all PD had more accurate judgments after walking across the ELEVATED plank compared to the GROUND. Additionally, it appeared that dopaminergic medication did not influence judgments accuracy after crossing the ELEVATED plank, but slightly worsened accuracy after crossing the GROUND plank in both PD groups based on a near-significant interaction between medication state and condition for absolute error (AE: $F(1,20)=3.31$, $p=0.08$).

A condition x size interaction (AE: $F(4,80)=3.16$, $p=0.02$; CE: $F(4,80)=3.45$, $p=0.012$) showed that during the GROUND condition, all PD participants had worse judgments on the narrowest plank (underestimated the 60 cm plank), whereas on the ELEVATED condition, judgment error became worse on the wide plank (overestimated the 100cm). Judgments of the mid-range planks were not affected by condition. Interestingly, there was also an interaction that approached significance between condition and feedback within the PD group for absolute error (AE: $F(1,20)=4.17$, $p=0.054$), which revealed that visual feedback about their limbs increased judgment error in both PD groups while walking in the GROUND condition,

however it decreased judgment error while walking in the ELEVATED condition. Additionally, an interaction between feedback and size (AE: $F(4,80)=2.61$, $p=0.042$; CE: $F(4,80)=2.16$, $p=0.08$) revealed that feedback reduced judgment error in the wide plank estimations, but increased error in the narrow plank estimations across all PD participants.

### 4.4.4 Gait Parameters: Effects of anxiety on utilizing lower limb visual feedback

Overall, HA-PD walked slower and with smaller steps compared to HC and had more variable gait compared to both LA-PD and HC. Additionally, all participants significantly walked with a slower velocity, shorter steps, wider step width and more variable steps when walking in the ELEVATED condition (above a deep pit) compared to the GROUND. HA-PD had significantly greater step time variability when walking across the ELEVATED plank compared to LA-PD and HC. Main effects and interactions for all gait variables are summarized in Table 2.

**Table 2. A summary of main effects, group interactions and three-way interactions between condition, feedback and size for all gait variables**

| | Main Effects | | | | Group Interactions | | | 3-way Interaction C x F x S |
|---|---|---|---|---|---|---|---|---|
| | Group | Condition | Feedback | Size | Condition | Feedback | Size | |
| Velocity | ***5.39 (0.008)*** | ***14.01 (0.001)*** | ***6.19 (0.017)*** | ***6.53 (<0.001)*** | 0.47 (0.627) | 0.52 (0.599) | ***2.0 (0.049)*** | ***13.2 (<0.001)*** |
| Step Length | ***5.38 (0.008)*** | ***55.09 (<0.001)*** | 2.11 (0.154) | ***51.26 (<0.001)*** | 0.70 (0.503) | 1.04 (0.361) | 0.66 (0.730) | ***5.40 (<0.001)*** |
| Step Time | 1.34 (0.272) | 2.77 (0.103) | 0.55 (0.463) | 1.56 (0.188) | 1.4 (0.256) | 1.29 (0.284) | 1.58 (0.134) | 1.56 (0.187) |
| Step Width | 1.3 (0.284) | ***11.73 (0.001)*** | *3.94 (0.053)* | *2.28 (0.062)* | *2.54 (0.09)* | ***8.76 (0.001)*** | 1.35 (0.221) | **3.41 (0.01)** |
| Step Length CV | ***5.29 (0.009)*** | ***26.9 (<0.001)*** | 0.11 (0.745) | ***26.59 (<0.001)*** | 1.63 (0.207) | 0.23 (0.799) | 0.96 (0.446) | **12.10 (<0.001)** |
| Step Time CV | ***7.29 (0.002)*** | ***25.86 (<0.001)*** | 0.31 (0.58) | ***11.17 (<0.001)*** | ***5.76 (0.006)*** | 0.11 (0.898) | 1.3 (0.245) | **5.45 (<0.001)** |
| Step Width CV | 1.28 (0.288) | ***17.26 (<0.001)*** | 0.22 (0.642) | *2.11 (0.081)* | 2.05 (0.14) | 2.27 (0.115) | ***2.86 (0.005)*** | **3.68 (0.007)** |

A significant interaction between condition, feedback and group was found for step width ($F(2,45)=64.98$, $p=0.011$) (see Figure 3). Tukey's post hoc revealed that with visual feedback about their limbs, HC widened their step width when walking in the GROUND condition, whereas neither PD group adjusted their step width. However, Fisher LSD additionally revealed that LA-PD significantly reduce their step width when visual feedback is available regardless of whether they walked in the ELEVATED or GROUND condition, yet HA-PD still did not adjust their step width with visual feedback on either condition.

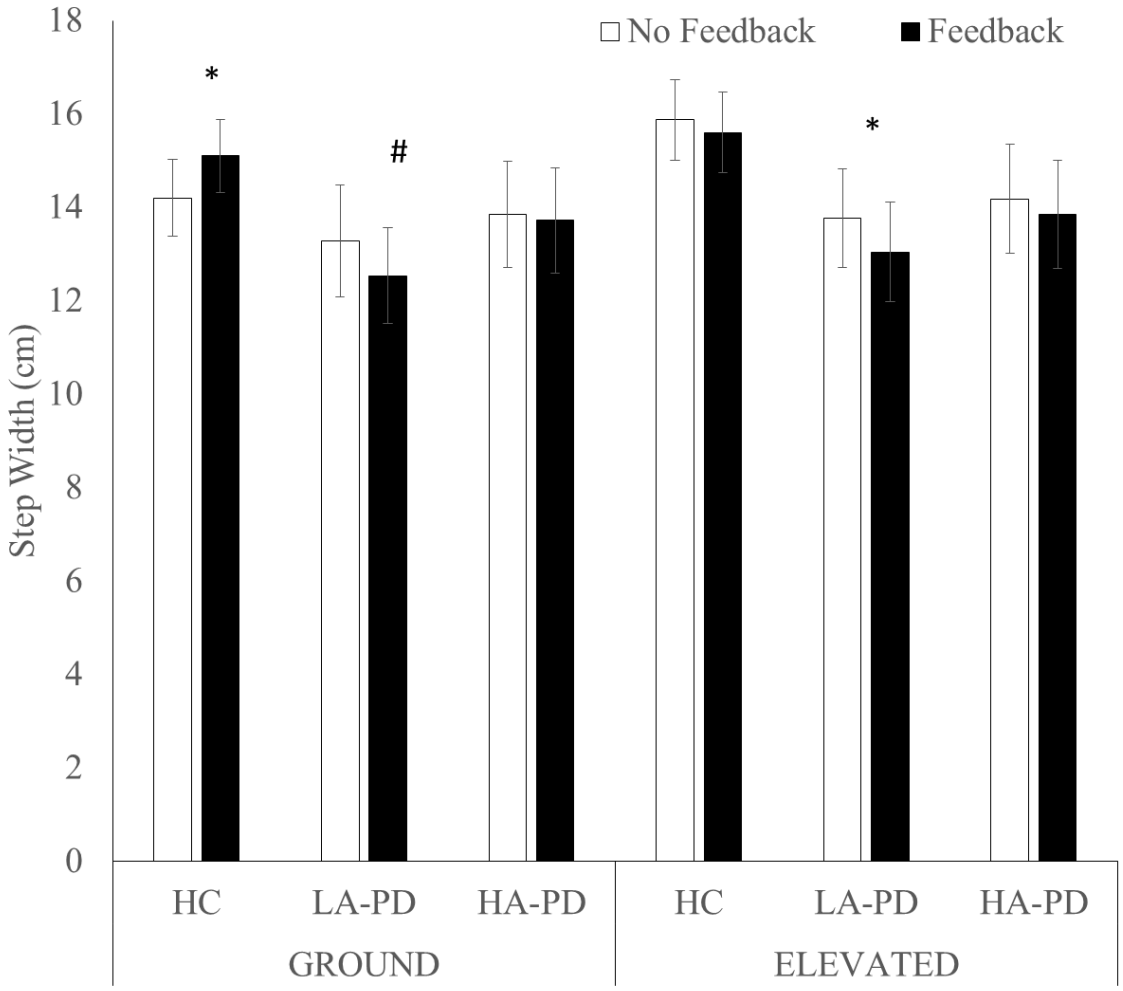


**Figure 3. This figure illustrates that healthy control participants significantly increase their step width and LA-PD reduce their step width when visual feedback about their lower limbs is available during the GROUND condition, while HA-PD did not change. During the ELEVATED condition, only LA-PD reduced their step width when visual feedback was available. *indicates p<0.05; #indicates Fisher's LSD p<0.05.**

A significant interaction between groups and condition was also found for step time CV ($F(2,45)=5.76$, $p=0.006$) which demonstrated that HA-PD had significantly greater step time CV when walking across the ELEVATED plank compared to GROUND and compared

to LA-PD and HC. Furthermore, feedback appeared to reduce step time CV in HA-PD when walking in the GROUND condition, but slightly increased it when walking in the ELEVATED condition, whereas HC and LA-PD were unaffected by feedback in the GROUND condition, while it slightly reduced step time variability (instead of increased as seen in HA-PD) during the ELEVATED condition. This interaction between condition, feedback and group for step time CV approached significance (F(2,45)2.67, p=0.08) (Figure 4).

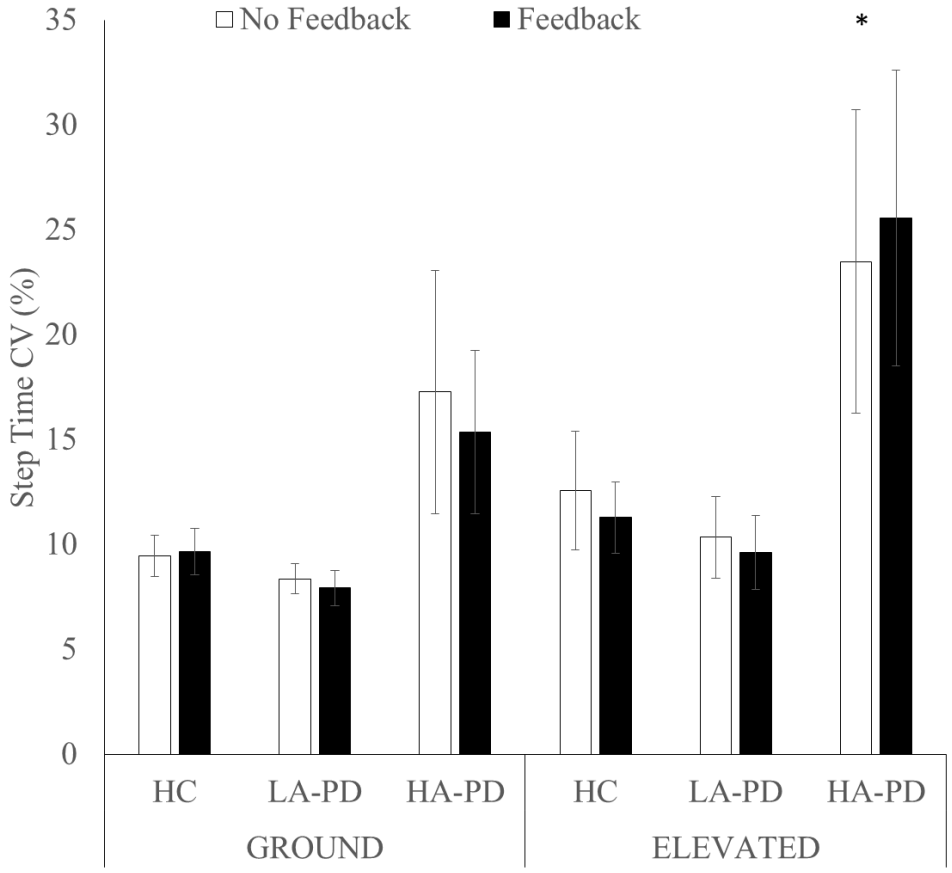


**Figure 4. Highly trait anxious PD demonstrated significantly greater step time variability when walking across the ELEVATED plank (with and without feedback) compared to the healthy control participants and low trait anxious PD, and also compared to walking across the GROUND plank.**

Additionally, a four-way interaction approached significance between condition, feedback, size and group found for step length CV ($F(8,180)=1.91$, $p=0.061$) resembling the pattern of results seen for step time CV. That is, only HA-PD showed significant increases in step length variability when visual feedback was provided when they walked across the GROUND narrow plank (60cm), whereas visual feedback reduced step length variability in HA-PD and HC when walking across the mid-range to wide GROUND planks (80-100cm). It also appeared that when visual feedback about their lower limbs was available, HC reduced their velocity when walking across the GROUND narrow plank (60cm), whereas they increased their velocity when feedback was available while they walked over the GROUND mid-range sized plank (80cm). However, feedback did not significantly change velocity in either of the PD groups. This interaction between condition, feedback, size, and group for velocity also neared significance ($F(8,180)=1.96$, $p=0.054$).

#### 4.4.4.1 Dopaminergic effects on utilizing sensory feedback

Most importantly, an interaction between medication state, feedback, size and group was found for step time CV ($F(4,88)=2.6$, $p=0.041$). Tukey's post-hoc revealed that dopaminergic medication reduced step time variability specifically when feedback was available only in the HA-PD group when walking across the narrow plank (60cm) (see Figure 5). Fisher's LSD additionally showed that dopaminergic medication reduces step time variability in HA-PD without feedback when walking across the mid-range sized planks (80-

90cm). Notably, dopaminergic medication did not influence step time variability or feedback in LA-PD.

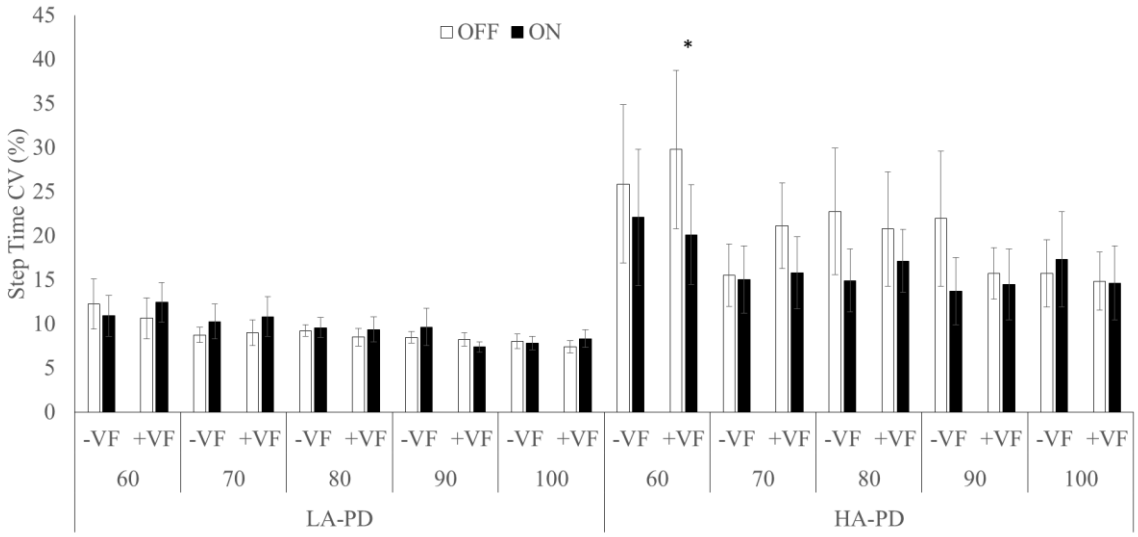


**Figure 5. This figures shows that step time variability when crossing the narrowest plank (60cm) is significantly reduced in HA-PD, specifically when visual feedback (VF) is available in their ON state compared to the OFF state. *indicates Tukey's $p<0.05$.**

In support of these results, a main effect of medication state were found for step length ($F(1,22)=12.99$, $p=0.002$), and an interaction approached significance for step length between medication, condition, feedback and group ($F(1,22)=3.37$, $p=0.08$). Dopaminergic medication significantly improved step length in both groups during the GROUND condition, however dopaminergic medication had a more drastic influence on the HA-PD group's step length, making it similar to that of LA-PD. In the OFF state, HA-PD had a significantly smaller step length when walking across the GROUND plank with visual feedback about their lower limbs

compared to without feedback. However, when in their ON state, HA-PD had a similar step length regardless of whether visual feedback was provided in the GROUND condition. It is noteworthy that dopaminergic medication significantly increased overall step length ($p=0.005$) in HA-PD but not in LA-PD.

An interaction between medication state and condition for step width variability ($F(1,22)=5.41$, $p=0.03$) showed that dopaminergic medication had a larger impact on step width variability on the GROUND condition compared to the ELEVATED condition, even though medication significantly increased step width variability in both conditions compared to OFF in both PD groups. Dopaminergic medication appeared to also increase step width variability ($p=0.02$) in HA-PD but not in LA-PD which was revealed by a trending interaction between medication and group ($F(1,22)=3.09$, $p=0.09$). Other trends included an interaction between medication, size and group for step width ($F(4,88)=2.11$, $p=0.086$) which showed that HA-PD significantly reduced their step width when tested in the ON state compared to the OFF state, whereas step width in LA-PD was similar in both medication states.

## 4.5 Discussion

It has been suggested that threatening stimuli can capture the attention of those with high levels of anxiety, potentially interfering with other necessary information processing that also requires resources from a common pool (Eysenck et al., 1987). It has been established that gait in PD shifts from automatic control to become consciously controlled in PD presumably to compensate for their basal ganglia deficit (which also draws from the common resource

pool) (Iansek et al., 2013). Thus, individuals with PD, especially those who are highly anxious, may be even more susceptible to processing deficits when walking in threatening situations. Additionally, it was postulated that deficits in processing either visual information (specifically about the constraints of the environment) or feedback about self-motion might disturb gait since these two sources of information are crucial for navigating through a complex environment. Thus, the aims of the study were to evaluate (i) whether anxiety influences processing threat-related aspects of the environment, and/or one's ability to utilize sensory feedback, and (ii) whether dopaminergic treatment modulates either of these proposed mechanisms.

In order to address each of these aims a virtual reality paradigm that has been previously shown to effectively manipulate anxiety in PD and HC was carried out. Similar to previous studies, we found that all participants reported greater levels of anxiety when they walked across the ELEVATED plank compared to the GROUND. The current study also replicated previous findings that individuals with PD who are highly anxious demonstrated more variable gait (i.e. step time CV) compared to less anxious PD. Additionally, further evidence that anxiety was in fact elicited in the virtual environments was exemplified by a more cautious gait pattern (i.e. slower velocity, shorter step length, and greater step-to-step variability) in all participants, when walking across the ELEVATED plank. This cautious gait pattern has been demonstrated in older adults and PD when walking across an elevated plank in both a "real world" and virtual setting (Caetano et al., 2009; Gage et al., 2003), and confirms that all groups

in the current study found the virtual environment immersive and realistic enough to elicit more cautious gait. Taken together, it was confirmed by the current findings that our experimental manipulation using anxiety-provoking environments was effective.

A novel feature of the current study was the additional manipulation of sensory feedback (i.e. visual feedback about self-motion from vision of their lower limbs). Results from this study also suggest that the visual feedback manipulation was effective since all participants walked with a faster velocity, longer step length, and reduced step-to-step variability when visual feedback was provided while walking across the GROUND mid-range sized planks.

### 4.5.1 Does anxiety interfere with accurate processing of the plank size?

Since it has been suggested that anxiety reduces one's capacity to process other information in the environment (Eysenck et al., 1987; Williams, Watts, Macleod, & Mathews, 1997), we expected that all participants would demonstrate poor judgment accuracy of the plank width when walking across the ELEVATED plank compared to the GROUND, and that HA-PD would have the greatest judgment errors compared to the other groups. Results from the current study suggest the opposite however, since all PD participants had more accurate judgments of the plank width after walking across the ELEVATED plank compared to the GROUND. Therefore, it appears that anxiety (from walking across the ELEVATED plank) may heighten one's awareness to threat-related information in PD which has been previously found in healthy adults with high trait anxiety and those with clinical anxiety (Broadbent & Broadbent, 1988; Macleod, Mathews, & Tata, 1986; Mogg et al., 1995, 1992; Mogg &

Bradley, 1998). In sum, the current study did not find any evidence that anxiety impairs with perception of the environment, but rather that when participants were more anxious, their perception of threat-related objects was heightened.

Although anxiety did not impair processing of the plank size, there was an influence of feedback on judgment accuracy specifically within the two PD groups. Both HA-PD and LA-PD improved their judgment accuracy when visual feedback about their lower limbs was provided while walking across the ELEVATED plank, whereas feedback worsened judgment accuracy while walking across the GROUND plank. Limb-position sense has been known to be affected in those with PD (Suilleabhain et al., 2001; Zia, Cody, & Boyle, 2000), and vision of the limbs aids in navigating and helps to compensate for sensorimotor impairments, even when walking through threatening situations (Almeida et al., 2005; Ehgoetz Martens, Pieruccini-Faria, & Almeida, 2013; Pieruccini-Faria, Ehgoetz Martens, Silveira, Jones, & Almeida, 2014). Thus, one possible explanation might be that when walking with threat, visual feedback becomes more relevant to movement and helps anchor their focus on the plank and movement relative to the plank, thus enhancing their judgment accuracy. When threat is low and the consequence of movement errors is less however, visual feedback about self-motion becomes less relevant and instead of helping to focus attention on the plank, it distracts the participant resulting in less accurate judgments. This explanation also addresses the absence of effect of feedback in the HC group, since sensorimotor deficits are not as prominent, and thus visual feedback may add very little additional information.

### 4.5.2 Does anxiety interfere with using feedback from the lower limbs?

It was hypothesized that if anxiety interfered with processing of online sensory feedback like visual feedback about self-motion, then we expected that providing participants with visual feedback while walking across the GROUND condition would improve gait (i.e. increase velocity, step length and reduce gait variability). However, we expected that visual feedback may not be utilized while walking across the ELEVATED plank, since anxiety levels during this condition might consume resources and interfere with utilizing sensory feedback information. As stated above, we did observe that visual feedback improved gait when walking across the GROUND mid-sized planks, confirming that feedback was utilized by all participants on the majority of the GROUND trials. It is noteworthy that visual feedback did not improve gait when participants walked across the narrowest GROUND plank, instead a reduction in velocity, step length and increased step-to-step variability was observed. This gait pattern resembles a similar adaptation participants made when walking across the ELEVATED planks, suggesting that constraining the width of the plank might increase the demand on resources to control gait, and consequently interfere with participants' ability to use visual feedback about self-motion.

Evidence suggesting that anxiety interfered with utilizing feedback from the lower limbs was found when examining both step width and step time variability. Results showed that both HC and LA-PD participants changed their step width (HC widened while LA-PD narrowed their step width) when feedback was provided during the GROUND condition,

whereas highly anxious PD did not use visual feedback to make any adjustments to their step width. Importantly, when all participants walked across the ELEVATED plank, HA-PD still did not adjust step width when visual feedback was available nor did HC, however, LA-PD continued to reduce step width even in the ELEVATED condition when feedback was available. These results align with previous findings (Ehgoetz Martens et al., 2015a) and provide support for our hypothesis that when anxiety levels are high, participants might not be able to utilize visual feedback to make postural adjustments that improve stability. It is important to note that the highly anxious PD participants had significantly greater levels of anxiety compared to the HC and LA-PD participants even during the GROUND condition. This might be one explanation for why HA-PD did not adjust their step width even while walking across the GROUND plank. It is also important to consider whether providing visual feedback helps or hinders gait in HC, since they do not rely on visual feedback about their limbs as much as PD patients. Visual feedback appeared to influence gait in HC when walking in the non-threatening environment (adopted a wider step width), however this behavior was not observed when they walked across the ELEVATED plank, even though they reported similar levels of anxiety as LA-PD. One explanation might be that HC relied more heavily on proprioceptive feedback rather than visual feedback when walking in the threatening environment, and thus no additional benefit was gained from providing visual feedback about their lower limbs for adopting a wider step width.

Furthermore, HC and LA-PD participants did use visual feedback to reduce step time variability when walking across the ELEVATED plank, whereas, HA-PD participants were only able to use visual feedback to reduce step time variability (and step length CV) when walking across the GROUND planks, but not when walking across the ELEVATED condition like the other two groups. It is important to point out that both step width and step time variability have been argued to reflect dual-task interference on gait (Rochester et al., 2014; Springer et al., 2006; Yogev et al., 2005). Taken together, our findings suggest that highly anxious PD participants are less able to utilize visual feedback especially when walking across the ELEVATED plank, since they did not adjust their step width or reduce their step time variability like the HC and LA-PD groups did, but they were able to use visual feedback to reduce step-to-step variability during the GROUND condition. The HC and LA-PD participants were able to utilize visual feedback to reduce step time variability in the ELEVATED condition but did not use visual feedback to adjust step width. Some researchers postulated that some gait characteristics are more sensitive to task demands than others and have suggested that cognition penetrates those variables under conscious control (such as step width and velocity) at a lower threshold than those that occur on a millisecond basis and are less amenable to online control (such as variation in the step-to-step fluctuations of gait) (Holtzer, Wang, & Verghese, 2013; Rochester et al., 2014; Yogev et al., 2005). Our findings are in line with this theory since anxiety interfered with step width (which is argued to be under greater conscious control) in all participants, whereas step time variability was only

"penetrated" by anxiety in HA-PD who had significantly more anxiety when walking across the ELEVATED plank, supporting the notion that variability may have a higher threshold for interference. Therefore, this study provides evidence that anxiety interferes with utilizing sensory feedback and may impair one's ability to consciously increase stability in order to increase safety and reduce the risk of falling.

### 4.5.3 Does dopaminergic treatment influence information processing?

The final objective of this study was to further understand the role of dopaminergic medication on information processing in threatening situations in PD. Based on previous findings, it was hypothesized that dopaminergic treatment might reduce anxiety and/or possibly facilitate more information processing at the level of the basal ganglia. Importantly, both PD groups demonstrated significant improvements in motor symptom severity (assessed using the UPDRS-III) when tested in their ON state compared to their OFF, confirming that dopaminergic state was adequately manipulated.

The most interesting result was that dopaminergic medication only significantly reduced step time variability when feedback was available in the HA-PD participants. This significant reduction was present in both GROUND and ELEVATED conditions, and suggests that dopaminergic medication may have improved information processing allowing HA-PD participants to utilize visual feedback to reduce step time variability. It is not surprising that dopaminergic medication did not significantly improve judgment accuracy in PD, since there was no judgment deficit found in PD. These results suggested that sufficient resources were

allocated to processing threat-related information regardless of dopaminergic state. However, dopaminergic medication may have allowed PD participants to allocate resources to process both the plank and visual feedback about their limbs rather than just the plank in the OFF state. In sum, the current study provides strong evidence that dopaminergic treatment can improve information processing in PD especially in threatening situations.

Also in line with previous studies, we found that dopaminergic medication reduced self-reported anxiety levels specifically in HA-PD participants, and selectively influenced their gait (i.e. increased step length, reduced step width and increased step width variability) (Blin, Ferrandez, Pailhous, & Serratrice, 1991; Ehgoetz Martens et al., 2015a). Notably, dopaminergic medication also increased step width variability in LA-PD participants. Although increases to step width variability have been argued to make an individual more adaptable when navigating complex environments, this is often coupled with widening of their step width to stabilize postural stability and reduce the risk of falling. However, neither PD group increased step width in their ON state, arguably putting them at greater risk of falls.

### 4.5.4 Limitations and Considerations

Although groups were matched in age, cognitive status, symptom severity and number of fallers, the HA-PD had significantly higher ratings of depression, fear of heights and autonomic nervous system dysfunction. Unfortunately, we cannot rule out the contribution of these differences to our data and the underlying mechanism in question. On a practical level, typically autonomic dysfunction and depression are co-morbid conditions that present with

anxiety, and thus disentangling these may not be important for clinical implications of the study, since most patients will most often have all three. Additionally, due to our small sample size of PD and many trending results, caution should be taken when interpreting the data from this study. Since this study is the first to explore mechanisms underlying anxiety's influence over gait in PD, we opted to be descriptive to help guide future research and encourage replication of these results. Finally, we acknowledge that asking participants to recall the plank size at the end of the trial may not have been the most effective method to measure their plank size perception since it incorporates an aspect of memory. Instead, having participants estimate the plank size while viewing the plank might have been a better measure of perception. However, we expected that if perception of plank width was not encoded with high fidelity, then memory for the width would also be relatively poor. Our results indicate the resources were allocated to processing the size of the plank, since participants' ability to recall the plank size was not impaired, but instead heightened in the threatening environment. Thus, in some respects, the current measure of judgment accuracy may have been more sensitive to the influences of anxiety.

## 4.6 Conclusion

This study suggests that anxiety in PD influences gait by consuming shared resources and disrupting the ability to use sensory feedback. Individuals with PD who are highly anxious are particularly susceptible to interference with information processing, and as a result, their gait impairments become exacerbated, especially in threatening situations. Dopaminergic

treatment however, appears to reduce anxiety and/or improve resource capacity for sensorimotor processing especially in those PD who are highly anxious.

# Chapter 5

# GENERAL DISCUSSION

The focus of this thesis was to understand how anxiety influences gait in Parkinson's disease. The first goal was to quantify anxiety-provoked changes to gait across a spectrum of PD patients with gait impairments (e.g. those who experience freezing of gait compared to those who do not), and different levels of anxiety (e.g. those who have high trait anxiety compared to those with low trait anxiety). The second goal was to determine the means by which anxiety elicits gait disturbances by examining the influence of anxiety on processing threat-related aspects of the environment and one's ability to use self-motion feedback when walking in an anxiety-provoking environment. The third goal of this thesis was to gain a better understanding of whether this relationship between anxiety and gait was mediated by dopaminergic replacement therapy. Within this final chapter, results from all of the studies will be summarized to address each of these three goals and will be discussed in terms of how these results fit within the theoretical framework outlined at the beginning of this thesis.

## 5.1 Major Contributions of the Thesis

### 5.1.1 Anxiety-provoked changes to gait in Parkinson's disease (Goal # 1)

Overall, very little research has been done to understand whether anxiety influences gait behavior and control especially in Parkinson's disease. Throughout the studies presented

in this thesis, threatening environments (i.e. state anxiety induced by walking across a plank above a deep pit) provoked very robust changes to gait in all participants. For example, healthy older adults and individuals with PD all adopted a slower velocity and smaller step length when walking across the ELEVATED plank compared to the GROUND. This behavior has been previously reported in young adults and in older adults (Gage et al., 2003; McKenzie & Brown, 2004; Nibbeling, Daanen, Gerritsma, Hofland, & Oudejans, 2012; Young, Wing, & Hollands, 2012) as well as in those with PD (Caetano et al., 2009) and is thought to reflect a more cautious and controlled gait behavior. However, in the majority of previous studies, step-to-step variability has not been captured. Based on previous balance control studies, research suggests that adopting a cautious behavior includes restricting one's degrees of freedom (Adkin et al., 2000, 2002; Carpenter et al., 2001) and thus reducing the variability in their movement. Although this might be most strategic, in the current thesis neither healthy older adults nor individuals with PD tightened their control over gait by reducing their variability when walking across the ELEVATED plank, instead increases to step length and step time variability were observed. At first glance this pattern of results might suggest that *increased variability* is adaptive in some way. For example, participants might monitor each step carefully, leading to more adjustments and thus greater variability. Alternatively, this highly variable gait behavior might also suggest that walking in a threatening environment increases the demands of the task, and thus consumes more resources, limiting one's ability to control gait effectively. Interestingly, increases in step-to-step variability were magnified in those with PD who were

highly anxious (i.e. have high trait anxiety) compared to those with low trait anxiety when walking in a threatening environment. Furthermore, individuals with PD who experience FOG also demonstrate a drastic increase in step-to-step variability when walking across the ELEVATED plank. This highly variable gait pattern has been argued to precede and trigger full-blown freezing of gait episodes (Blin et al., 1990; Hausdorff et al., 2003; Plotnik & Hausdorff, 2008), which was also observed in study 1. Therefore, it seems more likely that increases in step-to-step variability reflects a lack of gait control, rather than vigilant gait monitoring, otherwise it wouldn't be expected to be exacerbated in severely anxious or severely gait impaired PD participants. Additionally, in the current thesis increases in step-to-step variability were often accompanied by reductions in step width. Typically, increased gait variability would warrant a greater step width (Rochester et al., 2014) (which was adopted in healthy participants in studies 2 and 3), since widening one's base of support (i.e. step width) would be required to counteract this instability. However, in the highly anxious PD and Freezer PD participants, step width was not adequately increased and in some cases even reduced, providing additional support for the notion that anxiety may reduce one's ability to adapt their gait and lead to gait behaviors that are well-known to lead to falls in PD.

One of the most important contributions of this thesis was identifying step-to-step variability changes in highly anxious PD that make them more susceptible to falls. This relationship needs to be further explored but has huge implications for fall prevention in PD. In fact, future research should examine whether PD fallers (those who fall often) have higher

than normal levels of anxiety and whether this contributes to their falling frequency. An equally important contribution of this thesis was identifying anxiety as a cause of freezing of gait in order to progress and expand upon the current hypotheses of underlying mechanisms of freezing of gait. Considering that between 20 and 60% of those with PD eventually develop FOG (Bloem et al., 2004), it is important to understand whether this emotional dysregulation that causes step-to-step variability increases (a precursor of FOG) might be one of the driving forces that cause PD patients to develop FOG. Future research should examine whether highly anxious individuals with PD are more susceptible to developing FOG than those PD who have lower levels of anxiety. If so, therapeutic interventions focused on emotional control and stress management might be effective if delivered to those who are highly anxious prior to reaching this debilitating state, in attempt to prevent them from developing FOG altogether.

### 5.1.2 Understanding *how* anxiety effects gait: Sensory interference? (Goal #2)

Previous research has noted that gait disturbances in PD (including freezing of gait) might be a consequence of other deficits such as sensory impairments (Almeida et al., 2005; Ehgoetz Martens, Pieruccini-Faria, & Almeida, 2013; Patel et al., 2014), perceptual problems (Ehgoetz Martens et al., 2014a, 2015b; Ehgoetz Martens, Ellard, et al., 2013; Ehgoetz Martens, Pieruccini-Faria, Silveira, et al., 2013; Martens & Almeida, 2012) and resource management (Pieruccini-Faria, Ehgoetz Martens, et al., 2014; Pieruccini-Faria, Jones, & Almeida, 2014). Understanding the root cause of gait impairments in PD is extremely important especially for the development of rehabilitative strategies and treatment. However, up until the work

described in this thesis, emotional dysregulation was not considered as a potential cause or a contributing factor that interferes with existing sensory-perceptual deficits, and that can also explain exacerbated gait impairments (e.g. highly variable and unstable gait and FOG as a result of anxiety). Processing of threat-related aspects of the environment was not impaired in PD when walking in anxiety-provoking situations, which agrees with previous studies that have shown sensory-perceptual impairments are specific to processing and integrating sensorimotor feedback rather than visual aspects of the environment (Ehgoetz Martens et al., 2014a; Ehgoetz Martens, Ellard, et al., 2013; Martens & Almeida, 2012). Evidence from this thesis suggests that state anxiety does in fact interfere with using sensory feedback in all participants and is especially detrimental to those PD with high trait anxiety. Visual feedback is relied upon heavily by those with PD especially during walking in order to compensate for their sensory deficits (Azulay et al., 2002; Davidsdottir et al., 2008; Ehgoetz Martens et al., 2015b; Martens & Almeida, 2012). Thus, interference with this compensatory strategy would be expected to exacerbate gait impairments. Previous research has demonstrated this relationship by asking PD participants to walk in complete darkness or to cross an illuminated obstacle in the dark. In both of these studies gait suffered severely when visual feedback about their limbs was not available, but improved when their limbs were illuminated (Ehgoetz Martens, Pieruccini-Faria, & Almeida, 2013; Pieruccini-Faria, Ehgoetz Martens, et al., 2014). The current thesis presents novel findings, such that participants were not able to use visual feedback when walking in the anxiety-provoking environment, especially those PD who were

highly anxious. Therefore, one possible explanation that answers the "*how"* question might be that anxiety consumes resources and thus interferes with competing processes such as processing sensory feedback. Future research should carefully examine the influence of anxiety on sensory impairments in PD. Another explanation might be that anxiety exacerbates gait impairments by amplifying a noisy sensory signal in addition to consuming resources needed for consciously controlling gait. An interesting follow-up study could examine whether the influence of anxiety might be reduced after patients completed a sensory training exercise program known to improve proprioceptive deficits (Lefaivre & Almeida, 2015).

## 5.2 Is dopamine a rate limiting factor for processing capacity in the basal ganglia (Goal # 3)

It remains controversial whether anxiety is dopaminergic in nature and whether it is a dopa-responsive symptom. Even within the current studies, there was a mixture of results suggesting in some instances that anxiety was reduced with dopaminergic treatment, but in others it was not. In the majority of the studies, reported levels of anxiety (both at baseline and during the experiment) were reduced when tested in the ON state compared to the OFF state. In fact, in study 2 and 3 dopaminergic medication selectively reduced baseline state and trait levels and self-reported anxiety in HA-PD to levels similar to that of LA-PD, while both PD groups had similar improvements in symptom severity in their ON state compared to the OFF. Some researchers have argued that ON state reductions in anxiety may be a result of improved motor symptom severity (Burn et al., 2012; Dissanayaka et al., 2010; Prediger et al., 2012),

however, if this were the case, then both groups should have reduced their anxiety since both groups had improvements to their motor symptoms. Instead, the current results from study 2 and 3 show that anxiety in HA-PD only benefit from dopaminergic medication which suggests that dopaminergic medication might be independently treating anxiety in those PD who are highly anxious.

This thesis also presented strong evidence to suggest that dopamine mediates the effect of anxiety on gait. Firstly, FOG was notably reduced in the ON state compared to the OFF state, but only when walking across the ELEVATED plank. Additionally, gait improvements that were seen when walking across the ELEVATED plank in the ON state compared to the OFF state, but only in the highly anxious PD participants. Finally, dopaminergic medication also appeared to influence the ability for highly anxious PD participants to use sensory feedback. If these improvements were simply a result of dopaminergic medication improving sensorimotor integration, then differences between LA-PD and HA-PD would not be expected. Therefore, I propose that dopaminergic medication increases the basal ganglia's capacity to process information and also possibly increases the resources available for other processes at the level of the basal ganglia by reducing anxiety and subsequently reducing the limbic "load" thus restoring the processing efficiency.

In summary, dopaminergic treatment not only normalizes anxiety levels in highly anxious PD to be similar to those with low anxiety, but also it normalized their gait impairments. Results from the current studies all show that in the ON state HA-PD are similar

to LA-PD, and both PD groups are also similar to healthy older adults. This is an important point for future research to consider since many of the previous studies only investigated the effect of anxiety on gait and balance in the ON state and did not consider baseline levels of trait anxiety (or clinical diagnoses if available) in order to reduce the heterogeneity within PD. Therefore further research is needed to re-evaluate the influence anxiety has on balance control in PD specifically in the OFF state.

### 5.3 Anxiety as a "Load" on the Basal Ganglia

Based on the theoretical framework outlined at the beginning of this thesis, I had postulated the implications of high levels of anxiety in PD on resource management and processing capacity especially within the basal ganglia and suggested that dopaminergic treatment might improve resource management and, subsequently, information processing. Bringing together all of the results within this thesis there is substantial evidence that anxiety is acting as a "load" on the basal ganglia and in severe circumstances even overloads its capacity to process information, or allocate resources accordingly. Firstly, gait changes such as increased step-to-step variability, failure to adjust step width, and the presence of freezing of gait were observed across Studies 1-3 and resemble characteristic gait changes that are elicited with a cognitive load such as a dual-task. The primary measures that reflect dual-task interference are step time variability and step width (Rochester et al., 2014; Springer et al., 2006; Yogev et al., 2005) both of which were the most sensitive gait measures while walking in anxiety-provoking environments in this thesis. Thus, anxiety may be demanding resources

and interfering with other processes in a similar way that a dual task does in PD. In fact, Study 3 provides direct evidence that anxiety interferes with utilizing sensory feedback. Importantly, what is similar between cognitive interference and limbic interference is that they both induce a "load" on the basal ganglia, requiring information processing, and demanding shared resources in order to process that information. However, in my view, cognitive load and limbic load are similar but not synonymous.

Dual-tasking (e.g. walking while counting backwards by sevens) is inherently more difficult than performing a single motor task like just walking, since the brain is required to run two motor programs simultaneously that both draw upon similar pools of resources. It is important to point out that the motor tasks in our studies (i.e. walking in a threatening environment compared to walking in a non-threatening environment) were similar in difficulty because the demands placed on gait were held constant (i.e. plank width) in studies 1 and 2. In study 3, we did vary both task difficulty and anxiety by constraining the width of the plank in ELEVATED and GROUND conditions. While, gait changes were observed (and expected) when the task was more difficult (i.e. walking across the narrowest GROUND plank compared to a wide GROUND plank), the plank size did not influence self-reported levels of anxiety when walking across the GROUND plank, which suggested that anxiety was independent from difficulty. Therefore, in my view, it is not simply the difficulty of the task that drives these results but rather the overload of information that needs to be processed, and competition leading to interference.

There are additional differences between cognitive and limbic loads that are worth noting as well. Firstly, the secondary task (e.g. digit monitoring) in a dual-task divides attention and takes resources away from gait only if participants choose to attend to the secondary task and rather than solely prioritize their gait. In contrast, anxiety in the current study was not a voluntary response, and it did not appear that participants could chose to prioritize gait over their overwhelming feelings of anxiety and danger. We also showed that anxiety not only demands processing resources but it also allocates attention toward threat-related stimuli (i.e. plank size judgment). Therefore, due to the involuntary nature of anxiety and its resultant influence on gait, it could be argued that it is more detrimental to gait than a cognitive load, and is likely present but not accounted for in many other studies including those investigating the effects of a dual-tasking on gait. Further research should examine the relationship between cognitive load and anxiety by examining whether those with PD who are highly anxious experience greater dual-task interference while walking with a secondary task compared to those PD who have lower levels of anxiety.

It also appears that dopamine plays an important role in the relationship between anxiety and gait, since less freezing of gait was observed in the ON state, as well as a general improvement in gait in those highly anxious PD, and increased utilization of feedback to reduce step-to-step variability. Importantly, these improvements were not global, but often specific to those who were highly anxious and also specifically in the threatening environment. The fact that behavior changes were specifically in anxiety-provoking environments hints that

dopamine improves information processing at the level of the basal ganglia, and also highlights key differences in terms of the implications of anxiety on gait for those with basal ganglia damage (e.g. Parkinson's disease) compared to the healthy population.

## 5.4 Implications for Symptom Management and Treatments

Overall this thesis has bridged a large gap in the understanding of anxiety in PD and its' influence on gait while highlighting the necessary next steps for future research. It is also equally important to extend these findings to be clinically meaningful in terms of effective treatment strategies and rehabilitative methods. In this thesis, it was apparent that dopaminergic treatment benefited anxiety in those with PD, which is consistent with the hypothesis that one of the underlying etiologies of anxiety is rooted in a dopamine-depleted striatum (Ceravolo et al., 2013; Erro et al., 2012; Moriyama et al., 2011; Weintraub et al., 2005). Additionally, since both limbic and motor pathways utilize dopamine, those with PD who are highly anxious may also have more active limbic structures that demand and may metabolize greater amounts of dopamine (Coakeley, Ehgoetz Martens, & Almeida, 2014). Thus, clinicians may want to consider baseline levels of anxiety when prescribing the appropriate levodopa dosage, especially considering that management of anxiety symptoms greatly improves gait. Furthermore, dopamine receptor agonists (such as pramipexole and ropinerole) may also be more advantageous than levodopa since there is some evidence that suggests dopamine agonists can increase dopamine levels within the limbic system (D3 receptors) and alleviate anxiety symptoms (Chaudhuri et al., 2006; Coakeley et al., 2014;

Lemke, 2008) which also would reduce motor symptoms that are worsened by anxiety. Another advantage of dopamine agonists is that they also reduce motor fluctuations which have been shown to amplify anxiety in PD (Henderson, Kurlan, Kersun, & Como, 1992; Leentjens et al., 2012; Richard, 2005; Witjas et al., 2002) and possible accelerate the "wearing off" period. It is also important to point out that freezing of gait was also reduced in the ON state by a clinically significant amount, but specifically when FOG was elicited during an anxious situation. Thus, clinicians and future research should consider whether freezing of gait warrants a supramaximal dose of dopaminergic treatment especially if driven by anxiety-provoking situations, since anxiety (which might be elevated even higher during and after FOG episodes) might metabolize striatal levels of dopamine and lead to a faster OFF state which then increases FOG.

Alternatively, clinicians may want to consider other anxiety treatments such as selective serotonin reuptake inhibitors (citalopram), tricyclic antidepressants (desipramine, nortriptyline), tetracyclic antidepressants (mirtazapine) or anxiolytics (buspirone) as a method of managing anxiety in PD (for full reviews see (Coakeley et al., 2014; Prediger et al., 2012)) and possibly reducing freezing of gait and even milder gait impairments. Further research is needed to examine the efficacy of these treatments in reducing anxiety in PD and their effects on motor symptoms as well, since very little research or randomized control trials have investigated these treatments and their effectiveness for anxiety in PD. It is important for future research to explore whether early intervention and anxiety management may delay or even

prevent the development of severe gait impairments such as freezing. Research should also consider subtyping those with PD in their early stages with high and low trait anxiety in order to better understand whether specific subgroups may benefit more from early anxiety management interventions than others.

Finally, nonpharmaceutical strategies also demand more attention and research, since all of the above drug therapies come with a list of disturbing side effects for the patient. Cognitive behavioral therapy (CBT) is known to be an effective treatment for anxiety in healthy individuals and might be a viable approach for PD (Mohlman, Reel, Chazin, Ong, & Georgescu, 2010) although minimal research has investigated its effectiveness in PD. One blinded randomized control trial provided anxiety management with exercise, behavioral activation, relaxation therapy, worry control, and sleep hygiene, and showed promising results such that PD participants receiving this treatment saw significant improvements in anxiety, motor symptom severity, depression and quality of life outcomes, whereas the placebo group did not (Dobkin et al., 2011) . Therefore, further research is needed to determine whether CBT may be an effective intervention for those with severe gait impairments, and also further examining which of the CBT methods might be most effective at reducing anxiety whether their effectiveness is comparable to improvements seen with pharmaceutical treatments.

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