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INFLUENCE OF PLANNING RESOURCES ON GAIT CONTROL IN PARKINSON'S DISEASE

by

Frederico Pieruccini Faria

A thesis submitted to the Wilfrid Laurier University

in partial fulfillment of the requirements

for the degree of

Doctor in Philosophy

in

Psychology – Cognitive neuroscience

Waterloo, Ontario, Canada, 2014

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Acknowledgements

First of all, I would like to thank my supervisors Dr. Jeffery Jones and Dr. Quincy Almeida for giving me the opportunity and excellent conditions to develop my doctoral studies. Dr. Jeffery Jones and Dr. Quincy Almeida have acted not only as my supervisors, but also as extraordinary mentors for my academic career and for my life.

Dr. Lilian Gobbi and Dr. Renato Moraes for encouraging me to pursue my doctoral studies in Canada and for giving me important advices.

Dr. Felipe Moura for helping me every time I was in trouble with my Matlab routines.

Patricia Freeman for participant recruitment and for your “chill pills”.

Kaylena Ehgoetz Martens for your friendship and for our discussions about life and science. I learned a lot from you in many aspects during these years.

My wife Carolina for the love you dedicated to our family, and for accepting to come to Canada with me to live this adventure. You were my joy and my motivation during these years. Thanks for comprehending me.

My mother Ivete, my siblings Flavia and Franco for everlasting love and for believing in my skills and decisions whatever I was intending to accomplish in life.

Veronica Miyasike-da-Silva and Rodrigo Villar for receiving me so kindly at your house when I got in Canada and for sharing your experience with me. Thank you guys for your friendship.

Thanks to all MDRC members who helped me with data collections and patients recruitment: Rachel Boehm, Haseel Bhatt, Trish Knobl, Matt Sacheli, Matt Lasswell, Eric Beck, Shannon Lafraive. It was a pleasure for me to share the lab with you guys!

Thanks to all members from Dr. Jone’s lab who helped me with editing.

Finally, I would like to thank CNPq for supporting my doctoral studies.

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Dedication

This dissertation is dedicated to all patients with Parkinson's disease from

Sun Life Financial Movement Disorders Research & Rehabilitation Centre

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Abstract

Movement disturbances in individuals with Parkinson's disease (PD) have been associated with difficulties to plan complex actions. Performance of simple and complex actions overloads resources for individuals with Parkinson's disease (PD). However, it is unclear if central resources required to plan gait adjustments while walking exacerbate gait disturbances of patients with PD. More specifically, it is unclear how gait impairments, sensory processing, and the dopaminergic system influence the load on processing resources (e.g. cognitive load) during the planning of step modifications. In order to investigate the relative influence of these factors on cognitive load and its impact on gait control, three experiments were conducted that utilized a naturalistic gait task, which challenged planning resources during obstacle avoidance. While the tasks were being performed, dual task interference on gait, and dual task performance were assessed in order to estimate participants' cognitive load during these tasks. Gait control during obstacle approach and crossing were also evaluated to observe dual task interference on steps known to demand greater planning. In experiment 1 (chapter 2), the influence of gait impairments on planning resources was investigated. The results of this study demonstrated that the planning of gait adaptations in participants with freezing of gait (PD-FOG) resulted in a greater increase in cognitive load, relative to participants with more preserved gait PD-nonFOG (same disease severity without severe gait impairments). The influence of sensory processing on movement planning was investigated in experiment 2 (chapter 3). The results of this study revealed that removal of visual feedback of self-motion affected gait control when the planning of gait adjustments was necessary for successful crossing. In addition, PD patients prioritized

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walking over the secondary task when visual feedback was reduced, in order to compensate for impaired proprioceptive processing. Lastly, experiment 3 investigated the influence of the dopaminergic system on gait adjustments. The results of this study revealed that dopaminergic replacement partially decreased the effect of cognitive load on gait and drastically improved gait velocity as participants approached obstacles. This study also demonstrates that the cognitive load and the dopaminergic impairments in PD, did not force patients to rely more than healthy participants, on visual information from obstacle as to correct step adjustments. In sum, the current thesis suggests that increases in cognitive load during the planning of gait adaptations causes gait impairments, in individuals with PD. These increases in cognitive load appear to be associated with impaired sensorimotor processing during gait. Dopaminergic activity modulated sensorimotor processing during movement planning and partially the cognitive load caused by movement planning. Finally, the results of these studies suggest that the complexity to plan gait adjustments, while walking, overtax processing resources of individuals with PD causing some observable gait impairments.

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CHAPTER 1 - INTRODUCTION

Pathophysiology of Parkinson's disease

Parkinson's disease (PD) is a neurological syndrome caused by the degeneration of dopaminergic neurons in the substantia *nigra pars compacta* of the basal ganglia (BG). PD is the second most common neurological disease affecting people over 60 years of age (Alves, Forsaa, Pedersen, Dreetz Gjerstad, & Larsen, 2008). The cardinal symptoms of PD are resting tremors, bradykinesia, and rigidity (Hughes, Ben-Shlomo, Daniel, & Lees, 2001). During the early stages of PD, the symptoms are predominantly unilateral, but as the disease progresses the symptoms become bilateral. Gait and postural control can also be affected by the disease. The Parkinsonian gait is usually characterized by short steps, slowness, hesitations, "freezing of movement," while changes in postural control are characterized by difficulties compensating for postural instabilities in a rapid and complete manner; with a minimum of steps (Bloem, 1992; Hoehn & Yahr, 1967). These motor abnormalities correspond in great part with BG and dopaminergic dysfunction in individuals with PD.

The BG are tonically active structures that regulate motor, sensory, and complex cognitive functions through segregated and parallel cortico-striatal-thalamic loops (Alexander & Crutcher, 1990a, 1990b, 1990c; Alexander, Crutcher, & DeLong, 1990). The BG are composed of five structures: caudate nucleus, putamen, globus pallidus, subthalamic nucleus, and substantia *nigra*. The majority of the cortical inputs that are processed by the BG are received by the striatum, which is composed of the caudate nucleus and the putamen. The substantia *nigra* is

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the structure with the greatest concentration of dopaminergic neurons in the brain. Dopaminergic neurons in the substantia *nigra* are projected to the striatum and compose the nigrostriatal pathway. The dopamine has important inhibitory/disinhibitory function on the striatum. Dopamine modulates two dopaminergic receptors in the striatum that are important to motor functions: D1 and D2 receptors. These receptors have distinct contributions to the control of movements. The D1 receptor modulates BG structures that comprise the direct pathway, which is responsible for reinforcing "ongoing" movements (e.g. maintenance of amplitude, velocity and acceleration during execution). On the other hand, the D2 receptor modulates BG structures (e.g. subthalamic nucleus), that comprise the indirect pathway, which is responsible for inhibitory processes such as initiating and stopping movements (Wichmann, DeLong, Guridi, & Obeso, 2011). The indirect pathway is primarily involved with the selection of motor plans, whereas the direct pathway is involved in the execution and maintenance of motor plans (Obeso, et al., 2009; Wichmann, et al., 2011). However both pathways work synchronically in order to optimize motor performance especially during movement sequencing.

In the BG caudal and dorsal regions of the putamen, have distinct contributions to sensory and motor functions, while rostral and ventral regions of the striatum, specifically the caudate nucleus, are important to modulate cognitive and motor functions. The putamen receives dense dopaminergic projections from somatosensory areas and from the visual eye fields (Alexander & Crutcher, 1990a, 1990b, 1990c). Lesion in the putamen is associated with sensorimotor deficits and difficulties to generate automatic movements. The caudate nucleus receives dopaminergic projections mostly from prefrontal cortex such as the dorsolateral,

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ventral, and orbitofrontal cortex (Middleton & Strick, 2000a, 2000b). Thus caudate nucleus has important contribution to high order cognitive processing (Lewis et al., 2003; Owen, 2004). As PD progresses, cortical-striatal connections become weaker and are eventually disconnected due to degeneration of the dopaminergic neurons. The dopaminergic degeneration progresses from sensorimotor regions to cognitive regions of the striatum as the disease progresses (Kish, Shannak, & Hornykiewicz, 1988). This pattern of dopaminergic denervation explains why motor difficulties in PD patients are more debilitating than cognitive impairments during the initial stages of the disease. Therefore, the striatal dopaminergic unbalance determines the severity of motor and cognitive impairments in PD.

Dopaminergic denervation in patients with PD disrupts the balance between excitatory and inhibitory activity in the BG. Specifically in PD, increased inhibition of the thalamus, and decreased excitation of other cortical areas, disrupts the functioning of motor, cognitive, and sensory loops (Obeso, et al., 2008). Motor deficits are more evident than cognitive deficits in PD, since the majority of the output from the BG is directed to motor areas such as premotor cortex, supplementary motor area, and primary motor cortex (Alexander & Crutcher, 1990a; Alexander, et al., 1990). Dopaminergic replacement using L-dopa is the gold standard treatment for PD. Motor symptoms such as bradykinesia (e.g. slowness and hypometria) can be alleviated using dopaminergic medications. Cognitive dysfunctions such as working memory capacity and cognitive planning can also be improved after dopaminergic medication intake. However, only PD patients in later stages of the disease benefit from dopaminergic medication to improve cognitive capacity (Owen, 2004; Owen, Downes, Sahakian, Polkey, & Robbins, 1990). Interestingly, some studies showed worsening of motor, sensory and cognitive functions in PD

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patients after dopaminergic treatment. These impairments caused by dopaminergic treatment can happen because high concentrations of striatal dopamine create noise, which impairs signal processing by striatal-frontal pathways (Cools, Barker, Sahakian, & Robbins, 2001). In the other hand dopaminergic release on striatal areas with reduced dopaminergic activity, caused by dopaminergic denervation, can re-establish the balance between excitatory and inhibitory activity improving the functioning of the BG.

Some theoretical models suggest that the remaining striatal dopaminergic activity in PD allow patients to perform a limited number of motor activities (Lewis & Barker, 2009b). Reduced striatal dopaminergic activity results in over activation of the *globus pallidus internus* (GPi) and substantia *nigra pars reticulata* (SNr) causing inhibition of locomotor centres in the brainstem such as the Pedunculopontine (PPN). This increased inhibitory activity caused by dopaminergic depletion in the striatum, affect motor output which can be observed by increased movement slowness and rigidity. Recent evidences also suggest that deficits in the motor output can be exacerbated when individuals with PD negotiate external stimuli that needs to be processed in one or more than one loops within basal ganglia, when there is not sufficient striatal dopamine (e.g. “OFF” state) to achieve the goal of the task (Lewis & Barker, 2009a, 2009b). Thus dopaminergic replacement therapy can normalize the processing flow within basal ganglia loops preventing that external stimuli exacerbate motor deficits in individuals with PD.

Recent theories about BG suggest that deficits in sensorimotor loops in PD, associated with more automatic and habitual behaviours, induce PD patients to rely more on brain

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circuitry that underline less automatic or goal-directed behaviours. Redgrave et al. (2010) argued that: “These patients (PD) may therefore be forced into a progressive reliance on the goal-directed mode (less automatic and more attentional controlled) of action control that is mediated by comparatively preserved processing in the rostromedial striatum” p.760. Consequently PD patients will require greater conscious control over behaviours that should be performed with a minimum of central processing resources when being internally guided (i.e. without external feedback). This can explain why salient sensory information in the environment (e.g. visual and auditory cues) can help PD patients to improve motor control and the automaticity of movements.

Cognitive processing and motor control in PD

An important function of the BG is associated with movement automaticity. BG is responsible to process information at a subconscious level thus reducing cortical demand to perform actions. Impaired movement automaticity depletes resources to perform simple tasks in PD. In addition, performance of concurrent tasks or multiple tasks simultaneously affect PD patients more than healthy people. This exacerbated effect of multiple tasks on motor performance, among PD patients, is associated with an increased use of processing resources to perform motor tasks. Thus when two tasks are performed simultaneously both tasks might be sharing the same resources, which compromises the performance of one or both tasks (Brown & Marsden, 1991). Since humans have limited resources to perform tasks (Wickens, 1976, 2008), the increased demand for processing resources can lead to an overload in central capacity, consequently decreasing performance of tasks. It is important highlight that in PD the

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processing resources can be limited by dopaminergic depletion and consequently by BG dysfunction (Poletti & Bonuccelli, 2013).

Norman and Shallice (1980) proposed a model for attentional control over willed actions that was called the "supervisory attentional system" (SAS). The SAS has a limited capacity and can be called upon in specific contexts. The contexts where SAS is recruited are: (1) when planning and making a decision; (2) during novel or poorly learned tasks where preprogrammed schemata are not available; (3) and situations where a strong habitual response or temptation is involved (e.g., go/no-go task; Stroop test). In terms of movement control, the SAS can be important when movement complexity is increased, such as when the coordination demand is more complex (e.g., bimanual control out-of-phase, shifting motor plans, walking on a narrow beam, turning during walking, avoiding obstacles, walking on a busy sidewalk, etc.) or during the early stages of motor learning when movement is not automatized yet.

Previous research has argued that PD "depletes" the SAS's resources. Using a dual task paradigm Brown and Marsden (1988) argued that movement performance can deplete central resources of individuals with PD more than healthy controls. It was argued that individuals with PD use attentional resources to supervise the production of faulty motor plans (e.g. foot tapping). The authors also demonstrated that movement complexity also influence the amount of central resources allocated to supervise movements (e.g. foot tapping vs lip movements). Other studies have suggested that the effects of cognitive tasks on movements in individuals with PD could be explained by sharing capacity theory (Pashler, 1994). According to this theory when two tasks use the same resources the performance of one or both will be compromised. More recently imaging studies suggest increased processing demand in basal-cortical loops

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(limbic and cognitive) may exacerbate the abnormal inhibitory output from basal ganglia to motor centers. However, the neural basis for such attentional demand has been a matter of debate.

However, these early theories do not distinguish between resources overload and depletion. An overload can be defined based on the amount of neural activation necessary to perform a task whereas depletion is defined as a reduction in resources available to perform tasks. These ideas about resources overloading and depletion have been recently explored by imaging studies in PD. Imaging studies have found that individuals with PD recruit more neural resources to overcome BG dysfunction to perform automatic movements (Wu & Hallett, 2005). Interestingly, even simple movements (e.g. finger tapping) performed by patients with PD may demand more neural activation (e.g., dorsolateral prefrontal cortex, anterior cingulate cortex, temporal cortex, parietal areas) compared to healthy controls. Difficulties automating movements and deficits in networks underlying executive functions may both overload cognitive processing during movements in PD (Wu & Hallett, 2008). Although an overload in cortical-subcortical neural resources in PD was seen in these studies, we cannot ignore the fact that basal ganglia have reduced (depleted) capacity to process information because of decreased striatal dopaminergic activity. Therefore, the performance of more complex movements that demand greater planning and organization may have a higher demand on cognitive processing for individuals with PD. Consequently, the planning demand necessary to perform these movements may compromise the motor output.

Dual tasks are helpful to estimate the demand for resources when a movement is performed in PD. Studies have found that dual tasks have a larger impact on well learned

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movements, such as gait, of patients with PD, compared to healthy controls (Rochester et al., 2010; Rochester et al., 2004). Remarkably, presenting external cues to patients with PD while they walk (e.g., metronome, transversal lines on the floor, proprioceptive cues) has been found to help reduce the effects of dual tasks on their gait (Baker, Rochester, & Nieuwboer, 2008; Rochester, et al., 2007). These studies suggest that the abnormal attentional control over gait in patients with PD may be associated with difficulties monitoring or allocating attention to relevant sensory information used to plan and prepare steps. Additionally, increased demand in cognitive, sensory and limbic loops may exacerbate inhibitory output from BG to motor centres (Lewis & Barker, 2009a). Therefore, although cognitive resources can be used to compensate gait impairments, an overload in cognitive processes may also exacerbate movement impairments in individuals with PD causing slowness and variability. Thus, it is important to carefully distinguish between the terms depletion and overload when considering how the basal ganglia contribute to movement control in PD.

Gait variability and dual-task performance in PD

Movement variability is often associated with a lack of automaticity during motor performance. Hence measures of variability may be indicative of the amount of conscious processing necessary to perform movements. Although self-paced gait is controlled in great part at the spinal level, recent studies have demonstrated that degeneration of mental functions, such as attention and executive functions, is related to increased variability and slowness in elderly individuals and individuals with PD (Hausdorff, Schweiger, Herman, Yogev-Seligmann, & Giladi, 2008; Montero-Odasso et al., 2009; Yogev-Seligmann, Hausdorff, & Giladi,

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2008). This suggests that cognition has an important role on gait control for individuals with neurological impairments in general. It is speculated that dual-task influence on gait is increased among individuals with neurological impairments due to the increased conscious control required to maintain gait stability while planning resources are shared with processing of the dual task.

Gait variability among individuals with PD is higher than in healthy individuals (Hausdorff, Cudkowicz, Firtion, Wei, & Goldberger, 1998). In addition, when patients perform dual-tasks, gait slowness and variability are significantly increased compared to healthy individuals performing the same dual-task (O'Shea, Morris, & Iansek, 2002; Yogev et al., 2005). These studies speculated that decreased gait automaticity make PD patients more susceptible to dual-task costs. Although it is unknown exactly why dual-tasks affect movements in PD patients, limited processing resources in the striatum could potentially be the core cause of the movement impairments provoked by dual-task or multi-task performance. This idea has been confirmed by recent imaging studies, that show increased inhibitory output from basal ganglia to motor centers in individuals with PD, when they perform tasks with increased cognitive and sensorimotor load (i.e., performing a Stroop task while passing through virtual narrow apertures) (Lewis & Barker, 2009b; Shine, Matar, Ward, Bolitho, Gilat, et al., 2013; Shine, Matar, Ward, Bolitho, Pearson, et al., 2013). Therefore limited resources for cognitive and sensorimotor processing in the striatum might exacerbate gait impairments in PD.

The variability of the step times has been considered the key variable to understand the influence of dual-task on gait. This variable is sensitive to increases in central processing.

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However it is important to note that other important gait variables such as spatial variables have not been evaluated in previous studies because of methodological limitations. Gait in these studies was assessed by using foot switches that are only able to measure the duration of each step cycle. The importance of measuring spatial variables resides on the fact that BG regulate the amplitude of movements (Desmurget, Grafton, Vindras, Grea, & Turner, 2004). Regulation of the step amplitude is extremely important in situations where individuals need to modulate distances to avoid contact with objects in the environment. Increased spatial variability may reveal deficits to plan and/or maintain the amplitude of steps that was centrally set (Morris, Iansek, McGinley, Matyas, & Huxham, 2005). Increased spatial variability of steps prior an obstacle would suggest that the movement plan was incomplete so individuals had to perform more adjustments or re-plan the obstacle avoidance. However little is understood about the dual-task interference on spatial planning in PD.

Several types of dual-tasks have been used in previous studies with individuals with PD. However, the effects of secondary tasks on gait in PD may be confounded with increased demand on either cognitive or motor systems. Dual-tasks in previous experiments included tasks with cognitive *and* motor components (e.g., speech articulation), such as number subtraction (Yogev et al., 2005) where participants were required to perform mental calculations but also say the results aloud, which added an additional motor load to the tasks. Verbal fluency tasks as secondary tasks have also been used in previous experiments (Camicioli, Oken, Sexton, Kaye, & Nutt, 1998) where participants were asked to say as many words that begin with a specific letter. However, it should be acknowledged that this task also involves jaw and vocal cord voluntary movements, since individuals are required to say the words aloud.

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Carrying trays while walking (Bond & Morris, 2000; Rochester et al., 2004) has also been used as a secondary task, however the fact that individuals need to move their upper limbs while walking to stabilize the cups on the tray increases the overall motor load during the gait task. Thus, because of the lack of specificity of secondary tasks, it is difficult to isolate the influence of cognitive load from motor load during gait control. Therefore, the influence of cognitive load on gait should be better understood with secondary tasks that only involve cognitive processing and do not involve interfering secondary motor requirements.

Phoneme monitoring is an example of a secondary task that requires the exclusive use of cognitive resources, since no verbal motor response is required. This task consists of monitoring or silently counting one or more phonemes (e.g. "of") spoken in an audio track. The complexity of phoneme monitoring can be increased by asking individuals to monitor more than one phoneme in an audio track (Pieruccini-Faria, Jones, & Almeida, 2014; Yogev et al., 2005). Sustained attention and working memory are the main cognitive processes required to perform this task. Although this task is exclusively cognitive, gait performance and mental performance (counting) in PD patients can be significantly affected when individuals attempt to count the number of phonemes spoken on an audio track. This suggests that sensorimotor processing and cognitive processing may share the same processing resources in individuals with PD, although this requires further study.

Freezing of gait (FOG): The extreme case of loss of automaticity in PD

Freezing of gait (FOG) is an extreme case of gait dysfunction in patients with PD. FOG is an episodic phenomenon that affects nearly 30% of patients with PD (Giladi, et al., 2001). This

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phenomenon is characterized by sudden and involuntary interruptions in the progression of patients' gait, which can be elicited by environmental conditions such as narrow apertures, turning, dual tasks, and obstacles on the walkway. FOG has been consistently associated with a severe loss of movement automaticity and impaired cognitive resources such as executive functions (Amboni, Cozzolino, Longo, Picillo, & Barone, 2008; Camicioli, Oken, Sexton, Kaye, & Nutt, 1998; Heremans, Nieuwboer, Spildooren, et al., 2013; Naismith, Shine, & Lewis, 2010; Vercruysse, et al., 2012). Within the gait spectrum disorder observed in individuals with PD, FOG can be characterized as the extreme case of gait impairment among individuals with PD. FOG symptoms lead individuals with PD to progressive loss of independence and disability.

Patients with FOG (PD-FOG) may display distinct and more severe gait impairments compared to patients with PD who do not experience FOG (PD-nonFOG), such as greater step-to-step variability, shorter step length, slower gait velocity, and gait asymmetry (Nanhoe-Mahabier, et al., 2011; Plotnik, Giladi, Balash, Peretz, & Hausdorff, 2005; Plotnik, Giladi, & Hausdorff, 2008) during free gait. These gait abnormalities in PD-FOG are usually magnified when environmental conditions challenge gait control, such as when they need to turn; especially if the turning requires sharp angles (Bhatt, Pieruccini-Faria, & Almeida, 2013; Spildooren, et al., 2010; Spildooren, et al., 2012), to pass through narrow apertures (Lebold & Almeida, 2011), or to avoid unexpected obstacles (Snijders, et al., 2009). In situations when these patients freeze, increased visuospatial processing, sensorimotor integration (Ehgoetz Martens, Pieruccini-Faria, & Almeida, 2013; Ehgoetz Martens, Pieruccini-Faria, Silveira, & Almeida, 2013), and greater cognitive load (Bhatt, Pieruccini-Faria, & Almeida, 2013; Shine et

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al., 2012; Spildooren et al., 2010) are required. Therefore, impaired cognitive and sensorimotor processing may contribute to FOG behaviours.

Studies demonstrate that PD-FOG patients often require extra attentional resources to control self-paced gait compared to non FOG patients (Camicioli et al., 1998); during more complex situations such as when turning (Spildooren et al., 2010); during unusual situations such as walking backwards (Hackney & Earhart, 2009), or passing through narrow doorways (Knobl, Kielstra, & Almeida, 2012) compared to PD-nonFOG. These studies demonstrated that the performance of secondary tasks while walking affects the gait parameters of PD-FOG more than they do for PD-nonFOG. According to previous studies the influence of dual-tasks on gait of PD-FOG is associated with cognitive loading, and not with poor dual-task abilities (e.g. shifting between tasks; Knobl, et al., 2010; Shine et al., 2013). Researchers have proposed that reduced automaticity (Heremans, Nieuwboer, & Vercruysse, 2013; Nieuwboer & Giladi, 2013; Shine, Matar, et al., 2013) and impaired cognitive processing (e.g. executive functions) may be disruptive to gait control, and movements in general when PD-FOG patients have to voluntarily adapt gait behaviour to environmental conditions. However the nature of FOG behaviours in patients with PD remains unclear, and warrants extensive investigations using gait tasks that can trigger FOG episodes.

Sensorimotor processing during gait in PD

Impaired sensory processing has been considered one of the causes of motor disturbances in patients with PD. Impaired kinesthesia (Demirci, Grill, McShane, & Hallett,

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1997), impaired proprioceptive integration (Adamovich, Berkinblit, Hening, Sage, & Poizner, 2001; Konczak et al., 2012) and poor visual spatial processing (Davidsdottir, Cronin-Golomb, & Lee, 2005; Lee, Harris, Atkinson, & Fowler, 2001a, 2001b) could contribute to abnormal movement planning (e.g. hypometric movements) in patients with PD. As a result of sensorimotor impairments that causes poor movement control, individuals with PD may exhibit an abnormal reliance on visual input control gait (Almeida et al., 2005; Azulay et al., 1999; Schubert, Prokop, Brocke, & Berger, 2005) and posture (Azulay, Mesure, & Blin, 2006). External feedback not only helps individuals with PD to overcome motor impairments, but also make them to operate in a more automatic mode. Therefore, PD patients may reweigh the use of sensory information, especially vision, while walking in order to improve motor performance and to decrease the workload during gait.

Imaging studies have revealed that gait disturbances in patients with PD are correlated with reduced activation in the right posterior parietal cortex, an area that is important for visual and proprioceptive integration (Cremers, D'Ostilio, Stamatakis, Delvaux, & Garraux, 2012). Other studies also suggested that the right putamen is involved in the processing of proprioceptive information in healthy older adults (Goble, Coxon, et al., 2012) and the subthalamic nucleus may play an important role on proprioceptive processing deficits in PD (Konczak et al., 2009). Interestingly, it has been demonstrated that individuals with PD have cognitive and sensory loops that overlap in striatal regions that still have greater dopaminergic activity, such as the ventral striatum (Helmich, et al., 2010). The authors suggested that this neuroanatomical abnormality in PD could explain why dual tasks affect more patients than

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healthy individuals, since cognitive and sensorimotor processing might be sharing the same neural resources in basal-cortical loops

In sum, movement deficits in patients with PD can be caused by multiple factors that involve the motor, cognitive, and sensory dysfunctions. Impaired sensorimotor processing may force patients with PD to use external sensory cues to improve gait control. In addition, more attentional resources may be necessary to monitor the generation of steps' motor plan during self-paced walking. Interestingly, sensory cues may improve gait automaticity decreasing dual task interference on gait. Therefore, the cognitive processing of PD patients during walking can be more sensitive to external sensory feedback restrictions.

Movement planning in PD

Motor planning is a hierarchical process that involves the selection and organization of appropriate motor responses to achieve a goal (Schmidt, 1982). Complementary to this definition, Wolpert (1997) defined motor planning as: "the computational process of selecting a single solution or pattern of behaviour at all levels within a motor hierarchy from the many alternatives that may be consistent with the goal of the task" (p.210). According to this approach, an example of bad planning would be grasping an empty glass with the same amount of force employed to grasp a full glass. In this situation, an inappropriate plan, amongst other possible plans, was selected to accomplish the goal. The neural computation for motor planning has been found to tax higher order cognitive resources such as attention and working memory, that are mostly resident in prefrontal areas of the brain (e.g., dorsolateral prefrontal

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cortex) (Liu, Chua, & Enns, 2008; Spiegel, Koester, & Schack, 2013a, 2013b; Spiegel, Koester, Weigelt, & Schack, 2012). These authors demonstrated that motor planning, but not execution, demand attentional resources.

Studies have investigated the impact of motor planning complexity on movement preparation and performance (i.e., delayed responses, errors) in patients with PD using different paradigms, such as movement imitation (ideational gesture; Goldenberg, Wimmer, Auff, & Schnaberth, 1986), reproduction of remembered sequences of movements (Jokinen, et al., 2013; Rogers & Chan, 1988), planning sequences while controlling upper limb movements (Benecke, Rothwell, Dick, Day, & Marsden, 1987a; Smiley-Oyen, Lowry, & Kerr, 2007) and mental imagery (Helmich, de Lange, Bloem, & Toni, 2007). Based on the results of these studies, it has been suggested that the complexity of a motor action that involves the performance of sequences of movements can exacerbate motor deficits, such as slowness and hesitations, in PD. Benecke et al. (1987a) argued that motor deficits in PD may be associated with problems to organize and switch between sequences that compose a motor plan. Situations that demand greater motor planning complexity (e.g. multiple unrelated sequences) may be detrimental for movement performance of individuals with PD. However it is unclear if motor deficits caused by the planning of complex actions would be a consequence of poor cognitive or sensory processes since basal ganglia has an important contribution to sensorimotor integration and cognitive functions.

Recent fMRI studies demonstrate that the performance of complex sequential movements, such as learned alternated finger tapping and movements out-of-phase, in PD can

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demand more brain activation in areas that are associated with high order cognitive and sensory processing (e.g. dorsolateral prefrontal cortex, precuneus, cerebellum and premotor areas) (Wu, Wang, Hallett, Li, & Chan, 2010). In addition, individuals with PD overactivate brain areas, such as, medial frontal cortex to switch between motor plans (Helmich, Aarts, de Lange, Bloem, & Toni, 2009). Individuals with PD compensate difficulties to generate motor plans over activating brain areas that process visual information (Helmich et al., 2007). According to Lewis & Barker (2009) the processing demand required to negotiate external stimuli can exacerbate the abnormal inhibitory output from basal ganglia to motor centers that cause motor symptoms, such as slowness in individuals with PD. Thus, the cognitive and sensory demands required to plan complex actions might exacerbate motor disturbances in individuals with PD.

In sum, motor disturbances in patients with PD can be caused by difficulties preparing motor responses that demand greater organization. The planning and organization of complex movements in PD can overload brain processing resources as a result of BG impairments. Interestingly the impact of complex motor planning on walking performance in PD has received much less attention by the literature. Finally, the understanding of how cognitive and sensory processing contributes to motor planning deficits during walking in PD also needs further investigation.

Movement planning while walking in PD: the obstacle paradigm

Walking through uneven and cluttered terrain requires frequent gait modifications to avoid collisions. Although a motor plan formulated before participants start to walk toward an

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obstacle can be performed, adjustments in the initial motor plan has to be performed when individuals are approximately three steps away from the obstacle (Berg, Wade, & Greer, 1994; Patla & Greig, 2006). During the last steps prior obstacle crossing, small adjustments on steps allow successful crossing (Berg, et al., 1994; Bradshaw & Sparrow, 2001). However in order to perform these step adjustments the central nervous system needs to integrate multiple sensory inputs (visual, somatosensory) that will inform how, based on current state of the body in relation to obstacle, the motor plan must be adjusted to avoid an obstacle collision.

During an obstacle approach greater voluntary control may be employed to avoid obstacle contact. Supra-spinal regions (e.g. dorsolateral prefrontal cortex) take over gait control modulating the basic rhythmic and spatial patterns of gait to avoid an obstacle contact (Haefeli, Vogeli, Michel, & Dietz, 2011). Prefrontal cortex is involved with attentional control and planning of forthcoming actions (Pochon et al., 2001). Increased voluntary control to modify gait to avoid obstacle collisions have a cost compared to self-paced gait (Brown, McKenzie, & Doan, 2005; Siu, Catena, Chou, van Donkelaar, & Woollacott, 2008; Sparrow, Bradshaw, Lamoureux, & Tirosh, 2002). This increased cost may be associated to the planning of foot clearances to avoid an obstacle contact. Animal models revealed that the execution of gait adjustments, such as crossing an obstacle, is underlined by the motor cortex (Drew, Andujar, Lajoie, & Yakovenko, 2008; Drew, Jiang, Kably, & Lavoie, 1996), while the planning of gait adjustments, such as gait patterns during obstacle approach, is underlined by the parietal cortex (Lajoie & Drew, 2007; Marigold & Drew, 2011). Taken together, the studies mentioned above suggest that when individuals walk toward an obstacle, the cognitive resources utilized

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to plan foot clearances in advance of an obstacle may influence the resources required to maintain gait stability.

Gait of individuals with PD is more affected by complex secondary goal-oriented visuospatial tasks (e.g. carrying a tray with glasses) (Bond & Morris, 2000; Rochester et al., 2005). The allocation of attentional resources to perform a secondary goal-oriented visuospatial task (e.g. carrying a tray with glasses), disturbed gait control in PD more than in healthy people. Walking with obstacles is a complex functional goal-oriented task that individuals perform every day. Previous research has demonstrated that individuals with PD can present gait abnormalities (e.g. slowness) during obstacle approach and crossing (e.g. short foot-clearances) (Galna, Murphy, & Morris, 2010; Pieruccini-Faria et al., 2013). However, it is not known what causes such deficits during obstacle avoidance in PD. The high demand for processing resources to plan step adjustments to avoid an obstacle contact, compared to self-paced gait, could overload central resources of individuals with PD causing gait abnormalities. Decreased capacity to process information for planning in subcortical-cortical networks while individuals plan complex movements could disrupt gait control in PD. It is also important to determine if processing resources used to plan and control gait adaptations are influenced by low striatal dopaminergic activity in PD. Lewis and Barker (2009a) argued that dopamine increases the resources (in the striatum) used to negotiate complex stimuli in the environment. These authors suggested that low concentration of striatal dopamine may be enough for self-paced walking but may not be enough to deal with environmental complexity during gait. Dopamine may modulate the processing load on cognitive, motor and limbic loops in the basal ganglia, which can cause severe motor impairments in PD such as movement slowness and freezing of

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gait (Shine, Matar, Ward, Bolitho, Gilat, et al., 2013). The abnormal motor output triggered by an overload on cognitive, sensorimotor, limbic loops will depend on what type of stimulus is being negotiated in the environment. However, recent studies have illustrated that motor and cognitive deficits in PD are not exclusively generated by dopaminergic and basal ganglia impairments (Bohnen et al., 2007; Bohnen et al., 2006; Bohnen et al., 2012; Bohnen et al., 2010b; Rochester et al., 2012). Therefore, it is important to investigate in what extent different deficits associated with PD contribute to gait disturbances when motor planning resources are used to navigate in complex environments.

Summary and aims

Motor disturbances in patients with PD can be caused by impaired cognitive and sensory processing. These impairments can contribute to motor planning difficulties, which may be the core reason for the deficits in voluntary movements in patients with PD. Greater limitations in processing resources can compromise the ability of individuals with PD to perform complex goal-oriented tasks that involve planning of sequential actions. Patients with severe gait impairments but similar disease severity may have impaired cognitive and sensorimotor processing that can influence gait behaviours in complex environments. Sensory feedback can improve movement control by helping patients to allocate less attentional resources to control gait. However it is unclear if deficits in sensorimotor integration affect motor planning in individuals with PD. Although dopaminergic replacement may improve motor symptoms caused by PD, it is unclear the contribution of the dopaminergic system to cognitive and sensorimotor processing when individuals are planning and controlling complex gait adaptations. The aim of

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this thesis was to understand the impact of planning resources on gait control of individuals with PD. This thesis will attempt to understand the causes of motor disturbances associated with performance of a naturalistic complex goal-oriented gait task with increased planning demand.

Gait measures and their meaning

In order to describe motor planning difficulties while patients with PD approached obstacles the gait velocity, and the step-to-step variability were measured during far and close steps relative to the obstacle. The pilot study indicated that patients and healthy participants started to make gait modifications only in the last three steps of an obstacle approach. This result is in agreement with a previous study (Pieruccini-Faria et al., 2013) that found that healthy controls and patients with PD patients, regardless of medication state, start to make significant gait adjustments during the last three steps prior an obstacle crossing. Hence the last six steps, of a total of eight steps, were split into early (first three) and late phases (last three). Differences in gait between early and late steps might indicate when processing resources are being allocated to plan foot-to-obstacle distances.

While participants approach an obstacle gait control has to be adjusted and may suffer the interference of central resources used to plan obstacle crossing. Step-to-step time variability is sensitive to cognitive overloading in patients with PD (Hausdorff, 2005; Hausdorff et al., 1998). This variable may indicate when processing resources are being allocated to plan gait adaptations. In addition, this variable is associated with dynamic stability during gait. Step

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length variability could also be a sign that movement was not entirely set from the beginning, thus indicating that participants needed more voluntary control to adjust the initial motor plan to avoid an obstacle contact (Berg, Wade, & Greer, 1994b; Lee & Lishman, 1977). The foot-obstacle trajectories during obstacle crossing were measured in order to investigate if the plan/execution of those trajectories were affected by experimental manipulations (FOG, dual task, sensory feedback, dopaminergic medication). The cognitive load during each phase was estimated by asking participants to perform a secondary task while patients approached and crossed an obstacle. Gait changes during the performance of a secondary task could reveal differences between PD and healthy participants. PD patients use attentional resources to compensate movement impairments caused by basal ganglia dysfunction.

Specific aims and hypotheses

Specific aims of Experiment 1 (Chapter two)**:** *Motor planning in Parkinson's disease patients experiencing freezing of gait: the influence of cognitive load when approaching obstacles.*

Specific aims: Decreased gait automaticity and problems in executive functions are characteristic of patients with freezing of gait (FOG), and can influence gait of individuals with PD while walking in complex environments. This study evaluated the impact of FOG on motor planning and processing resources during locomotion. We also tested if FOG affects processing resources during the preparatory steps where participants are planning or re-planning the foot clearances to cross an obstacle.

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Hypotheses: Because planning during gait may have a cost on central processing resources, it was predicted that a dual task would deteriorate gait control during the approach phase of an obstacle more in PD-FOG than in PD non-FOG and healthy controls. The impact of the secondary task (auditory digit monitoring) should be observed in the closest steps (last three steps) to the obstacle compared to previous steps, since adjustments on gait are only initiated in the last steps prior an obstacle approach in general. It is also expected that PD-FOG will have the poorest performance on the cognitive task, because of the increased demand on their processing resources to plan and control gait adjustments.

Specific aims of Experiment 2 (Chapter three) : Interaction between *cognitive and sensory load while planning and controlling gait adaptations in Parkinson's disease.*

Specific aims: PD patients have an abnormal reliance on visual feedback to plan and control movements. Relevant visual feedback not only improves gait control, but also decreases the cognitive load when individuals with PD walk. Thus visual feedback may also facilitate the sensorimotor and cognitive processing of PD patients to plan and control complex movements. Experiment 2 evaluated whether increasing participants' cognitive load while walking, would magnify difficulties with specific aspects of gait that are associated with the planning to avoid an obstacle, as visual feedback of self-motion is manipulated.

Hypotheses: Reduced visual feedback of self-motion will cause gait disturbances in patients with PD during an obstacle approach when visual feedback of self-motion is reduced. The effects of performing dual tasks on gait control of patients with PD will be more evident during conditions of reduced visual feedback. Foot-to-obstacle distances during obstacle crossing and

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obstacle contacts in patients with PD may be more affected when visual feedback of self-motion is decreased. Performing the dual task may exacerbate these deficits if patients with PD are using more processing resources to compensate for their sensorimotor processing deficits in situations of decreased visual feedback during locomotion.

Specific aims of Experiment 3 (Chapter four) : *Dopaminergic and eye-gaze contributions to movement planning in Parkinson's disease: The influence of cognitive load*

Specific aims: Besides motor regulation, dopaminergic activity also regulates cognitive and sensory processing. Gaze analyses during gait could also reveal if there is an abnormal utilization of visual feedback that could be associated with motor planning deficits and sensory processing deficits. The aims of this experiment were to investigate if visual utilization and central processing resources are equally affected by PD and dopaminergic replacement when individuals plan and control gait adaptations.

Hypotheses: It was hypothesized that PD patients would spend more time extracting visual information from the obstacles (i.e. longer and more frequent fixations) and from their lower visual field (tilting their head downwards) compared to healthy controls. We also hypothesize that the withdrawal of dopaminergic medication ("OFF" state) would magnify the effects of the dual task on gait and visual utilization of individuals with PD compared to when patients are medicated ("ON" state) and healthy participants. These effects will be better observed during the steps closer to an obstacle when the foot-obstacle distances are planned or re-planned to avoid a contact.

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General methods

Kinematic recording: Active markers (IRED markers using an Optotrak® system) were used to track body movements in relation to an obstacle. The area captured by cameras covered at least six steps prior to obstacle crossing, the obstacle crossing step, and one step after the crossing step.

Gait task: Participants were asked to walk at their regular pace and step over an obstacle adjusted at 15% of the participant's height. Gait variables such as gait speed, step length, step to step variability, and phases duration were used to describe gait control and the effect of cognitive load in all conditions. Gait events such as toe-offs and heel-contacts were defined using the foot vertical velocity (O'Connor, Thorpe, O'Malley, & Vaughan, 2007). These events were then used to find the position of iRED markers on both feet when they were in contact with the floor allowing the calculation of the step length; Duration of each step was defined as the interval of time elapsed between toe-offs of each foot (Winter, Patla, Frank, & Walt, 1990). Foot-obstacle distances were also calculated in order to describe the execution of the motor plan and to avoid an obstacle during gait adjustments under different conditions. Foot-obstacle distances were calculated by subtracting the position of the marker, in the sagittal plane, placed on the 5th metatarsal of each foot, from the obstacle position during obstacle crossing. Lead and trail horizontal distances before and beyond the obstacle were defined during toe-off and heel contact (respectively) during obstacle crossing. Foot-obstacle vertical clearances (lead and trail) were calculated by subtracting the position of the markers placed on 5th metatarsals of each foot, from the obstacle height when the marker was at the obstacle position during

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crossing. For Experiment 3 the head pitch was calculated in order to quantify head rotation in the sagittal plane of the participants' displacement.

Dual-task: In order to investigate the cognitive processing during gait, we used an auditory digit monitoring task, which required sustained attention and working memory. This task required individuals to count the number of times a specific digit from 1 to 9 (e.g. digit "2") was spoken in the audio track, while walking. The interval inter stimulus between digits was randomized from 100 ms to 1000ms (with increments of 100ms). The audio track lasted for 12 seconds.

Gaze behaviour recording: A mobile eye tracker (Applied Science Laboratories ASL®) was used to investigate how participants acquired visual information from an obstacle during their approach. This equipment was only used in the study 3 (chapter 4).

Neuropsychological measures: Neuropsychological tests were used to describe the cognitive characteristics regarding executive functions and the general mental status. The Modified Mini Mental State Exam (3MS) measured the general cognitive status of participants with a cut-off score of <76 (risk of dementia) as an exclusion criteria; Corsi block test: This test assessed visual spatial working memory by asking participant to point to a sequence of blocks presented by experimenter; Digit span: this test assessed phonological working memory and attention. Participants had to verbally repeat a sequence of numbers forward and backwards; Trail Making Test: this test assesses the cognitive flexibility to shift from one motor plan to another action plan quickly and accurately. This is also a good predictor of the general status of executive functions. This test has two parts (motor and cognitive) that are subtracted from each other in order to separate the motor component from the cognitive component of the test. In

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this test participants were asked to link a sequence of numbers and letters, alternately, keeping the numeric and alphabetic order (e.g. 1-A-2-B-3-C…). The TMT part A was also used to estimate the visual scanning speed of participants.

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CHAPTER 2 - MOTOR PLANNING IN PARKINSON'S DISEASE PATIENTS EXPERIENCING FREEZING OF GAIT: THE INFLUENCE OF COGNITIVE LOAD WHEN APPROACHING OBSTACLES

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This chapter has been published in *Brain & Cognition:*

Pieruccini-Faria, F., Jones, J. A., & Almeida, Q. J. (2014). Motor planning in Parkinson's disease patients experiencing freezing of gait: the influence of cognitive load when approaching obstacles. *Brain and Cognition, 87*, 76-85.

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ABSTRACT

Freezing of gait (FOG) in Parkinson's disease (PD) is typically assumed to be a pure motor deficit, although it is important to consider how an abrupt loss of gait automaticity might be associated with an overloaded central resource capacity. If resource capacity limits are a factor underlying FOG, then obstacle crossing may be particularly sensitive to dual task effects in eliciting FOG. Participants performed a dual task (auditory digit monitoring) in order to increase cognitive load during obstacle crossing. Forty-two non-demented participants (14 PD patients with FOG, 13 PD who do not freeze, and 14 age-matched healthy control participants) were required to walk and step over a horizontal obstacle set at 15% of the participants' height. Kinematic data were split into two phases of their approach: early (farthest away from the obstacle), and late (just prior to the obstacle). Interestingly, step length variability and step time variability increased when PD patients with FOG performed the dual task, but only in the late phase prior to the obstacle (i.e. when closest to the obstacle). Additionally, immediately after crossing, freezers landed the lead foot abnormally close to the obstacle regardless of dual task condition, and also contacted the obstacle more frequently (planning errors). Strength of the dual task effect was associated with low general cognitive status, declined executive function, and inappropriate spatial planning, but only in the PD-FOG group. This study is the first to demonstrate that cognitive load differentially impacts planning of the final steps needed to avoid an obstacle in PD patients with freezing, but not non-freezers or healthy controls, suggesting specific neural networks associated with FOG behaviors.

Keywords: Freezing of gait; gait with obstacle; motor planning; cognitive load; dual task;

Parkinson's disease

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INTRODUCTION

Parkinson's disease (PD) is a movement disorder that is characterized by marked gait impairments, including freezing of gait (FOG) which occurs in approximately 30 % of people with PD (Giladi et al., 2001). FOG episodes have been associated with other gait deficits such as increased gait variability, increased gait asymmetry, slower gait velocity, and shorter steps (Hausdorff, Schaafsma, et al., 2003; Nanhoe-Mahabier et al., 2011; Plotnik, Giladi, Balash, Peretz, & Hausdorff, 2005). Interestingly, these gait abnormalities and FOG episodes tend to occur more commonly during goal-oriented gait tasks that require a greater level of planning (i.e., increased level of conscious control), such as turning (Spildooren et al., 2010), passing through small apertures (Almeida & Lebold, 2010), avoiding a sudden obstacle (Snijders et al., 2008).. Since these situations involve a greater level of conscious control, it may be suggestive of a limited central resource capacity in those PD patients who experience FOG (PD-FOG). Furthermore, it might be expected that areas of the brain that are known to be involved with attention and planning of forthcoming actions, such as the prefrontal cortex (Pochon et al., 2001), contribute to the impairments seen in FOG. Given this potential limited capacity, PD FOG might be hypothesized to be more susceptible to the influence of a secondary cognitive task, while attempting to step over an obstacle. While it has been well documented that in dual task situations PD often walk slower and with greater step to step variability (Yogev et al., 2005), it is important to evaluate the interaction between cognitive load and motor planning in PD-FOG.

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Recent research has demonstrated that increased planning demand during a locomotor task has a direct influence on movement control in PD-FOG only (Knobl, Kielstra, & Almeida, 2011). PD-FOG have also been shown to have a greater percentage of FOG episodes in situations where participants have more time available to plan for an unexpected obstacle (compared to less time available to plan a step over) (Snijders et al., 2010). Thus, both of these studies seem to suggest that goal-directed planning during gait may serve as a dual task, thereby imposing increased load on those who experience FOG, hence the resultant FOG behaviour. Recent research (Moreau et al., 2008) has suggested that so called "modulated gait", is controlled through a specific pathway involving prefrontal cortex projections through the subthalamic nucleus and downstream to the locomotor centers of the brainstem, and this is only employed during gait tasks that require a higher level of processing (i.e. no longer automatic gait).

Recent imaging work has associated FOG with problems processing complex visual information, with the notion that PD FOG may have an impaired ability to recruit cortical and sub cortical areas in such complex tasks (Lewis & Barker, 2009a; Naismith, Shine, & Lewis, 2010; Shine, Matar, Ward, Bolitho, Gilat, et al., 2013; Shine, Matar, Ward, Bolitho, Pearson, et al., 2013). These studies point to a direct link between the limited cognitive resources and impaired step generation, where the dorsolateral prefrontal cortex specifically is overactive during freezing behaviours. Interestingly, Almeida, Wishart, and Lee (2003) showed that shifting motor plans from a more automatic to a more consciously controlled form of inter-limb coordination may overload attentional resources mediated by the dorsolateral prefrontal cortex of PD patients, thus causing motor blocks and other motor control abnormalities. Thus, it

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seems possible that the increased demands associated with complex gait tasks may limit the resources available for other secondary tasks in PD-FOG. Arguably, obstacle crossing could be considered a secondary task in itself, since shifting from a more automatic gait (during the early stages of approach toward an obstacle) to a more consciously controlled gait pattern (to plan for safe clearance over an obstacle), becomes necessary as one approaches an obstacle. Thus, studying this behaviour allows us to evaluate the contributions of the prefrontal cortex-basal ganglia network to freezing behaviour. While it has been well documented that in dual task situations, PD often prioritize a secondary task over gait control (Bloem, Grimbergen, van Dijk, & Munneke, 2006), leading to increased gait variability and decreased gait speed (Yogev et al., 2005), it is important to evaluate how cognitive load might influence motor planning in PD-FOG during complex gait tasks, such as obstacle crossing. Perhaps more importantly, evaluating when cognitive overload may influence gait control during the approach to an upcoming obstacle, might yield important insight into the underlying mechanisms of basal ganglia dysfunction. Specifically, the current study sought to investigate if (and when) the transition from a more automatic to a less automatic control of gait might be a primary contributing factor in FOG behaviours, and if this could be systematically associated with the depletion of resources mediated by prefrontal areas of the brain in PD-FOG.

The aim of current study was to manipulate cognitive load during the approach and crossing phases, when PD patients with and without FOG, were asked to step over an obstacle. Furthermore, by comparing the results of neuropsychological tests of spatial working memory, cognitive flexibility and general cognitive status across our groups, we also aimed to address

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whether a specific cognitive issue (related to the neuroanatomical correlates described above) might explain FOG behaviours.

MATERIAL AND METHODS

Participants

Twenty-seven PD patients were recruited for the current study: 14 with FOG and 13 without FOG, who were matched for disease severity, duration (Table 1), and severity of asymmetry in lower limbs (see Table 2). All patients were tested while "on" regular anti-Parkinsonian medication. Patients were excluded from the sample if they could not independently walk, or had musculoskeletal problems, uncorrected visual problems or other neurological or cardiac diseases. Motor symptom severity and FOG episodes were assessed prior to data collection. In order to assess the frequency of FOG episodes outside of our laboratory all patients answered with at least a score of 2 on question number 3 of the FOG questionnaire (Giladi et al., 2009), as well as a number of clinical tests previously described in (Almeida & Lebold, 2010) to confirm the presence of FOG episodes. A sample of 14 healthy age-matched participants was also evaluated to compare with PD patients' behaviour. The study was approved by the research ethics board at Wilfrid Laurier University, and written informed consent was obtained from all subjects prior to the experiment according to the Declaration of Helsinki.

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Table 1 - Demographics, clinical and neuropsychological measures

	PD-FOG	PD-nonFOG	CONTROLS	Group effect
Sex	14M	10M/3F	8M/6F	*p* value
Age(years)	73.6(7.7)	69.6(6.1)	74.7(8.2)	.202
UPDRS-III(total)	37.3(5.1)	33.1(10.7)	NA	.236
Years with PD	8.3(5.0)	7.6(4.6)	0	.879
Height (m)	1.77(.08)	1.76(.09)	1.70(.11)	.141
FOG-Q (Item 3)	3.2(0.8)[a]	0.38(0.7)	0	.0001
Years of educ.	12.9(4.2)	13.6(4.4)	14.5(5.2)	.675
3MS	92.6(6.7)	90.7(14.0)	95.9(3.9)	.340
TMT A(s)	61.6(40.9)	44(29.3)	40.1(21.2)	.177
TMT B(s)	329.5(62.2)[a,b]	163.7(35.1)	106.9(15.4)	.002
TMT B-A(s)	267.8(53.9)[a,b]	119.7(30.5)[c]	66.8(11.9)	.001
Corsi block test	4.0(1)	4.2(1.2)	4.4(1.4)	.573

Legend - FOG-Q – freezing of gait questionnaire; TMT – trail making test; UPDRS – Unifying Parkinson's disease rating scale

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Table 2– Mean (standard deviation) of clinical characteristics and preferred leg to step over.

	PD-FOG (n=14)	PD-Non FOG (n=13)	Controls (n=14)
UPDRS III asymmetry-lower limbs(%)	2.71(1.25)	2.30(1.05)	NA
Disease severity score of lower limbs	6.50(2.08)	5.03(2.37)	NA
UPDRS III -Postural score	4.71(1.7)[b]	2.79(1.5)	NA
Right side more affected than left side (# of patients)	6	7	NA
Right side less affected than left side (# of patients)	7	6	NA
Sides equally affected (# of patients)	1	0	NA
Trials which the right limb was the lead limb (%)	66.31(34.29)	48.71(35.63)	49.04(32.02)

[b] = PD-FOG different (worse) than PD-nonFOG

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Data collection and procedures

All participants completed three blocks of five trials for a total of 15 trials. The order of blocks was randomized between participants. Participants performed six practice trials without performing the dual task before the actual trials began. These practice trials were not included in the analysis. During the experimental trials, participants were free to choose the foot that would lead the crossing over the obstacle. Participants were required to walk at a comfortable pace on a dark-gray hard floor and to step over a non-solid obstacle. The obstacle was a bar made of white foam covered with a thick white paper (70 cm wide x 4cm high x 1.5cm depth; weight = 50 g) and suspended by two lateral plastic poles that were 30 cm in height (similar to high jump hurdles), and was set at 15% of the participant's height(Hahn & Chou, 2004), and positioned ~6.5m from the starting point. The start position was set depending on the number of steps each participant required to step over the obstacle. Participants made at least eight steps from the starting point to the obstacle; however, because the initial two steps were outside the capture area only six steps prior to the obstacle were analyzed. The mental task involved attending to an audio track while walking. This secondary task was chosen because there was no motor component involved thus allowing us to exclude the possibility that the secondary task caused motor interference on the gait task. Participants were instructed to mentally count the number of times they heard a digit spoken by a female voice in the audio track. The numbers participants heard ranged from 1 to 9. In The low demand condition participants were asked to mentally count the number of times they heard a single target digit (C1), while in the high demand condition participants counted the number of times they heard two target digits (C2). The baseline condition involved participants walking and stepping over

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the obstacle without performing the dual task (NC). The order of presentation of each digit in the audio track was randomized across the trials. The auditory interstimulus interval was also randomized to prevent gait synchronization and the interval of presentation of each digit could vary from 100 ms to 1000 ms. Participants were instructed to initiate walking at the moment they heard the first digit. The sound track played for 12 seconds. The experimenter told the participant which digit would be the target digit(s) before each trial, and at the end of each trial, participants reported the number of times they heard the target digit(s). Participants were also instructed to count until the audio track finished playing, even if they had already finished the locomotor task. They were asked to equally prioritize the gait and the digit counting task. The volume of the loudspeakers was adjusted so that participants could comfortably hear the digits at the start and end position of the walkway. Feedback about their performance was not provided. The percentage of trials with perfect counting for each group and condition was computed. Participants' movements were tracked by three Optotrak® cameras (Northern Digital, NDI, Waterloo, Ontario); two lateral cameras (vertically oriented) 2.0 m away from each other facing participants in the frontal plane (these two cameras captured all steps until the obstacle), and one central camera (horizontally oriented) mounted 2.75 m above the floor at the end of the travel path (this camera was positioned to capture the obstacle area and surroundings). Active IREDs (infrared light emitting diodes) were fixed to the following anatomical regions: Xiphoid process, shoulders (acromium), iliac crests, lateral malleolus and 5th metatarsals. Gait events were visually defined using a validated method described by (O'Connor et al., 2007). All kinematic data were filtered using a 2nd order Butterworth filter with a cut-off

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frequency of 6 Hz using a dual-pass filter with zero lag delay. Kinematic variables were calculated using an algorithm created in Matlab 7.0 (The Maths Works Inc).

Outcome measures

Gait Parameters

To remove gait characteristics associated with gait initiation, only the last 6 steps before the obstacle for each participant were analysed. These six steps were divided into two sets of three steps each (an early and late phase prior to the obstacle). Baseline gait characteristics were determined based on the average of the six last steps prior to the obstacle during the NC condition. Step length, step time, and the variability of these gait parameters were calculated using the coefficient of variation (CV= Standard deviation of 3 steps/Mean of 3 steps) x 100). Gait velocity was calculated based on the distance walked in each phase divided by the time spent to complete each phase. The delta of the change between phases for each gait parameter was also calculated; that is, late phase subtracted (steps just prior to crossing the obstacle) from the early phase (steps prior to the last 3 steps before stepping over the obstacle). The result of that subtraction was considered the magnitude of change in a particular gait parameter. If the result of the subtraction was positive, this meant that the parameter increased from early to late phase during the approach. For example, positive step time variability would indicate that participants increased variability as they got closer to the obstacle.

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Obstacle Crossing Parameters

Foot clearance was calculated by subtracting the vertical position of the 5th metatarsal markers of each foot from the obstacle's height, at the frame or instant where the foot was directly over top of the obstacle (i.e., the crossing point). Lead and trail limb position before and after the obstacle were captured as horizontal distances between the foot and the obstacle, subtracting the position of the markers of the 5th metatarsal of each foot from the obstacle position in the sagittal plane (see Figure 1). Crossing velocity was also calculated by dividing the lead crossing stride by the stride duration. Step width was calculated by subtracting heel markers in the medio-lateral plane for the crossing step.

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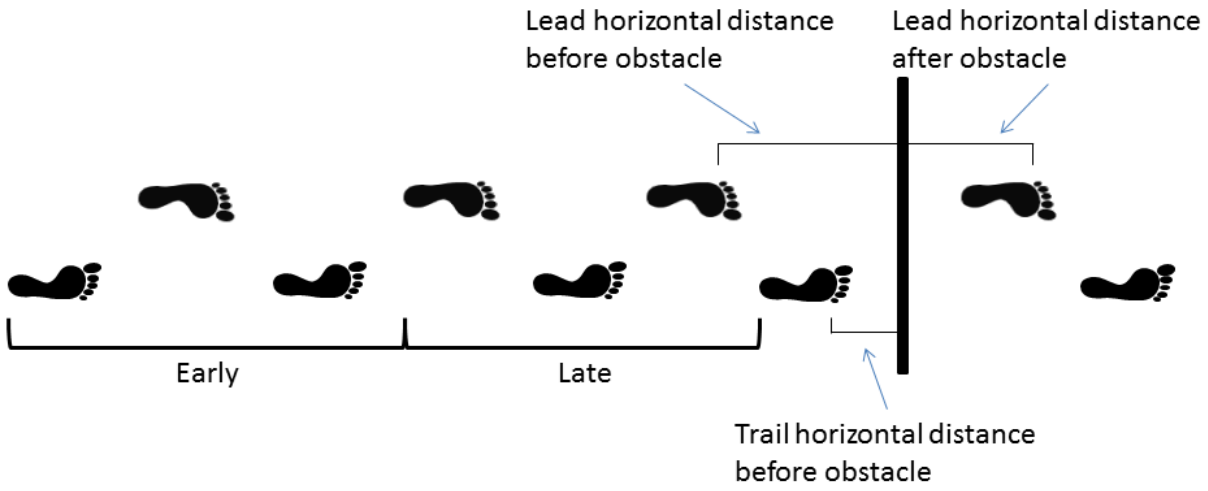

Figure 1- Depiction of the phases and steps where gait parameters were calculated and the horizontal distances during crossing phase

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Clinical and cognitive assessments

Motor symptom severity was assessed using the UPDRS-III (motor section) prior to data collection. Any cognitive status and/or executive function decline was assessed using the Mini-mental 3MS exam. Executive function related to attentional set-shifting and/or cognitive flexibility was assessed using the Trail Making Test, part A and B (Fitzhugh, Fitzhugh, & Reitan, 1962). Participants were instructed to perform this test as fast and accurately as they could. The motor component of the test was calculated by subtracting part A from part B. This test is considered the best cognitive predictor of FOG severity among these patients (Naismith et al., 2010), and also associated with the integrity of motor planning resources in PD (Xanthopoulos et al., 2008). The Corsi block test was used to test the spatial working memory resources of participants in order to rule out any memory effects that might be associated with obstacle crossing performance. Asymmetry of PD severity was calculated based on the absolute value resulting from subtraction of UPDRS scores of both lower limbs (Plotnik et al., 2005). Since we were specifically interested in lower limb symptomatology, only items 22b (leg rigidity) and 26 (leg agility) were taken into account. Items 27 and 28 were used to characterize patients' balance.

Data analysis

Baseline gait characteristics (walk without dual task) were compared between groups using a mixed ANOVA, with trial as the only within-subject variable as a repeated measure. Gait parameters for the Early and Late phases prior to the obstacle were analysed using mixed repeated measures ANOVAs (3x3x5) with group as the between factor (PD-FOG x PD-Non FOG x

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Controls), while cognitive load (NC x C1 x C2) and trial (trials 1 through 5) were the within-group factors. A one-way ANOVA was used to compare the demographic data and clinical scores between groups (see Table 1 and Table 2). The delta of gait parameters from early to late phase was analysed using the same mixed repeated measures ANOVA model created for the other variables.

The Kruskal-Wallis one-way analysis of variance was used to compare the percentage of correct answers (during the counting task) and the crossing success rate between groups and conditions. A Tukey-HSD post hoc analysis was used to make multiple comparisons between groups when main effects of group were found (p values ≤ 0.05). A Stepwise model regression analysis was performed using independent variables: age, UPDRS-III total scores, UPDRS-Postural Scores, TMT-A, TMT B-A, Mini-Mental 3MS, Corsi block test scores, to determine which factors (aging, motor, cognitive) significantly contributed to the differences observed between groups. These analyses were conducted in order to explain the nature of the behaviour observed, but only when a significant interaction or group difference was identified by ANOVA. Non-parametric tests (Kruskal Wallis and Wilcoxon tests) were used to compare accuracy of answers and the crossing success rate. All statistical analyses were performed using Statistica 8.0.

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RESULTS

Overall Gait Characteristics

The typical gait differences expected between healthy controls, PD-non FOG and PD-FOG were confirmed and are reported in Table 3.

Gait during obstacle approach

Only dependent variables with identified significant interactions between group and dual task are described in this section. All other results for dependent variables that did not have interactions are described in the Table 4.

An interaction between group and dual task for step length variability was identified F (4,76) =3.376; p=.013 (Fig. 2). Post hoc analysis revealed that only PD-FOG showed increased step length variability in conditions C1 and C2 compared to NC (p=.03 and p=.002). PD-FOG also showed greater step length variability compared to healthy controls in conditions C1 (p=.011) and C2 (p=.008) (see Figure 2b).

An interaction between dual task and group, F (4,76) =3.572; p=.011, was also found for step time variability.. Post hoc comparisons revealed that step time variability for PD-FOG significantly increased in the C1 condition compared to NC (p=.046) condition. Step time variability in conditions C1 (p=.022) and C2 (p=.034) for PD-FOG were higher compared to controls in the same dual task conditions (see Figure 2d).

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Table 3– Typical gait differences (without dual task) between groups.

	PD-FOG	PD-nonFOG	Controls	Group effect (*P* value)
Gait velocity (cm/s)	72.9(±7.3)[a]	87.6(±6.8)[c]	113.8(±7.0)	.006
Step length (cm)	49.2 (±2.9)[a]	59.5 (±3.0)	66.0 (±2.9)	.001
Step length variability (CV%)	16.8 (±2.4)[a,b]	8.2 (±2.5)	6.3 (±2.4)	.01
Step time variability (CV%)	7.0 (±0.9)	5.4 (±0.94)	4.9 (±0.9)	0.203

Legend - a= PD-FOG x Controls; b= PD-FOG x PD-nonFOG; c= PD-nonFOG x Controls

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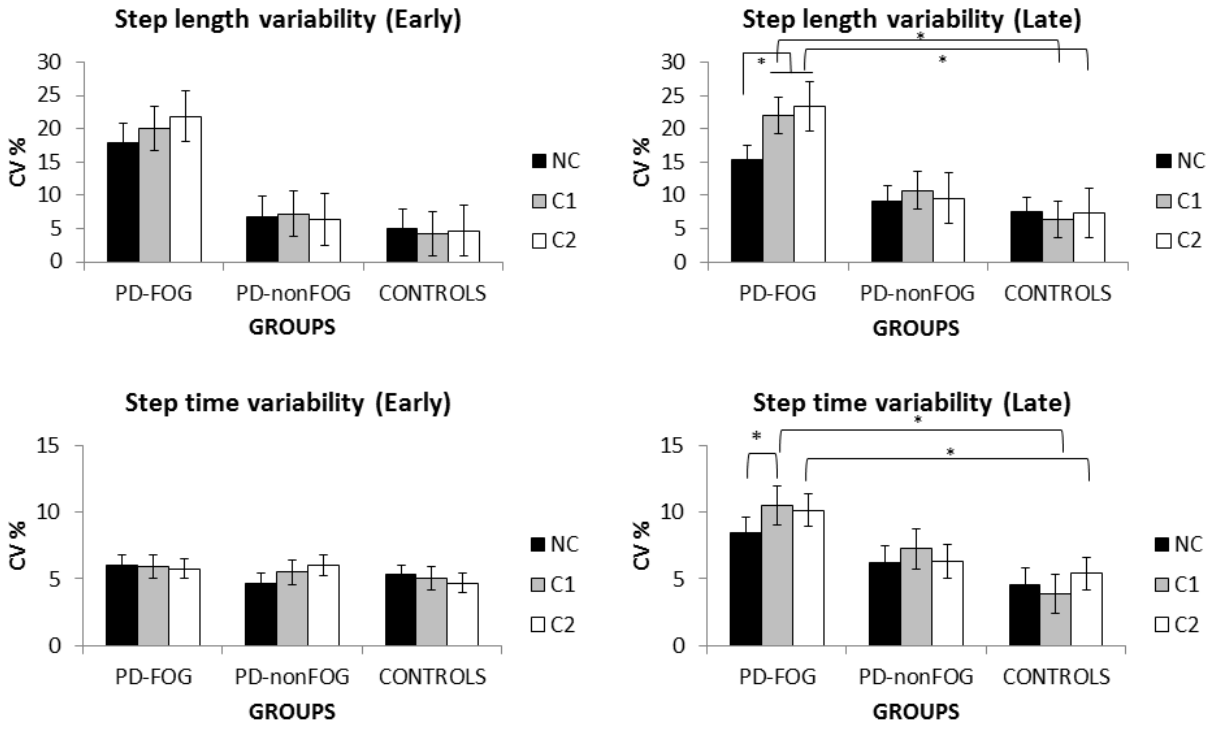

Figure 2 - Mean and standard errors (error bars) of step length and time variability for the PD-FOG, PD-nonFOG and control groups for both in early and late phases respectively. Graphs b and d plot the significant interactions. Asterisks indicate significant differences $p < .05$.

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Change in gait parameters between early and late phases

An interaction between group and condition was only found for the magnitude of change in step time variability F (4,76) =3.061; p=.021. This interaction showed that the dual task magnified the increase in step time variability, between phases, but only in PD-FOG (confirmed by post hoc) (see Figure 3).

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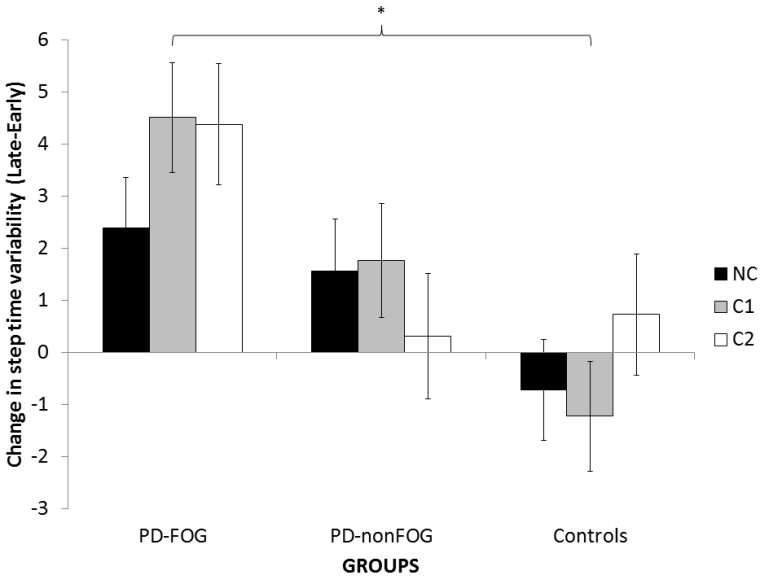

Figure 3 - Mean and standard errors (error bars) of the change between phases - Asterisks indicate differences between conditions. Symbols indicate differences found between groups in each condition. *= p<.05. Only C1 are different than controls

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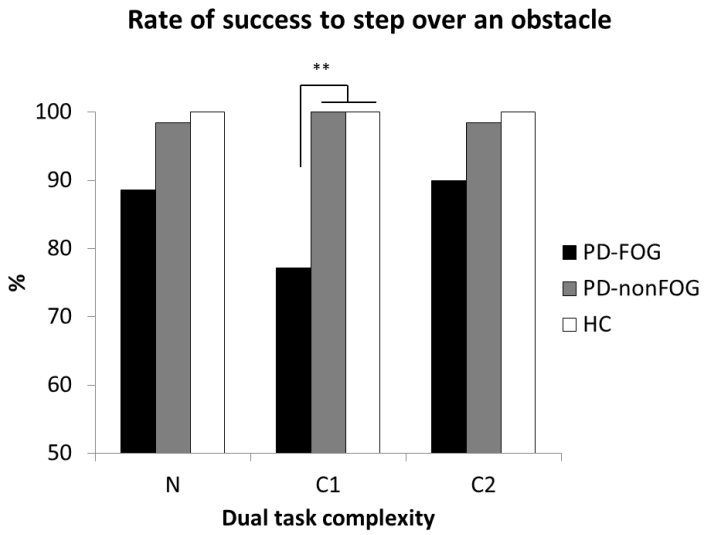

Figure 4 – PD-FOG had lower rate of success to cross an obstacle compared to other groups when monitoring one digit (C1).

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Table 4- Effects of dual task and group on gait parameters in the Early and Late phases

	Early			Late					
	NC	**C1**	**C2**	**NC**	**C1**	**C2**	**Group effect (p values Early / Late)**	**Dual task effect (p values Early / Late)**	**Group*dual (p values Early / Late) task**
Gait velocity (cm/s)									
PD-FOG	74.57(23.8)	71.50(23.4)	66.89(22.5)	76.59(24.11)	69.43(22.48)	65.6(25.32)			
PD-nonFOG	89.3(24.7)	86.34(26.0)	85.73(25.8)	85.1(28.71)	82.02(26.39)	78.68(26.05)			
Controls	122.4(20.8)	116.9(22.1)	114.3(22.9)	104.5(22.3)	98.31(21.8)	96.15(22.2)	**.002[b]/.002[b]**	**.001[b]/.0001[a,b,c]**	**.729/.700**
Step length (cm)									
PD-FOG	45.61(14.96)	44.3(14.70)	41.34(14.35)	54.22(15.29)	50.84(16.48)	49.24(16.73)			
PD-nonFOG	57.74(8.54)	55.60(9.74)	54.76(9.97)	60.56(14.80)	60.28(11.57)	58.31(12.19)			
Controls	64.25(7.62)	63.08(8.70)	61.83(8.89)	67.95(9.65)	67.06(10.72)	67.10(10.29)	**.0001[a,b]/.001[a,b]**	**.0001[a,b,c]/.013[b]**	**.555/.421**
Step length variability (CV%)									
PD-FOG	17.95(18.57)	20.06(20.66)	21.81(23.7)	15.40(11.69)	21.90(17.67)	23.40(25.88)			
PD-nonFOG	7.01(4.47)	7.33(3.88)	6.62(4.05)	9.19(6.76)	10.68(7.89)	9.59(6.01)			
Controls	5.00(3.14)	4.22(2.06)	4.49(2.42)	7.57(4.43)	6.38(2.75)	7.29(5.63)	**.003[a,b] /.004[a,b]**	.738/**.035**	**.373/.013[†]**
Step time variability (CV%)									
PD-FOG	6.02(3.65)	5.94(5.00)	5.77(3.20)	8.41(7.40)	10.46(8.51)	10.15(6.95)			
PD-nonFOG	4.65(1.80)	5.49(2.13)	6.04(2.18)	6.22(2.41)	7.25(4.07)	6.35(3.34)	.076/**.024[b]**	.345/**.038[b]**	.456/**.011[†]**
Controls	5.30(2.70)	5.06(2.61)	4.66(2.27)	4.58(1.51)	3.83(1.15)	5.40(1.97)			

Legend – NC = not counting; C1 = counting one number; C2 = counting two numbers ; Within comparisons - a = NC x C1; b = NC x C2; c = C1 x C2; Between groups comparisons - a = PD-FOG x PD-nonFOG ; b = PD-FOG x Controls; c = PD-nonFOG x Control. [†] Interactions revealed that the dual tasks increased the step-to-step variability only among PD-FOG and only in the Late phase

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Table 5– Mean and (standard errors) of change from early to late phase

Change from Early to Late (Late - Early)						
	NC	C1	C2	Group effect (p values)	Dual task effect (p values)	Group*dual task (p values)
Gait velocity (cm/s)						
PD-FOG	0.92(14.1)	-2.06(14.9)	-2.18(13.8)			
PD-nonFOG	-4.23(14.7)	-4.31(15.4)	-7.05(14.4)	.144	.123	0.803
Controls	-17.8(14.1)	-18.63(14.9)	-18.18(14.2)			
Step length (cm)						
PD-FOG	8.60(3.5)	6.53(3.3)	7.89(3.4)			0.352
PD-nonFOG	2.82(3.6)	4.67(3.4)	3.55(3.3)	.084	.779	
Controls	3.70(3.5)	3.98(3.3)	5.26(3.4)			
Step length variability (CV%)						
PD-FOG	-2.55(3.5)	1.84(3.3)	1.58(4.2)			0.441
PD-nonFOG	2.33(3.4)	3.50(4.5)	3.27(4.4)	.372	.213	
Controls	2.49(3.3)	2.12(4.3)	2.62(4.2)			
Step time variability (CV%)						
PD-FOG	2.39(4.95)	4.51(5.04)	4.38(5.86)			
PD-nonFOG	1.56(2.35)	1.76(4.08)	0.31(2.83)	**.010**[a]	.344	**.021**[b]
Controls	-0.71(2.25)	-1.22(1.94)	0.73(3.36)			

Legend – a = difference between PD-FOG x Controls found by post hoc analysis. [b] The post hoc comparisons of this interaction are described in the Fig. 3.

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Table 6– Mean (standard errors) of crossing parameters for each group in each condition.

	NC	C1	C2	Group effect (p values)	Dual task effect (p values)	Group*dual task (p values)
Crossing velocity (cm/s)						
PD-FOG	64.5 (12.6)	59.6(12)	56.9(12.04)	.075	**.001**[b]	
PD-nonFOG	66.5(13)	63.5(12.5)	60.9(12.8)			.943
Controls	81.5(12.6)	75.4(12)	74.3(12.4)			
Crossing step (cm)						
PD-FOG	70.9 (7.9)	71.2(6.6)	71.2(6.4)	.641	571	
PD-nonFOG	72.7(6.9)	75.0(5.8)	73.8(5.6)			
Controls	74.5(6.6)	75.1(5.6)	74.3(5.4)			.942
Trail foot horizontal distance before obstacle (cm)						
PD-FOG	38.1(5.7)	37.1(5.0)	36.3(5.2)	.263	.782	
PD-nonFOG	33.5(5.2)	35.4(4.6)	35.6(4.8)			
Controls	32.0(5.0)	33.3(4.4)	32.2(4.6)			.645
Lead foot horizontal distance after obstacle(cm)						
PD-FOG	35.8 (4.1)	34.2(4.1)	35.0(3.7)			
PD-nonFOG	38.8(3.7)	40.1(3.8)	37.8(3.4)	**.014**[a]	.101	.274
Controls	42.9(3.7)	42.3(3.8)	40.6(3.4)			
Lead foot vertical clearance(cm)						
PD-FOG	16.9(3.4)	17.4(3.8)	16.9(4.1)			
PD-nonFOG	15.7(3.0)	16.9(3.3)	16.9(3.6)	.472	.256	.261
Controls	19.1(2.8)	19.4(3.2)	18.1(3.5)			
Trail foot vertical clearance(cm)						
PD-FOG	18.3(6.1)	18.5(5.6)	17.1(5.3)			
PD-nonFOG	17.0(5.3)	15.5(4.8)	16.0(4.5)	.211	.873	.201
Controls	20.9(5.3)	21.3(4.8)	22.4(4.5)			
Crossing step width(cm)						
PD-FOG	33.8 (5.5)	33.6(5.1)	31.0(6.2)			
PD-nonFOG	31.9(4.8)	30.4(4.5)	32.5(5.4)	.542	.598	.137
Controls	29.3(4.6)	30.0(4.3)	29.1(5.2)			

Legend – a = difference between PD-FOG x Controls found by post hoc analysis; b=C1 and C2 different than NC

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Crossing parameters

No significant interactions were identified (see table 6).

Dual task performance and crossing success rate

A main effect of group was found in the C1 condition (χ^2=7.730; p=.021; df = 2) for the accuracy of answers (dual-task performance). Wilcoxon tests for independent samples showed that the percentage of trials with perfect counting was significantly lower for PD FOG (50%±36) compared to PD-nonFOG (84%±24)(p<.007). Since all groups performed poorly in the two digit monitoring task (27%) compared to one digit (69%) (p=.0001), there were no further significant differences identified between groups (p=.867) for C2.

A main effect of group was also found for the crossing success rate (i.e., number of contacts with obstacle while crossing), but only during C1 condition (χ^2=13.124; p=.001; df = 2). Post hoc analysis using Mann-Whitney U tests showed that PD-FOG had ~23% more obstacle contacts than PD-Non FOG and healthy controls (p=.009), who made no contacts and 100% performance (p=.009) (see Figure 4).

Regression analysis

As described in the methods, a *stepwise* regression model was created by entering the cognitive tests, clinical characteristics and demographic features of each PD population tested (PD-FOG and PD- nonFOG separately). The Mini-Mental 3MS was the only predictor of the step length variability for freezers, F (1, 13) = 9.183; p=.010; r=.658; R^2=.433. Step time variability of

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freezers was also significantly predicted by Mini-mental 3MS, F (1, 13) = 11.523; p=.005; r=.700; R^2=.490. The 3MS was also the best and only predictor of the change from early to late phases in step time variability among the PD FOG group, F (1, 13) = 5.568; p=.036;r= .563; R^2=.317. The TMT B-A was the best predictor of the lead horizontal distances after obstacle when only PD-FOG were included in the model, F (2, 34) = 4.857; p=.046; r=.534; R^2=.285.

In contrast, step time variability among PD-non FOG was only predicted by TMT B-A scores F (1, 11) = 12.787; p=.005; r=.749; R^2=.561; P=.005, while change in step time variability from early phase to late was only predicted by UPDRS-III, F (1, 11) = 11.007; p=.008; r=.725; R^2=.526. The percentage of correct answers in the C1 condition was only predicted by the TMT B-A scores in PD-FOG, F (1, 13) = 8.317; p=.014; R^2=.306, whereas for PD-nonFOG the best predictor was age, F (1, 13) = 4.935; p=.046; R^2=.335. There were no predictors of accuracy of answers for the C2 condition.

In sum, the regression analysis showed that, increased gait variability (spatial and temporal) during dual task conditions in PD-FOG was predicted by 3MS scores (lower scores = higher variability) and Dual task performance (accuracy of answers) of PD-FOG was predicted by TMT B-A scores (longer TMT times = more inaccurate answers). During the crossing phase the shorter placement of the lead limb beyond obstacle (in PD-FOG) was predicted by lower scores on TMT B-A (longer TMT times = shorter distances).

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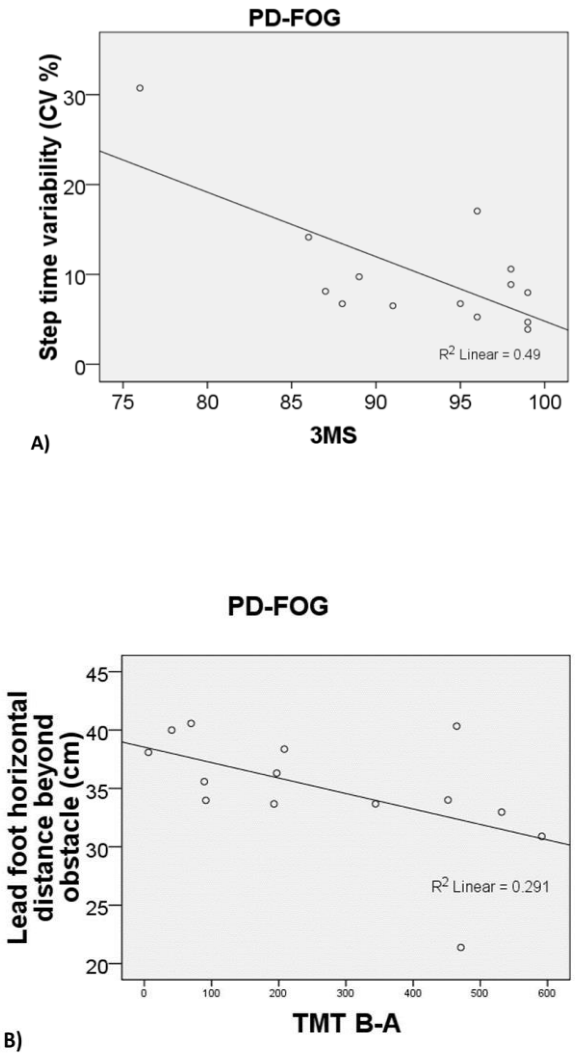

Figure 5 – Scatter plots showing the relationship between gait characteristics and cognitive scores: A) 3MS scores with step time variability in the late phase during C2 (only in PD-FOG). Freezers with low 3MS scores had increased step time variability; B) TMT B-A was the best predictor (for all groups) of foot-obstacle distances. Individuals who had more difficulties (longer times) to perform the TMT test also tended to land their foot closer to the obstacle.

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DISCUSSION

The objective of the current study was to evaluate how increasing cognitive load might influence the gait of PD patients with and without FOG during obstacle crossing, since it requires more planning than straight line walking. More specifically, given our expectation that cognitive load would lead to increased FOG, we aimed to identify 'when?', during the approach to an obstacle might cognitive load start to influence gait planning and control. As expected, the results of the current study demonstrated that the dual task affected PD-FOG more than both healthy controls and PD-nonFOG participants, and more importantly, this was more evident as they drew nearer to the obstacle (i.e., in the late phase of their approach). These findings are supported by interactions between group and dual task condition for both step length and step time variabilities. During crossing itself, it should also be noted that, PD-FOG landed their lead foot significantly closer to the obstacle when landing the foot that was responsible for more planning errors (obstacle contacts). Interestingly, the regression analysis showed that this crossing behaviour was only associated with declined executive function (specifically with attentional set-shifting) and not with any other cognitive or motor issue. In other words, the transition from a more automatic gait to a more consciously controlled gait revealed a profound influence over the PD-FOG group only. These results are discussed in greater detail in the sections below, with respect to the neuroanatomical correlates for these findings.

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Anticipatory gait regulation, motor planning and cognitive load in PD

The current study found that PD-FOG was the only group influenced by dual task when walking. However, this influence was only significant when they were about to step over the obstacle, as seen in the step length and step time variability during the late phase. Fluctuations in step time in participants with PD have been found when attentional resources were shared with gait control (Hausdorff, 2005; Hausdorff et al., 1998). The current results showed that the change in step time variability between early and late phases was similar in both PD groups in the baseline condition where no dual task was involved; however, the PD-FOG group increased variability incrementally, specifically in the late phase, with each level of dual task complexity. These results suggest that the planning of gait adjustments is not as automatic in PD-FOG, as it is in PD-nonFOG and healthy controls. In fact, the current results support the notion that as PD-FOG draw nearer to an obstacle, greater resources are dedicated to gait. In dual task conditions however, the demand for these limited resources is shared with the cognitive task, thus leading to increased gait variability (as seen in both step time and step length variability interactions between group and dual task condition). Chee et al (2009) also showed that exaggerated step length variability is associated with FOG episodes, induced by the maintenance of a predetermined short step length at the beginning of a walking trial. However, if this 'sequence effect' explained the increased variability identified for PD-FOG in the current study, we would have expected a decrease in step length from Early to Late phase, but this was not the case. Thus, the current study provides new evidence that cognitive overload is likely associated with the simultaneous processing of a secondary task plus the motor planning of an approaching

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obstacle, but this occurs predominantly in the late phase (as the individual with PD is closest to the obstacle).

FMRI studies using a mental imagery paradigm have associated gait impairments in freezers with problems within neural mechanisms that underlie planning and execution of gait tasks. For example, Snijder et al. (2011) found that PD-FOG and PD-nonFOG had lower activation of the right superior parietal cortex and right anterior cingulate cortex when planning a precision gait task, relative to healthy control participants. Their study also showed that although PD-FOG tended to have lower activation in both of these areas, compared to PD-nonFOG, only PD-FOG presented hypo-activation in the SMA. Cells in the SMA are involved with the advanced planning of movement sequences (Makoshi, Kroliczak, & van Donkelaar, 2011; Tanji & Shima, 1994). However, in the current study, significant differences between PD-FOG and PD-nonFOG were found only with the secondary task present, and in the late phase of their approach to an obstacle. It is unlikely that this difference would be caused by the secondary auditory monitoring task directly affecting SMA activity. Indeed, this secondary task was specifically chosen because it did not require motor involvement to ensure that the gait impairments we observed would not be associated with shared motor control resources.

Although it is possible that the neural mechanisms supporting motor control are more affected in PD individuals who freeze compared to those who do not, it is important to consider how the gait variability effects of a cognitively demanding secondary task in PD-FOG might be caused by visuo-spatial processing deficits; since they may be important for the planning of gait adjustments when avoiding an obstacle, especially in the late phase of the obstacle approach.

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Neurophysiological studies that evaluated the activity of parietal cells in cats, while stepping over obstacles, showed higher activation only during the final stride before crossing the obstacle (Andujar & Drew, 2007; Drew et al., 2008; Marigold & Drew, 2011), thus providing evidence that parietal regions mediate gait with obstacles during the approaching phase. Lesions in the superior parietal cortex of cats generated temporal and spatial abnormalities to regulate the penultimate stride before the obstacle, as well as more obstacle contacts (Lajoie & Drew, 2007). Prefrontal areas in the brain of healthy young adults associated with planning and sustained attention are activated when an obstacle is about to be stepped over (Haefeli et al., 2011). These previous studies indicate the importance of fronto-parietal areas in the brain during the preparatory and crossing phases of an obstacle crossing. Dual-task performance in PD patients has been characterized by abnormal greater activation of fronto-parietal networks compared to healthy controls(Wu & Hallett, 2008). Recently neuroimaging studies revealed that PD-FOG hyper activate areas in the brain associated with the cognitive control (e.g. dorsolateral prefrontal cortex and parietal cortex) during gait simulation in a virtual environment with different cognitive loads (Shine, Matar, Ward, Bolitho, Pearson, et al., 2013). The authors argued that the abnormal hyper vigilance or monitoring would be a compensatory mechanism to prevent and/or to stop a FOG episode. However this compensatory cognitive strategy in PD-FOG may overload central resources specifically those mediated by the dorsolateral prefrontal cortex that are important in planning and control of gait in more complex situations, such as when avoiding obstacles during gait.

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FOG symptoms affect obstacle crossing performance of PD patients

The only significant main effect of group while crossing the obstacle was that PD-FOG landed their lead foot closer to the obstacle after crossing. The current study did not find the same results as previous studies (Galna et al., 2010; Vitorio, Pieruccini-Faria, Stella, Gobbi, & Gobbi, 2010), where PD-nonFOG also landed their lead foot significantly closer to the obstacle after crossing it, but it should be recognized that this may be the result of the previous studies not having included a PD-FOG group. Since crossing step length and height were similar for all groups, it is also possible that shorter horizontal placement of the lead limb of freezers after obstacle clearance (as well as their greater number of obstacle contacts) could be partially explained by deficits in planning needed to successfully crossover an obstacle. In addition, the increased number of obstacle contacts in PD-FOG compared to other groups when performing the dual task (C1), suggests that successful obstacle crossing may demand greater central resources for PD-FOG.

Using Neuropsychological Tests to Understand the Role of the Cognitive Resources during gait with obstacles in PD

The absence of a relationship between visuospatial memory (Corsi test), attentional/cognitive flexibility (TMT B-A), disease severity (UPDRS-III and Gait and Posture section), and gait parameters in PD-FOG patients suggest that the observed deficits in gait of PD-FOG during the dual task conditions were not related to one specific executive function. Rather a more general cognitive decline in PD-FOG may underlie problems with the motor planning necessary to avoid an obstacle. Indeed, the regression analysis showed that Mini-

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Mental 3MS scores was the only variable that predicted the increased step time and step length variabilities in PD-FOG. However, this relationship is somewhat unexpected because the groups' 3MS scores were not statistically different. Nevertheless, it is well known that Mini-Mental scores are worse in patients with deficits in cholinergic function and cortical degeneration. For example, Perry et al. (1993) showed that the cholinergic activity in Parkinson's disease without dementia can be even lower than patients with Alzheimer disease (also known to be affected by a severe cholinergic dysfunction). Recently, studies have suggested that PD-FOG have lower cholinergic activity compared to PD-non FOG (Moreau et al., 2012; Rodriguez-Oroz, 2012). One possible explanation for the current results is that the cognitive resources affected by cholinergic dysfunction may be responsible for the gait variability observed when approaching an obstacle. Another possible explanation is that 3MS scores are based on the assessment of the general cognitive status, which is supported by several brain areas. This might suggest that when PD-FOG are required to perform tasks with greater planning demand, they tax brain areas needed to accomplish the task more than those with PD who do not freeze. Over activation of brain areas (e.g., right dorsal premotor area, precentral gyrus, right inferior parietal lobe, bilateral precuneus) was recently observed in an fMRI study in which PD patients had to imagine themselves walking and stepping over an obstacle (Wai et al., 2012). The authors argued that the activation of additional neural resources observed in PD patients represents a compensatory mechanism to improve the efficacy of gait with obstacles. However an actual gait test was not performed in that study. Future studies should investigate the hypothesis that PD-FOG patients recruit additional neural resources by correlating brain activity with an active gait test.

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The current study found that all participants (on average) adopted a slower crossing velocity, specifically when performing the two-digit monitoring task. Slower velocities while dual-tasking in free gait, and also when crossing obstacles has been shown to be associated with executive function decline, including attentional set-shifting capacity (TMT B-A) (Ble et al., 2005; Springer et al., 2006; Yogev-Seligmann et al., 2008). Slower velocities may be necessary to facilitate the monitoring of the dual task as well as movement characteristics that might help prevent a trip or loss of balance while crossing. Although no interactions between dual task and group were found (for velocity) in the current study, performance on the TMT B-A was significantly correlated with crossing velocity in all conditions, for all groups ($r > -.393$; $p<.01$). This correlation suggests that limited cognitive resources (related to executive function) play some role in movement control during obstacle crossing. Although PD-FOG had poorer clinical postural scores compared to PD Non FOG (see Table 3) this did not influence crossing parameters. The absence of this relationship may in part be explained by increased arousal during obstacle crossing that compensates for negative effects on postural control (Brown, Doan, McKenzie, & Cooper, 2006). Situations provoking greater postural instability may increase the conscious processing of gait (Huffman, Horslen, Carpenter, & Adkin, 2009), which has the potential to partially compensate for postural control deficits in PD.

The regression analysis also revealed that the TMT B-A was the best and the only predictor of lead horizontal distance (landing distance) after the obstacle for all groups. Thus, it is unlikely that a motor impairment caused by aging, dopaminergic degeneration or deficits in postural control affected the participants' performance. The TMT B-A is a test that measures the capacity to quickly shift between action plans while monitoring the overall motor planning

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required to complete the entire action effectively (Petrova, Raycheva, Zhelev, & Traykov, 2010). Performance in this test has been related, in part, to left parietal, left temporal areas and dorsolateral prefrontal cortex in healthy young adults (Jacobson, Blanchard, Connolly, Cannon, & Garavan, 2011). These two areas are related to working memory and manipulation of the perceptual representations stored in working memory, respectively (Fiehler et al., 2011; Fuster, 2004). Thus cognitive decline related to these brain areas are likely to play an important role during gait adaptations when vision is required to plan tasks such as obstacle avoidance.

Limitations

Some limitations regarding the current study should be acknowledged. The variability calculated in current study might have been obtained from too small a number of steps. Previous studies have reported the effect of dual task on variability calculated from hundreds of steps (e.g., Yogev et al., 2005). However in the current study, all gait variables were calculated from the same number of steps in each phase of the approach for all participants. Another limitation was the use of only one modality for the secondary task (auditory tracking). Previous studies have investigated the impact of different modalities on gait performance (e.g., phoneme monitoring and subtracting a sequence of numbers backwards) in order to infer the nature of the dual task deficit (e.g., sharing or bottleneck theoretical explanation), however, one the goals of the current study was to avoid a secondary motor task that might overload the motor system. A baseline score for the dual task performance during free gait or in a 'without walking' condition was not included in the current experiment, thus whether the groups of participants in the current study may have suffered from an auditory digit monitoring deficit,

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although unlikely, cannot be verified. A more detailed cognitive assessment was not included due to time limitations for this study. The current study also did not provoke FOG episodes during experimental trials. However a previous study (Snijders et al., 2010) showed that even when PD-FOG were in "off" or unmedicated state, not all patients presented FOG episodes when stepping over a suddenly dropped obstacle on a treadmill, thus the lack of FOG may not be all that surprising. The authors recognized that an obstacle can not only act as a distractor, but also as a visual cue to enhance motor performance.

CONCLUSION

In summary, the current study demonstrated that approaching an obstacle increases the need for planning resources prior to stepping over an obstacle in PD patients with FOG. Cognitive overload (associated with dual task performance) likely affects gait control of PD with FOG, especially during the late phase, where motor planning of the sequence of steps was most crucial to avoid tripping over the obstacle. This result suggests that depleted cognitive resources are likely associated with the prefrontal cortex, specifically when a cognitive dual task is being processed as patients with PD FOG get closer to an upcoming obstacle. Although no FOG episodes occurred, the current study suggests that the FOG status of patients with PD is associated with a limited resource capacity to plan and enact the gait adjustments necessary for crossing obstacles. This is more evident when PD-FOG are simultaneously engaged in a cognitively challenging secondary task developed to overload cognitive functions associated with pFaulty foot regulation in PD-FOG when crossing the obstacle can be explained by a decline in executive functions that may have caused an impaired capacity to plan and monitor

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movement. From a therapeutic point of view, the results of current study suggest that the complexity of gait tasks must be considered during interventions, in order to decrease the probability of falls and gait impairments among PD patients with FOG symptoms.

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CHAPTER 3 - INTERACTIONS BETWEEN COGNITIVE AND SENSORY LOAD WHILE PLANNING AND CONTROLLING COMPLEX GAIT ADAPTATIONS IN PARKINSON'S DISEASE

Running title: Sensory and cognitive interactions during movement planning in PD

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Parts of this chapter have been accepted for publication in *BMC Neurology:*

Pieruccini-Faria F.; Ehgoetz Martens K.A.; Silveira C.R.A.; Jones J.A.; Almeida Q.J. *(in press)* Interactions between cognitive and sensory load while planning and controlling complex gait adaptations in Parkinson's disease. *BMC Neurology*

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ABSTRACT

Recent research has argued that removal of relevant sensory information during the planning and control of simple, self-paced walking can result in increased demand on central processing resources in Parkinson's disease (PD). However, little is known about more complex gait tasks that require planning of gait adaptations to cross over an obstacle in PD. In order to understand the interaction between availability of visual information relevant for self-motion and cognitive load, the current study evaluated PD participants and healthy controls while walking toward and stepping over an obstacle in three visual feedback conditions, including: (i) no visual restrictions; (ii) vision of obstacle and lower limbs in complete darkness and (iii) vision of obstacle alone in complete darkness; as well as two conditions of cognitive load (single task versus dual task). Each walk trial was divided into an early and late phase to examine changes associated with planning of steps adjustments when approaching the obstacle. Interaction between visual feedback and dual task conditions during the obstacle approach was not significant. Patients with PD showed greater deceleration and step time variability in the late phase of the approach to the obstacle while walking in both dark conditions compared to the controls. As well, only participants with PD had increased obstacle contacts when vision from lower limbs was not available during the dual task condition. Dual task performance was worse in PD compared to healthy controls but notably only in the 'walking in darkness' conditions. These results suggest that planning resources, to step over an obstacle, affect gait control of PD patients, especially when visual feedback is reduced. This influence happens because PD patients dedicate more cognitive resources to interpreting proprioceptive information when visual feedback of self-motion is reduced. Overall, trips and falls among individuals with PD may result from increased demands in sensorimotor integration and cognitive processing.

Keywords: Parkinson's disease; Visual Feedback; Dual task; Gait with obstacle; cognitive load

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INTRODUCTION

It has been well documented that people with Parkinson's disease (PD) rely more on visual feedback than healthy individuals to plan and control their movements (Desmurget, Grafton, Vindras, Grea, & Turner, 2003; Ghilardi et al., 2000; Klockgether & Dichgans, 1994). Although the cause of this increased reliance on vision in PD patients is not well understood, previous studies have suggested that the reliance on visual information during goal-directed tasks may be compensation for proprioceptive deficits (Adamovich et al., 2001; Azulay et al., 1999; Contreras-Vidal & Gold, 2004). Specifically, studies have demonstrated that patients with PD rely on optic flow more than healthy individuals to modulate gait parameters (Schubert et al. 2005; Azulay et al. 1999). As well, Almeida et al. (2005) found that patients with PD who walked towards a remembered target in a dark room had poorer estimation of the target location than healthy controls. However, when a small light-emitting diode (LED) was attached to their chest, estimation of the target location improved. Yet, the authors suggested that the visual cue for body position, attached to patients' chest, helped them to update proprioceptive feedback into a motor plan. Together, these studies suggest that patients with PD are more dependent on visual feedback to update their sense of self-motion and body position, compared to healthy controls during gait. This dependence on vision may also be important for estimating the distance between their body and targets/obstacles that they have planned to negotiate in their environment.

The importance of visual feedback for perception of self-motion in higher demanding tasks, as well as, for compensatory stepping right after a postural perturbation, has recently

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been explored. For example, Vitorio et al. (2013) showed decreased rates of success (more obstacle contacts) when optic flow was disrupted by strobe lighting. This study suggested that visual feedback of self-motion may be important for accurate planning (decreasing accidental obstacle contacts) of obstacle crossing, although measures of gait control during the obstacle approach was not evaluated. However, it is important to note that strobe lighting might also affect the perception of an obstacle's spatial location, as well as the feedback from vision of the lower limb needed for accurate clearance over the obstacle. Jacobs and Horak (2006) showed that visual feedback (of the lower limbs) helps the patients with PD to improve accuracy of their step placement relative to a target (that they are asked to step on), during a postural task. Thus, while visual feedback has been argued to contribute to successful stepping adjustments, there have been no direct tests of the relative contribution of visual feedback for perception of self-motion, or accuracy of lower limb positioning, during complex gait tasks that involve obstacle clearance in PD. Additionally little is known about the influence of reduced visual feedback on gait control of individuals with PD when the demand for planning resources, to avoid an obstacle, increases while walking.

It is also important to consider how directing attention to relevant sensory feedback (stripes on the floor, somatosensory cues, timing cues) while walking, not only improves gait control, but is also argued to decrease processing demands required to control gait in PD (Baker, Rochester, & Nieuwboer, 2007; Rochester et al., 2007; van Wegen et al., 2006). Distorted signals from sensorimotor processing, overload cognitive processes in individuals with PD (Redgrave et al., 2010). Thus sensorimotor processing affects cognitive resources of individuals with PD, especially when patients cannot use external feedback to guide their

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movements. The availability of relevant sensory cues are thought to help patients with PD direct their attention to key elements of locomotion, thus automating gait control in a fashion that allows individuals with PD to compensate for faulty internal modulation of steps. Greater processing demands and decreased automaticity when walking is often reflected in decreased velocity and increased step-to-step variability (O'Shea et al., 2002; Yogev et al., 2005). Although the relationship between sensory and cognitive load for gait control is relatively well understood (Baker et al., 2007; Rochester et al., 2007), little is known about the interaction between visual feedback of self-motion and cognitive load during more complex gait tasks where planning and control are necessary to step over an obstacle.

Previous research has shown that a cognitive dual task did not affect the planning and control of step modifications to avoid an obstacle in patients with PD with mild gait impairment (Pieruccini-Faria et al., 2014). It was observed that gait control of individuals with PD and healthy controls during obstacle approach (where individuals plan foot clearances) and crossing (where individuals execute their motor plan) were similarly affected by increased cognitive load in both groups. However patients in this study were tested in conditions that did not impose visual restrictions (i.e., a typically well-lit room). Therefore, it is still unknown whether reducing the availability of visual feedback for perception of self-motion and lower limb positioning (e.g., walking in a dark room towards a visible obstacle) might affect planning resources available.

Our first objective was to determine whether increasing participants' cognitive load while walking, would magnify difficulties with specific aspects of gait that are associated with the planning to avoid an obstacle, as visual feedback of self-motion is manipulated. Since

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planning demand may increase as participants approach an obstacle (Bradshaw & Sparrow, 2001; Sparrow, Bradshaw, Lamoureux, & Tirosh, 2002), we split the approach phase into early (far from the obstacle) and late phases (close to the obstacle). Thus the secondary aim of this study was to evaluate whether the dual task interferes with gait in the late compared to the early phase of an obstacle approach differently during the visual manipulations. It was predicted that during dual task conditions combined with decreased visual feedback of self-motion, PD patients would show slower gait velocity, and also higher step-to-step variability than healthy controls, especially as participants walked closer to the obstacle. These gait changes might indicate the importance of visual feedback on planning resources necessary for complex gait tasks in PD. It was also expected that the foot clearance measures, including the obstacle contacts, would be affected by reduced visual feedback and the addition of cognitive dual task at the same time. In addition, if reduced visual feedback results in an increased dedication of planning resources (for appropriate gait control), then we should expect that dual task performance will be worse in PD during the most reduced visual feedback manipulations, as a result of the overload in planning resources.

MATERIAL AND METHODS

Participants

Eighteen people with PD and fifteen healthy controls (HC) were recruited for the current study. All patients with PD were tested while “on” regular anti-Parkinson’s medication. PD patients were excluded from the sample if they could not independently walk, had

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musculoskeletal problems, uncorrected visual problems, dementia, or other neurological or cardiac diseases. Patients with PD and HC were matched by age, height, and general cognitive status [assessed by Mini-Mental 3MS (Teng & Chui, 1987)](see Table 7). The study was approved by the research ethics board at Wilfrid Laurier University, and written informed consent was obtained from all subjects prior to the experiment according to the Declaration of Helsinki.

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Table 7- Demographics of groups. Comparisons were run using ANOVAs *one way* for each item in the table (except UPDRS III scores).

GROUP	AGE	HEIGHT(cm)	UPDRS III	3MS	DSPAN	TMT-B(s)	TMT B-A(s)
PD(n=18;4F)	71.5(±7)	1.74(±4)	25.0(±6)	98.1(±3)	16.3(±3)	134.7(±14)**	94(±12)**
HC(n=15;9F)	69.5(±6)	1.71(±5)	na	97.6(±2)	15.8(±3)	70(±15)	40(±14)

Asterisks indicate differences between groups *p<0.05;**p<0.01; F= females in each group; na = not available; 3MS = Mini mental 3MS; DSPAN = digit span; TMT= trail making test part B, subtraction B-A.

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Obstacle and data collection

Obstacle and capture area. In all trials, participants walked at a comfortable pace on a runway (gray carpet) and stepped over an obstacle. The obstacle was a bar made of white foam covered with thick white paper (70 cm width x 4cm height x 1.5cm depth; weight = 50 g) and supported by two lateral plastic poles (30 cm in height). The bar of the obstacle was horizontally set at 15% of the participant's height (~25cm), and positioned ~6.5m from the starting point. The whole obstacle structure was covered with glow-in-the-dark tape. The same tape (12 cm length x 3 cm width x 0.7 mm depth) was attached along the length of the participant's feet (aligned with the toe tips) and thighs (just above the knees) using Velcro® (Fig. 5). These illuminated strips were used to provide visual information regarding the position of the participant's knees and the anterior portion of their feet, as well as the location and height of the obstacle in the room.

Data recording and analysis. Participants' movements were tracked by seven synchronized Optotrak® cameras (Northern Digital, NDI, Waterloo, Ontario): three lateral cameras on each side of the runway (vertically oriented) and one central camera (vertically oriented) 2.5 m away from the end of the runway. These cameras tracked the entire runway (~10m). Active IREDs (infrared light emitting diodes) were fixed to the following anatomical regions: midpoint between iliac crests (defined by the umbilicus), lateral malleolus, and 5th metatarsals. Heel contacts and toe offs were visually defined using a validated method (O'Connor et al., 2007). The heel contact and toe off kinematics were used to calculate gait

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variables during the approach and crossing phases. All kinematic data were filtered using a 2nd order Butterworth filter with a cut-off frequency of 6 Hz using a dual-pass filter with zero lag delay. Kinematic variables were calculated using an algorithm created in Matlab 7.0 (The Maths Works Inc.).

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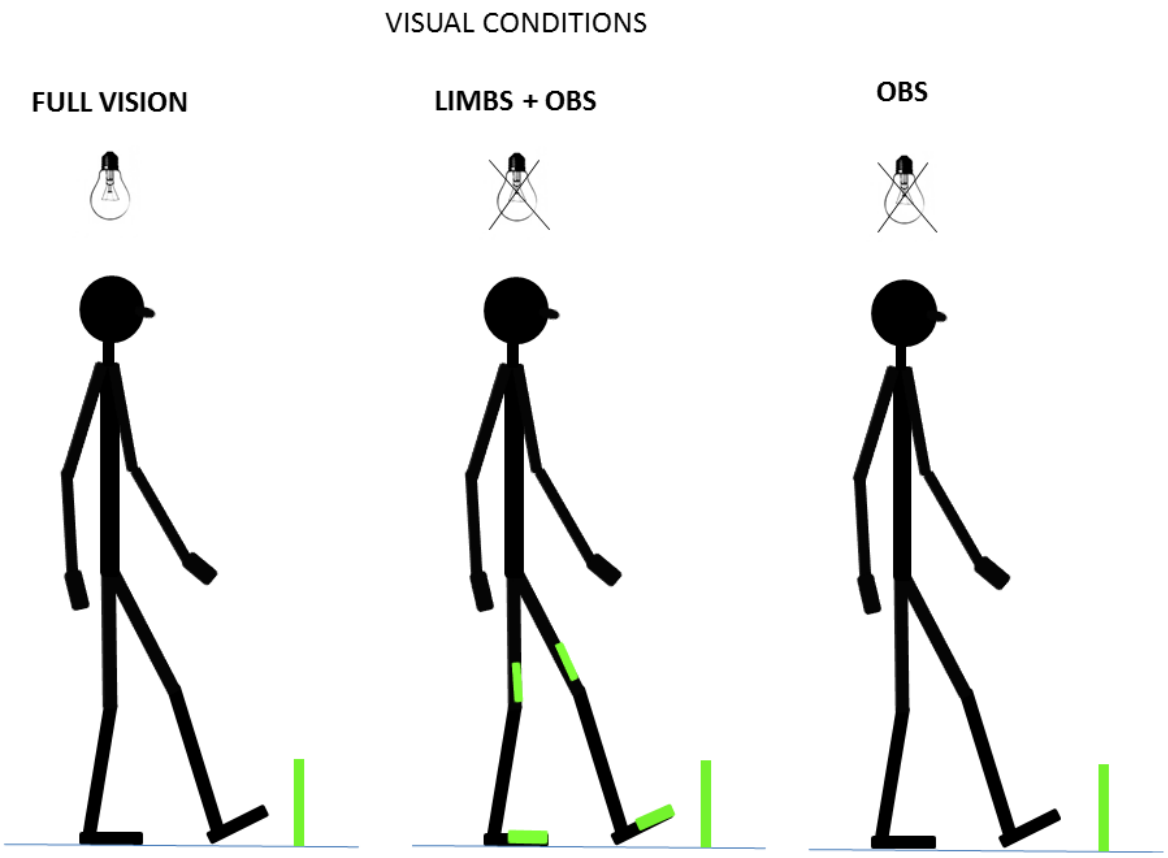

Figure 6- Depiction of visual feedback conditions. Bulbs with black cross indicate when the room was completely dark. Obstacle was visible in all conditions. Visual feedback restrictions- Obs: Only obstacle was visible in the dark; Limb+Obs: Obstacle and limbs visible in the dark; Full vision: no visual restrictions.

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Dual task

Cognitive task (dual task). During this protocol participants performed the gait task protocol with the addition of a secondary task (cognitive task). The cognitive task involved attending to a series of spoken digits. This task was chosen because there was no motor component involved; eliminating the possibility that the secondary task caused motor interference (motor output overload) on the gait task. Participants were instructed to silently count the number of times they heard two different digits (assigned by the experimenter at the beginning of each trial) spoken by a female voice on an audio track. Participants heard numbers ranging from 1 to 9. The order of presentation of each digit on the audio track was randomized across the trials. During each trial the auditory inter-stimulus interval varied randomly from 100-1000 ms to prevent gait synchronization. Each stimulus (digit) presentation last 500ms. Participants were instructed to initiate walking at the moment they heard the first digit. The audio track played for 12 s. Participants were also instructed to count until the audio track finished playing, even if they had already finished the walking task. Participants were asked to equally prioritize the gait and the digit counting task. The volume of the loudspeakers was adjusted so that participants could comfortably hear the digits at the start and end position of the walkway. At the end of each trial, participants reported the number of times they heard the target digits. Feedback about their performance was not provided. In addition to the dual task protocol, a baseline condition (BL) involving participants sitting on a chair (without visual restrictions) monitoring the digits on the audio track was also conducted.

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Visual feedback

Visual feedback manipulations. The experiment occurred inside a room isolated from natural light. Participants confirmed that they could not see their body or any other object when the lights were turned off. Three feedback manipulations were employed: 1) **Full vision -** In this condition the room was illuminated so that the obstacle, the environment around the obstacle, and the participants' limbs were fully visible; 2) In the **Limb+Obs** condition the room light was off, but participants could see the position of their lower limbs and the obstacle using luminescent stripes; 3) In the **Obs** condition, the room was dark and only the obstacle was visible. This condition was used to diminish visual feedback of self-motion and to eliminate visual feedback regarding lower limb movements. Participants completed 3 trials in each visual condition with and without performing the dual task resulting in a total of 18 trials. Trials were randomized for each participant.

Experimental protocol

Clinical and cognitive assessments. Motor symptom severity was assessed using the UPDRS-III (motor section) (Goetz, LeWitt, & Weidenman, 2003). Any cognitive status declines were assessed using the Mini-mental 3MS exam (Teng & Chui, 1987). Executive function related to attentional set-shifting and/or cognitive flexibility was assessed using the Trail Making Test, part A and B (Fitzhugh et al., 1962). Participants were instructed to perform this test as fast and as accurately as they could. The motor component of the test was calculated by subtracting part A from part B. This test is considered a good predictor of cognitive flexibility, motor planning resources and mobility in patients with PD (Xanthopoulos et al., 2008). The digit span

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test (forward and backward) (Blackburn & Benton, 1957) was administered in order to quantify the working memory/attentional status of our participants. These tests were used to characterize the cognitive status of all participants.

Gait task protocol. Each participant completed a minimum of eight steps prior to stepping over the obstacle. This procedure was adopted to ensure that the time it took for each participant to perform the dual task was similar. After each trial the starting position was adjusted 30 cm forward or backwards so that participants could not predict which leg they would step over the obstacle with.

Data analyses and statistics

Gait analysis

Gait Parameters during approaching phase

The data capture area permitted the analysis of the last eight steps prior to obstacle crossing. However, to remove gait characteristics associated with gait initiation, only the last 6 steps prior to the obstacle were analysed. These six steps were divided into two phases, an early phase and a late phase, each containing 3 steps. The speed of gait was calculated as the average of the step velocity of the three steps in each phase. Step-to-step time and length variability were calculated using the coefficient of variation (CV) of steps in each phase ((Standard deviation/Mean)*100).

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Dual task performance

Performance on the digit counting task was calculated using the formula:

Performance = |Correct answer – Given answer|

Obstacle Crossing Parameters

Lead toe clearance was calculated by subtracting the vertical position of the 5th metatarsal marker on each foot from the obstacle's height, at the frame or instant when the foot was directly over top of the obstacle (i.e., the crossing point). Trail horizontal distance before the obstacle and lead horizontal distance beyond the obstacle were captured as horizontal distances between the foot and the obstacle, subtracting the position of the marker on the 5th metatarsal of each foot from the obstacle position in the sagittal plane (see **Figure 6**).

Statistical analyses. In order to investigate the motor planning difficulties, step-velocity and step-variability were analysed using a two-way mixed repeated measures analysis of variance (RM ANOVA) with group (PD, Healthy controls (HC)) as a between-subjects factor on gait velocity, step-to-step time variability and step-to-step length variability [Conditions: visual feedback (3)x task (2) x phases (2)]. In order to investigate how conditions influenced foot clearance, another two-way mixed RMANOVA with group (PD, HC) as a between-subjects factor [Conditions: visual feedback (3) x task (2)] was used to observe the interactions between task and visual feedback on trail-limb horizontal distance before obstacle, lead-limb toe clearance, lead horizontal distance beyond obstacle and their variability (standard deviation of these distances). Tukey-HSD post hocs were applied when appropriate. The motor planning errors (obstacle contacts) were analyzed using non-parametric tests. Kruskal-Wallis and the Wilcoxon

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test were used to compare the rate of success of obstacle crossing. Differences were accepted when p values were ≤0.050. All statistical analyses were run in STATISTICA 8.0.

RESULTS

Baseline gait measures

Overall, the PD group showed gait characteristics that are typically observed in patients with PD: shorter step length (PD: 54.0 cm ±1.9, HC: 64.4 cm ± 2.1; $F_{1, 31}$=12.72, p=0.001) and slower gait speed (PD: 99.1 ±4.0 cm/s, HC: 126.2 cm/s ±4.4; $F_{1, 31}$ =15.41, p<0.001).

Gait during obstacle approach

Gait velocity

The hypothesized interactions between group, visual conditions, dual task and phase did not reach statistical significance. However, the results for gait velocity during obstacle approach showed significant main effects of group (PD patients were slower than the healthy controls) ($F_{1,31}$=16.67; p=0.001), phases (PD patients were slower in the late phase than healthy controls) ($F_{1,31}$=67.76; p<0.001) and task (both groups were slower when performing a dual task) . A main effect of visual feedback ($F_{1,62}$=61.82; p<0.001) was found and post hoc tests revealed that participants in general were slower in the Limb+Obs and Obs compared to Full vision condition. A three-way interaction between Group x visual feedback x phase for gait velocity ($F_{2,62}$=4.05; p=0.02) revealed that PD patients reduced their walking speed (i.e., greater

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deceleration in the late phase compared to early phase) more than healthy controls during their approach to the obstacle when the room was dark (Obs and Limb+Obs) (see Figure 7).

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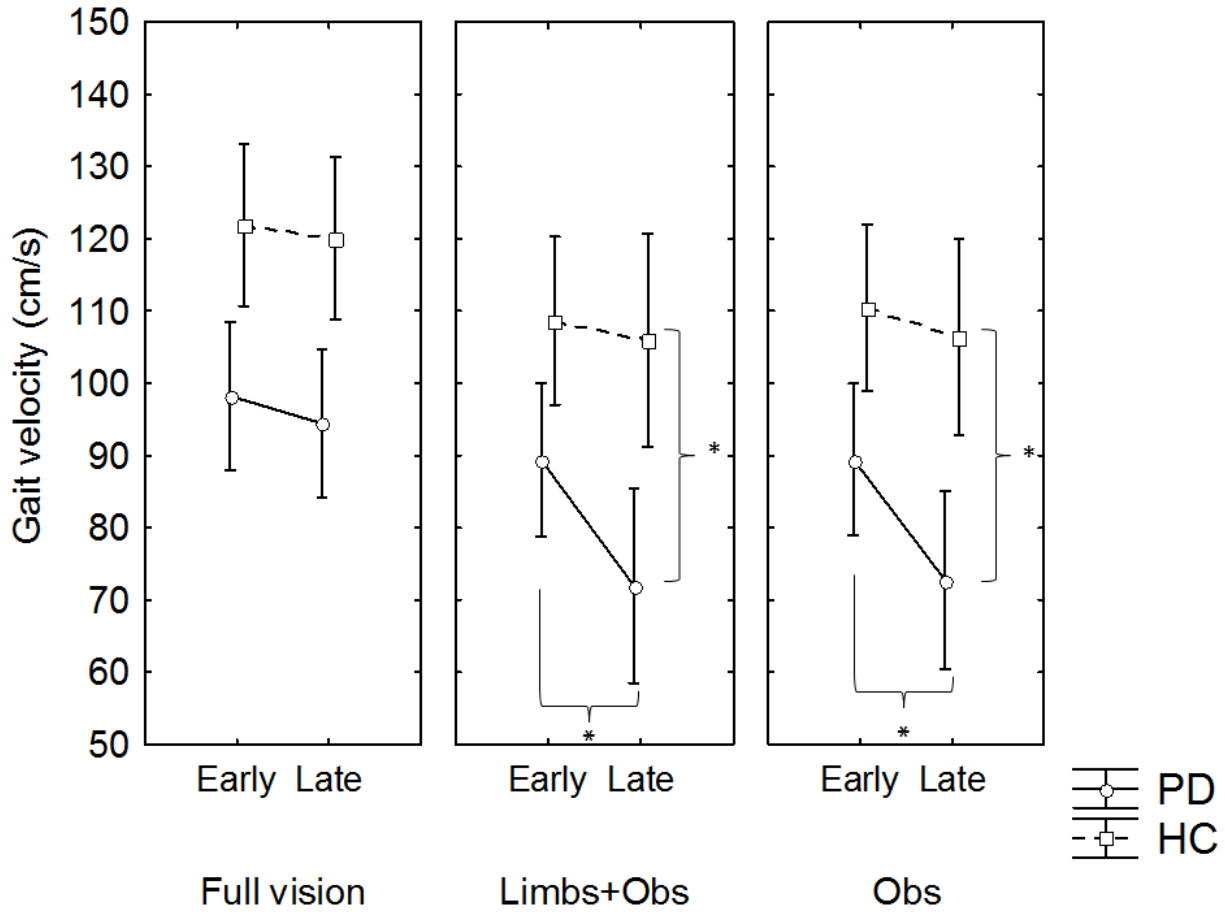

Figure 7 - Significant interactions between Phase x Vision x Group. PD patients had greater magnitude of deceleration when walking in the darkness.*p<0.05

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Step time variability

The hypothesized interactions between group, visual conditions, dual task and phase did not reach statistical significance. Main effects of group ($F_{1,31}$=5.39; p=0.021) (PD more variable than HC), and phase ($F_{1,31}$=14.14; p=0.001) (more variability in the late phase) were also found for step time variability (see Table 8). A main effect of visual feedback ($F_{1,62}$=9.52; p<0.001) was found and post hoc tests revealed that participants in general are more variable in the dark conditions compared to Full vision. As well, a three-way interaction between group, visual feedback, and phase ($F_{2,62}$=4.14; p=0.02) was identified for step time variability. Post hoc revealed that in the Obs and Limb+Obs conditions PD patients increased step time variability more so in the late phase (compared to early phase) than healthy controls, with these group differences apparent in only the late phase of their approach.

Step length variability

The hypothesized interactions between group, visual conditions, dual task and phase did not reach statistical significance. Main effects of group ($F_{1,31}$=10.07; p=0.003) (PD patients were more variable than healthy controls), and phase ($F_{1,31}$=32.52; p<0.001) (all participants were more variable in the late phase) were identified for step-length variability; however no interactions were significant. A main effect of visual feedback ($F_{2,62}$=4.10; p=0.021) was found, and post hoc tests revealed that participants in general were more variable in the Obs condition compared to Limbs+Obs but not compared to Full vision.

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Table 8- Mean and standard errors (in brackets) of gait parameters during obstacle approach in each phase. Visual conditions are collapsed in each task condition.

Groups	PHASE	Task	Gait velocity(cm/s)	Step time variability(%CV)	Step length variability(%CV)
PD	Early	No dual task	99.5(±12.6)	5.08(±0.7)	7.29(±3.4)
	Early	Dual task	87.8(±12.9)	6.33(±1.1)	5.79(±2.1)
	Late	No dual task	85.8(±15.3)	12.27(±6.2)	10.74(±3.4)
	Late	Dual task	76.2(±13.1)	13.45(±8.1)	11.13(±3.1)
HC	Early	No dual task	120.3(±13.8)	3.59(±0.8)	2.82(±3.7)
	Early	Dual task	106.9(±14.1)	3.73(±1.2)	2.92(±2.3)
	Late	No dual task	115.8(±16.8)	5.52(±6.8)	8.82(±3.7)
	Late	Dual task	105.7(±14.4)	6.10(±8.9)	8.07(±3.4)
Effects		Group	**P<0.001**	**P<0.05**	**P<0.001**
		Task	**P<0.001**	NS	NS
		Phase	**P<0.05**	**P<0.01**	**P<0.001**
		Group*task	NS	NS	NS
		Group*phase	NS	NS	NS
		Group*task*phase	NS	NS	NS

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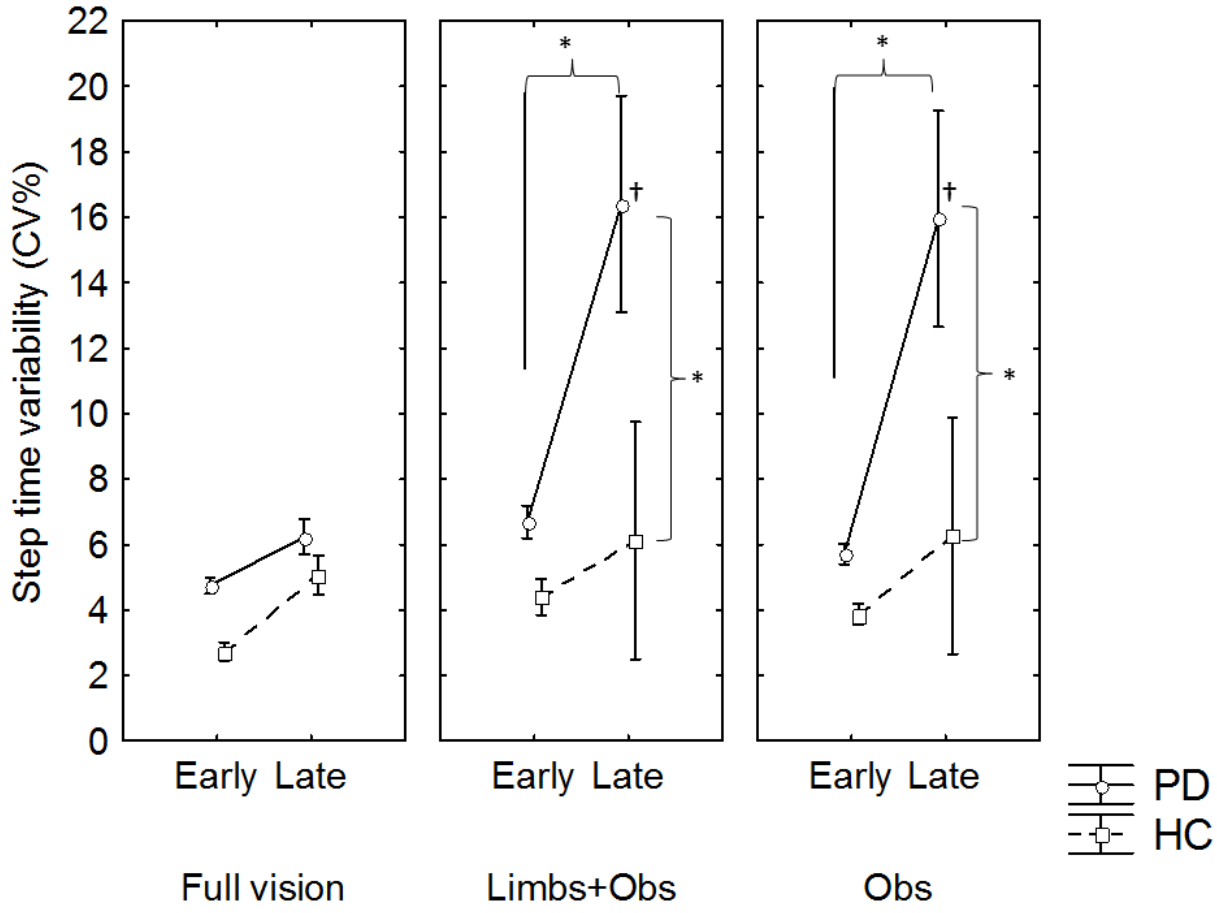

Figure 8- PD patients had an increase in step time variability when approaching the obstacle only in the dark. *p<0.05;† different from late phase in the full vision condition

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Foot clearances

Groups had similar foot-to-obstacle distances during obstacle crossing. There were no interactions between group, visual conditions, task. We found a significant interaction between visual feedback and task ($F_{2,62}$=5.62; p=0.001) for toe clearances. Post hoc revealed that lead toe clearances during Limb+Obs and Obs were larger compared to full vision, but it was shorter when performing the dual task only during Limb+Obs and Obs. A significant main effect of visual condition was found for trail horizontal distance before obstacle crossing ($F_{2,62}$=4.17; p=0.004). Post hoc revealed that all groups placed their feet farther from the obstacle during Limb+Obs and Obs conditions (see Table 8). Significant main effects of visual feedback ($F_{2, 62}$=59.34, p<0.001) and task ($F_{1, 31}$=17.94, p<0.001) were also identified for lead horizontal distances beyond obstacle. Post hoc revealed that in general during Obs and Limb+Obs and dual task conditions, participants had shorter lead horizontal distances beyond obstacle (see Table 9), compared to during full vision.

Variability of the foot clearances

The variability of foot clearances was not influenced by conditions and was similar between groups (see Table 9).

Crossing velocity

Individuals with PD crossed the obstacle slower than healthy controls in all conditions $F_{1, 31}$=5.29, p=0.02. Participants crossed the obstacle slower when performing the dual task $F_{2,}$

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$_{62}$=70.78, p<0.001. Participants also crossed the obstacle slower when walking in the dark with or without glow-in-the-dark tape attached to their lower limbs $F_{1, 31}$=7.5, p=0.01. Interactions were not significant.

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Table 9- Mean and standard errors of crossing variables (foot-to-obstacle distances) and its variability (standard deviation)

	Conditions	Trail horizontal distance before obstacle(cm)	Lead toe clearance(cm)	Lead horizontal distance beyond obstacle(cm)	Trail horizontal distance before obstacle variability(cm)	Lead toe clearance variability(cm)	Lead horizontal distance beyond obstacle variability(cm)	Crossing velocity (cm/s)
PD	Obs	30.44(±3.8)	23.86(±2.9)	35.26(±3.3)	3.64(±0.5)	1.96(±0.2)	3.55(±0.4)	440.0(±88.6)
	Obs+DT	30.41(±3.0)	23.23(±2.3)	32.72(±2.8)	4.09(±0.4)	1.92(±0.2)	3.80(±0.4)	381.1(±75.7)
	Limb+Obs	30.65(±3.4)	24.09(±2.5)	35.09(±2.8)	4.39(±0.5)	2.74(±0.3)	3.49(±0.4)	418.7(±86.7)
	Limb+Obs+DT	29.10(±2.7)	22.89(±2.3)	34.13(±2.3)	2.39(±0.5)	1.83(±0.2)	2.25(±0.3)	393.4(±73.9)
	Full vision	28.29(±3.5)	19.06(±2.3)	41.71(±2.7)	4.02(±0.4)	1.65(±0.1)	3.09(±0.4)	605.3(±79.3)
	Full vision+DT	27.29(±3.4)	18.90(±2.3)	39.63(±2.8)	3.69(±0.5)	1.92(±0.3)	3.51(±0.4)	551.4(±75.2)
HC	Obs	29.30(±4.2)	27.45(±3.2)	38.12(±3.6)	3.59(±0.5)	1.91(±0.3)	3.17(±0.5)	550.7(±97.1)
	Obs+DT	29.75(±3.3)	26.14(±2.5)	36.19(±3.0)	3.77(±0.5)	2.25(±0.2)	2.63(±0.5)	556.1(±73.0)
	Limb+Obs	29.74(±3.8)	26.02(±2.7)	37.25(±3.7)	4.07(±0.6)	1.80(±0.3)	4.49(±0.5)	582.5(±95.0)
	Limb+Obs+DT	29.42(±3.0)	25.24(±2.5)	36.75(±2.5)	3.87(±0.6)	2.48(±0.3)	3.28(±0.4)	560.5(±83.0)
	Full vision	27.67(±3.8)	21.59(±2.5)	45.36(±3.0)	3.73(±0.4)	1.68(±0.2)	3.65(±0.5)	747.6(±86.9)
	Full vision+DT	26.53(±3.8)	20.33(±2.6)	42.49(±3.1)	3.40(±0.6)	2.25(±0.3)	3.12(±0.5)	664.7(±82.4)
Effects	Group	NS	NS	NS	NS	NS	NS	**P=0.02**
	Vision	**P<0.001**	**P<0.001**	**P<0.001**	NS	NS	NS	**P<0.001**
	Task	NS	**P<0.001**	**P<0.001**	NS	NS	NS	**P=0.01**
	Group*vision	NS	NS	NS	NS	NS	NS	NS
	Group*Task	NS	NS	NS	NS	NS	NS	NS
	Vision*Task	NS	**P<0.001**	NS	NS	NS	NS	NS
	Group*vision*task	NS	NS	NS	NS	NS	NS	NS

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Obstacle contacts during obstacle crossing

Because the rate of success during obstacle crossing was not normally distributed, non-parametric tests were used to compare groups in each condition. The interaction between group, visual condition and dual task was found when running non parametric tests for the percentage of obstacle contacts. A Kruskal-Wallis ANOVA revealed that PD patients had lower rates of success compared to healthy controls participants in the Obs+DT condition (χ^2=9.71; df=1, p =0.002). Wilcoxon tests revealed a lower rate of success during obstacle crossing (more obstacle contacts) amongst PD patients during the Obs+DT condition compared to Full vision + DT (p=0.012) (Figure 9).

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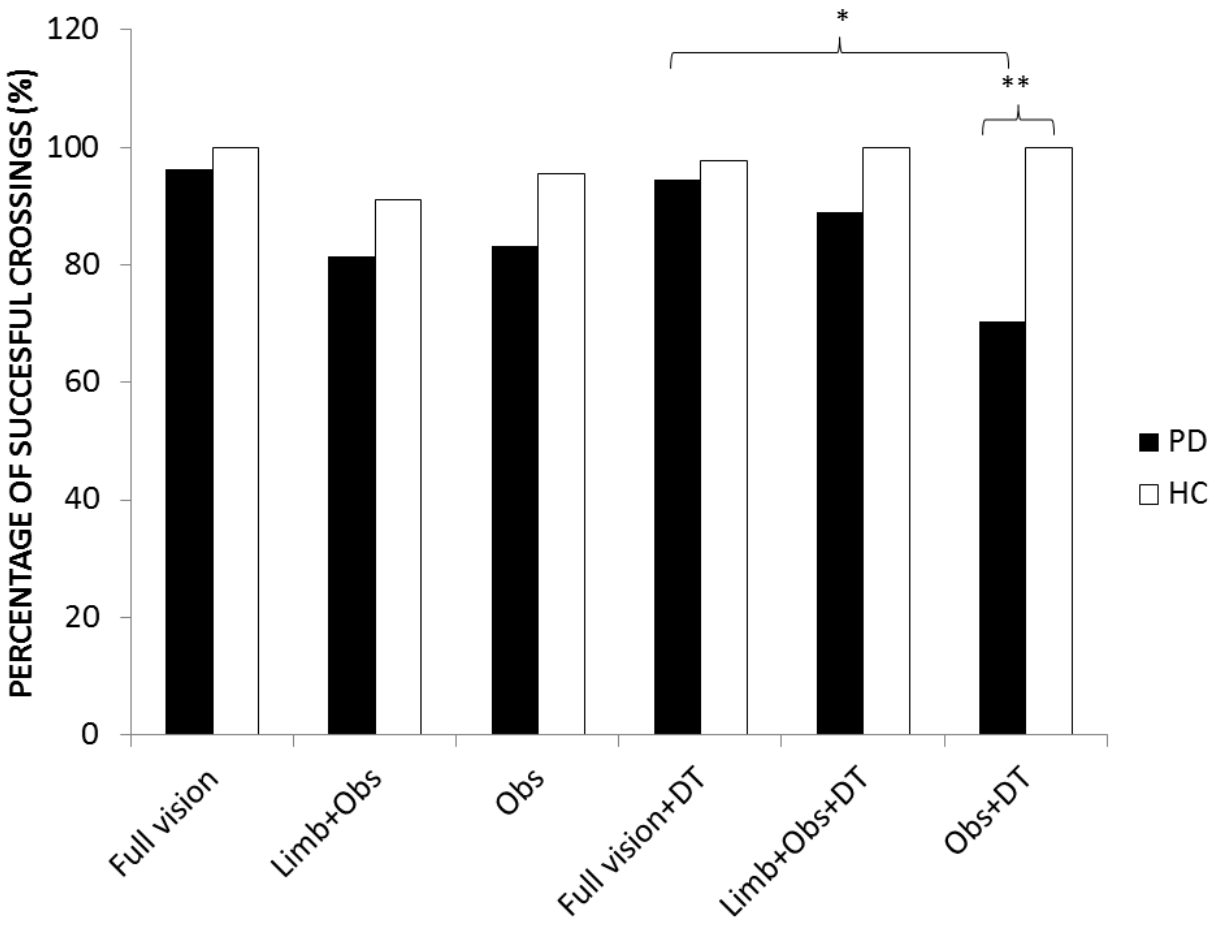

Figure 9- Bars represent the percentage of successful crossings in each condition for each group. Individuals with PD had more obstacle contacts when performing the dual task in the dark without position cues (tapes) on their limbs. *p<0.05;**p<0.01

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Table 10- Accuracy of the answers (error mean) of each group for each visual condition. Greater numbers represent worse performance. A zero score would represent an exact answer.

	BL	Obs	Limb+Obs	Full vision
PD	1.75(±0.29)	2.37(±0.29) [b]	2.29(±0.43)	2.53(±0.30)[a]
HC	1.51(±0.31)	1.64(±0.32)	1.42(±0.47)	2.00(±0.33)

Legend - BL = base line condition (performing the cognitive task sitting on a chair); [a] different from baseline $p<0.05$; [b] difference between groups $p<0.05$.

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DISCUSSION

The overall objective of this study was to investigate whether the impact of a dual task on gait (during obstacle approach and crossing) is amplified as visual feedback of self-motion is reduced in PD. While approaching an obstacle, utilization of planning resources increases as one gets closer to the obstacle. Thus, the secondary aim of this study was to evaluate whether a dual task interferes with gait, more so, in the late compared to the early phase in the reduced visual feedback conditions. It was found that when visual feedback about self-motion was reduced, individuals with PD had greater number of errors in the dual task compared to healthy control participants. Additionally, individuals with PD had a greater number of obstacle contacts specifically while walking with reduced visual feedback of self-motion and with the dual task compared to healthy control participants. Yet, the dual task influenced gait similarly in individuals with PD and healthy control participants, regardless of visual feedback manipulations. Furthermore, the dual task did not affect gait differently in the early and late phases. In summary, the dual task did not interfere with gait in either group, however, the increased number of obstacle contacts by individuals with PD, in the darkness (Obs), might suggest that the dual task interfered with planning during the late phase, when gait was most affected by reduced visual feedback; or shared resources in those with PD reducing their ability to process sensory feedback during obstacle crossing.

In this study, individuals with PD had worse performance on the cognitive task (i.e. number counting) while walking in the dark specifically when only the obstacle was visible (Obs condition) compared to healthy control participants. It is important to note that at baseline

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condition (i.e. when counting numbers seated) participants with PD performed similar to healthy participants (see table 10), highlighting that deficits in PD are specifically associated with reduction of visual feedback. This result suggests that individuals with PD may have been prioritizing the gait task when walking in the dark with reduced self-motion feedback. Prioritizing gait might be a strategy that individuals with PD employ, to allocate more resources (e.g. attention) to the processing of sensory information when critical pieces of visual information are not available. This notion that cognitive resources compensate poor sensorimotor integration has been supported by previous research that has shown that when visual feedback of self-motion is not available, elderly people allocate more attentional resources to their postural control (Meyer et al., 1991; Teasdale & Simoneau, 2001). Similar results are found in gait when proprioceptive feedback is reduced by peripheral neurological diseases (Courtemanche et al., 1996; Lajoie et al., 1996). Although dual task performance suffered, prioritization of gait likely allowed those with PD to control gait during the approach, in a similar fashion to healthy control participants. Additionally, our results are in line with recent theory, supporting the notion that individuals with PD operate in an attention-controlled mode due to an abnormal sensorimotor processing within basal ganglia loops (Redgrave et al., 2010). Hence, PD patients might be using more central resources to overcome distorted sensorimotor signals when visual feedback of self-motion is not fully available to achieve gait control.

Previous research has shown that sensory cues reduce the interference of a secondary motor task by reducing the demand on central resources (Baker et al., 2007; Rochester et al., 2007). In neither the current study, neither adding (i.e. Limb + Obs) nor reducing (i.e. Obs)

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visual feedback influenced the interference of the cognitive task on gait. This was contrary to our hypothesis and might be explained by the nature of the secondary task (e.g. carrying a tray with cups while walking) employed in these other studies. It might be the case that in previous studies, providing sensory cues may have made one of the motor tasks more automatic, however this did not directly evaluate whether sensory cues influence cognitive resources available. It is important to note that in the current study, the secondary task was purely cognitive, with the intention of understanding the demand of cognitive processing irrespective of motor interference. Therefore, based on the findings from this study, it appears that cognitive resources are used to compensate for the reduction of sensory feedback, to lessen the interference of the cognitive task and more successfully control gait in a task that involves increased postural threat.

Although foot clearance variables were not different between groups, we found that individuals with PD contacted the obstacle more frequently than healthy controls, specifically when PD participants walked with reduced self-motion visual feedback (Obs) and a dual task (Fig. 8). One possible reason for this discrepancy may be that our measure of toe clearance was based on distance from 5th metatarsal to obstacle, but did not take into account other parts of the foot (such as heel or shank of leg) that could have contacted the obstacle. This discrepancy has also been reported in a previous study that employed this same measure (Vitorio et al., 2013), and might explain why toe clearances were similar between groups while obstacle contacts were greater in those with PD. This result highlights how reduced self-motion visual feedback taxes central resources in PD. As a result of shared resources, motor planning may have been affected, resulting in greater number of obstacle contacts. Alternatively, shared

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central resources might impair one's ability to effectively process sensory feedback (Pashler, 1994) or update sensory feedback into a motor plan during obstacle crossing. Evidence from this study showed that providing additional visual feedback of lower limb position (i.e. Limb+Obs) minimized obstacle contacts, leading to similar performance as the full vision condition. This finding suggests that visual feedback of lower limb position compensates for proprioceptive impairment in PD as suggested by previous research (Jacobs & Horak, 2006; Konczak, Li, Tuite, & Poizner, 2008; Konczak et al., 2012). Importantly, when visual feedback is removed (i.e. in complete darkness) individuals with PD may allocate more attentional resources to the sampling of proprioceptive feedback, in order to compensate for the limited sensory feedback available. Increased number of errors with the dual task supports the notion that PD participants allocated more attentional resources to proprioceptive feedback while walking. However, since obstacle contacts were greater in the dark (Obs), this suggests that even with more resources being allocated to this mode of sensory feedback, PD participants were unable to fully compensate for proprioceptive deficits (Adamovich et al., 2001; Konczak et al., 2008). This finding can be further evaluated by examining the role of sensory feedback while approaching the obstacle.

A confirmation of the key role of sensory feedback especially in the late phase was demonstrated by significant deceleration (see fig 6) and increased step time variability (see fig 7) specifically in participants with PD in the late phase (but not healthy participants). This change in behaviour was only evident when individuals with PD were required to walk in the dark with reduced visual feedback (both Obs and Limb+Obs). Gait deceleration might reflect a strategy used by individuals with PD to provide more time to process incoming sensory

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information, as suggested by previous studies in elderly people (Rosano et al., 2012; Watson et al., 2010). Additionally, some researchers have suggested that increased step time variability represents difficulties to integrate sensory feedback to achieve timing control (Almeida, Frank, Roy, Patla, & Jog, 2007). Step time variability is also linked to less automatic gait control (Yogev et al., 2005), likely caused by greater dedication of resources to monitor sensorimotor processes. Therefore, it is important to consider that the late phase demands greater sensory integration to control movement just prior to crossing the obstacle, which may be why these differences are not seen in the early phase. Previous research has shown that visual feedback of body position improves gait control in PD while walking in the dark. Although the current study did not find that visual feedback of body position improved gait in the late phase, it was able to prevent obstacle contacts during the crossing phase when the cognitive load was increased. This might suggest that providing feedback about body limb position may provide partial compensation for proprioceptive deficits during more demanding gait adaptations in PD.

It is also important to acknowledge that walking in the dark could have generated anxiety in individuals with PD, since this situation may exacerbate the loss of balance in individuals with PD (Vaugoyeau, Hakam, & Azulay, 2011). Anxiety, created by postural threats, influences obstacle crossing kinematics of older adults, such as foot clearances and crossing speed (Brown et al., 2006). However, in current study, individuals with PD and healthy controls had similar crossing behaviours in the dark. Thus, it is unlikely that increased anxiety has contributed to the results in current study. Future studies could explore this issue further.

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Limitations

This study has some limitations that need to be acknowledged. The number of steps used to calculate step-to-step time variability is low compared to previous research (Yogev et al., 2005). However, variability between phases using the same number of steps for all groups was consistently compared. Other studies have also calculated step time variability from the same amount of steps (Cowie, Limousin, Peters, Hariz, & Day, 2012; Pieruccini-Faria et al., 2014). Another limitation is that it was not possible to know the performance of the secondary task in each phase. It might be possible that the performance of the secondary task in each phase changed as participants approached the obstacle. Poor performance in the secondary task would also indicate that the demand for central resources (e.g. cognitive processes, attention) during obstacle approach increased.

CONCLUSION

The current study sheds light on the importance of central resources for sensorimotor processing when individuals with PD are planning and controlling gait during obstacle avoidance. Visual feedback about self-motion reduces the demand on cognitive resources, however, this does not fully compensate for proprioceptive deficits that could be the reason of abnormal sensorimotor processing in PD. Increased demand in sensorimotor and cognitive processing during gait may increase the chances of trips and falls among individuals with PD. In sum, impaired gait adaptability in PD patients may be resultant from interactions between

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sensory and cognitive processing. From a clinical point of view, gait therapy programs for individuals with PD should include visual feedback and cognitive load manipulations to improve their safety and gait adaptability.

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CHAPTER 4 - EYE TRACKING TO UNDERSTAND MOVEMENT PLANNING IN PARKINSON'S DISEASE: DOPAMINE DEPENDENT SHARING OF COGNITIVE & SENSORY RESOURCES?

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Submitted to *Brain*

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ABSTRACT

Attention and sensorimotor integration are critical to successful adaptation of footsteps during complex gait situations, such as when individuals attempt to avoid obstacles. Increased cognitive load caused by allocation of resources for online planning during obstacle approach may exacerbate gait deficits of individuals with PD. However, little is understood about the dopaminergic contribution to central resources required to plan and control gait adjustments in PD. It is also unknown how individuals with PD use vision to optimize use of central resources while planning foot clearances. Patients simultaneously approached an obstacle to be stepped over while performing an auditory digit monitoring dual task. These tests were completed in both the ON and OFF dopaminergic medication states, and compared to age matched healthy controls. Dual task performance was used to understand if gait disturbances were associated with cognitive load. Gait and eye movements while approaching the obstacle were also recorded in order to investigate differences in visual strategies employed to avoid an obstacle. In order to investigate how motor planning demands affect gait during obstacle approach; steps prior obstacle crossing were split into two halves: early phase (steps while far away from obstacle) and late phase (steps when closest to obstacle). Results showed that PD OFF had a more abrupt deceleration in gait velocity, between early to late phases, which was ameliorated after dopaminergic medication intake. Dual task affected gait (specifically step time variability) in PD OFF, only during the late phase, when compared to healthy controls, however dopaminergic replacement did not decrease the dual task interference on gait control in the late phase. Visual strategies were similar between groups and medication conditions. In sum, deficits in dopamine dependent sensorimotor integration exacerbate gait disturbances in PD when online movement planning is required to avoid an obstacle.

Keywords: Dopaminergic system; Gait control; Obstacle; Motor planning; Visual strategies; Gaze behaviour

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INTRODUCTION

Individuals with Parkinson's disease (PD) exhibit poorer movement control when performing multiple tasks simultaneously. Dual tasks (walking while performing a secondary task) affect gait in PD patients more than healthy individuals (Baker et al., 2007; Bond & Morris, 2000; Brauer, Morris, Woollacott, & Lamont, 2009; Brauer et al., 2011; O'Shea et al., 2002; Plotnik, Dagan, Gurevich, Giladi, & Hausdorff, 2011; Plotnik, Giladi, & Hausdorff, 2009; Rochester et al., 2008; Wild et al., 2013; Yogev et al., 2005), suggesting that gait and secondary cognitive tasks may compete for the same central resources, leading to compromised performance of one or both tasks. In order to maintain some level of stability during gait, PD allocate more resources to walking than healthy people, and therefore, less resources are available for secondary tasks or even both tasks (O'Shea et al., 2002; Yogev et al., 2005). Overall, when PD patients allocate resources to secondary tasks, gait disturbances are exacerbated. Specifically, the dual tasks lead to slower gait velocity and increased step-to-step time variability in PD, more than in healthy participants. Although the impact of dual tasking on self-paced gait in PD patients is relatively well understood, little research has been conducted to investigate the effects of dual task performance during obstacle avoidance. To some extent, walking while planning gait adaptations could be argued to be a dual task in itself, since central resources are necessary to plan safe clearance (Brown, McKenzie, & Doan, 2005; McIsaac, Diermayr, & Albert, 2012; Spiegel, Koester, Weigelt, & Schack, 2012). Therefore, using a dual task would help to understand when gait is most affected by an overload in central resources provoked by the planning of foot clearances in PD.

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Interestingly, a recent study (Pieruccini-Faria et al., 2014) showed that only PD patients with severe gait impairments (Freezers) increased step-to-step variability and obstacle contacts, with a secondary cognitive task. However, PD patients with less gait impairments, but with the same disease severity, were not affected by the secondary task. One possible reason for the absence of dual task interference might be that PD patients were only tested in their "ON" medication state. Gait disturbances, such as slowness, in PD are exacerbated when patients attempt to perform tasks that demand greater resources, especially during "OFF" medication state (Lord, Rochester, Hetherington, Allcock, & Burn, 2010; Pieruccini-Faria et al., 2013). Lewis and colleagues (2004; 2005) proposed that dopaminergic replacement normalizes resource capacity of PD patients, which may be important in improving dual task performance. In addition, according to these authors, reduced dopaminergic "reserve" restricts the performance of tasks with increased cognitive and sensory processing demands. Additionally impaired motor output, such as slowness, caused by basal ganglia dysfunction can be exacerbated by the additional demands of cognitive performance and sensorimotor integration during complex goal-oriented tasks (Redgrave et al., 2010).Interestingly, PD patients can use visual strategies during goal-oriented tasks involving either upper limb and whole body displacement, to prevent an overload in central resources in which motor performance would consequently be affected (Galna et al., 2012; Ketcham, Hodgson, Kennard, & Stelmach, 2003). Therefore, further research is needed to understand the role of dopaminergic replacement therapy and visual strategies of PD patients while approaching an obstacle with dual task interference.

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While approaching obstacles, gait modifications to avoid a contact starts three steps prior to obstacle crossing in young, older and individuals with PD (Berg & Murdock, 2011; Berg, Wade, & Greer, 1994a; Bradshaw & Sparrow, 2001). These gait modifications, while approaching an obstacle, suggest that individuals are using increased conscious control or planning to regulate their footsteps in relation to the obstacle. Additionally, gaze fixations are used to update body-obstacle displacement which is important to maintain the accuracy of the motor plan (Patla & Greig, 2006; Patla & Vickers, 1997). Only one study has demonstrated, using a strobe effect, that PD patients might need increased visual sampling than healthy participants to cross the obstacle successfully (Vitorio et al., 2013). However, it remains unclear whether PD patients and healthy participants used different visual strategies to plan obstacle crossing.

The primary aim of this study was to investigate the impact of a dual task on gait in individuals with PD while they approached and crossed an obstacle, both "ON" and "OFF" their dopaminergic medication. We expected that dopaminergic withdrawal would magnify the effects of the dual task on gait in individuals with PD. Specifically, the dual task would affect gait in the steps closer to an obstacle, when individuals are planning foot clearances. The second objective was to understand the visual strategy employed by participants to extract visual information regarding the location of the obstacle by tracking their eye movements. We also measured the magnitude of the head tilt to infer the contribution of the lower visual field to the planning of step adjustments. It was expected that PD patients and healthy controls use different visual strategies to prevent a cognitive overload that would affect gait control and the

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planning of foot clearances. To our knowledge, this is the first study to evaluate gaze strategies during obstacle avoidance in PD.

MATERIAL AND METHODS

Participants

Twenty people with PD and 19 healthy control participants (HC) were recruited (see Table 11). PD patients were excluded from the sample if they could not walk independently, had musculoskeletal problems, wore bifocal lenses, cataract, dementia, or other neurological or cardiac diseases. PD participants were tested on two separate days (a week apart), once in their OFF state (after a period of at least 12 hour withdrawal from their regular dopaminergic medication) and once in their ON state (approximately one hour after taking their regular dopaminergic dose). Half of the participants with PD were initially tested while in their OFF state, while the other half were initially tested during ON state. Participants who had side effects from their medication such as severe dyskinesia and dystonia were excluded from our sample. This research project was approved by the Wilfrid Laurier University Research Ethics Board. Written informed consent was obtained from all subjects prior to the experiment according to the Declaration of Helsinki.

Clinical and cognitive assessments

Motor symptom severity was assessed using the UPDRS-III (motor section) (Goetz et al., 2007) prior to data collection. Neuropsychological assessments were performed only when PD patients were in their OFF medication state. Participants' general cognitive status was assessed

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using the modified Mini-mental 3MS exam (Teng & Chui, 1987). Visual scanning and executive function (set-shifting and cognitive flexibility) were assessed using the Trail Making Test, parts A and B, respectively (Fitzhugh, Fitzhugh, & Reitan, 1962). Participants were instructed to perform this test as fast and accurately as possible. The cognitive component of this test was calculated by subtracting part A from part B. The digit span test (forward and backward; Blackburn & Benton, 1957) was administered in order to quantify the working memory /attention capacity of our participants.

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Table 11– Demographics and neuropsychological measures (means and standard deviations).

Groups	Age (years)	Height (cm)	3MS	Digit span	TMT A (seconds)	TMT B (seconds)	TMT B-A (seconds)	UPDRS-III ON	UPDRS-III OFF
PD (16M/4F)	69.7 (±9.3)	171 (±8)	96.7 (±4.4)	18.1 (±3.4)	33.1 (±9)	122.2 (±112)	89.1 (±106)	22.65 (±9)‡	31.9 (±7)
HC (11M/8F)	69.3 (±8.9)	168 (±9)	97.8 (±1.8)	17.3 (±2.7)	29.1 (±6)	71.0 (±26)	41.9 (±26)	NA	NA

Neuropsychological assessments were performed when PD patients were OFF state. ‡ Motor symptoms significantly improved after medication intake. P<0.01.

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Dual task protocol

The secondary cognitive task involved attending to an audio track while walking. This secondary task was chosen because there was no motor component involved, allowing us to eliminate the possibility that the secondary task caused motor interference (motor output overload) on the gait task (Pieruccini-Faria et al., 2014). Participants were instructed to mentally count the number of times they heard two different digits, assigned by the experimenter at the beginning of each trial, spoken by a female voice in the audio track. The audio track produced numbers ranging from 1 to 9. The order of presentation of each digit in the audio track was randomized across the trials using the software Experiment Builder (SR Research Ltd., Kanata, ON, Canada). The auditory interstimulus interval was also randomized to prevent gait synchronization such that the inter-stimulus interval of presentation of each digit could vary from 100 ms to 1000 ms; and each digit lasted 500ms. The audio track played for 12 seconds and was initiated when a synchronized light signaled participants to begin walking. At the end of each trial, participants reported the number of times they heard the target digits. Participants were asked to equally prioritize the gait and the digit counting task. The volume of the loudspeakers was adjusted so that participants could comfortably hear the digits at the start and end position of the walkway. Feedback about their performance was not provided. The baseline condition (BL) involved participants sitting on a chair monitoring the digits from the audio track prior to the gait trials. The digit monitoring performance was calculated using the formula: $\text{Performance} = |\text{Given answer} - \text{Correct answer}|$

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Gait protocol and data collection

Participants walked and stepped over the obstacle at their own pace. Participants performed a total of six randomized trials (three with dual task and three without the dual task). Data collection was performed in a well lit room completely isolated from sunlight (room dimensions 20 m length x 10 m width). The data capture area permitted the analysis of the last eight steps prior to obstacle crossing, however, to remove gait characteristics associated with gait initiation, only the last 6 steps performed by each participant were analysed. These six steps were divided into two sets of three steps each (an early and a late phase prior to the obstacle). The steps were split into two phases since previous studies have revealed that gait modifications associated with planning begin during the last three steps before stepping over an obstacle (Berg, Wade, & Greer, 1994; Bradshaw & Sparrow, 2001). Gait speed was calculated, based on the average step velocity of the three steps in each phase. Step-to-step variability (time and length) was calculated using the coefficient of variation (CV) of steps in each phase ((SD/mean)*100). Foot clearances were calculated by subtracting the vertical position of the 5th metatarsal marker on each foot from the obstacle height, during the frame or instant when the foot was directly over top of the obstacle (i.e., the crossing point). Lead limb position before and after the obstacle was captured using the horizontal distance between the foot and the obstacle, subtracting the positions of the marker of the 5th metatarsal on each foot, from the obstacle position in the sagittal plane.

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Data recording for kinematic analysis

On each trial, participants walked at a comfortable pace on a gray carpet and stepped over an obstacle. The obstacle was a bar made of white foam covered with thick white paper (70 cm width x 4 cm height x 1.5 cm depth; weight = 50 g) and supported by two lateral plastic poles that were 30 cm in height. The obstacle height was set at 15% of the participant's height (~25 cm), and positioned ~6.5 m from the starting point.

Participants' movements were tracked (over 10m) by seven synchronized Optotrak® cameras (Northern Digital, NDI, Waterloo, Ontario). Active IREDs (infrared light emitting diodes) were fixed to the following anatomical regions: lateral malleolus and 5th metatarsal on each foot. Heel contacts and toe offs were defined using a validated method described by (O'Connor, Thorpe, O'Malley, & Vaughan, 2007) allowing us to calculate gait parameters during the approach and crossing phases. All kinematic data were filtered using a 2nd order Butterworth filter with a cut-off frequency of 6 Hz using a dual-pass filter with zero lag delay. Kinematic variables were calculated using an algorithm created in Matlab 7.0 (The Maths Works Inc; Natick, Massachusetts).

Gaze analysis

Eye movements were recorded using a wireless eye tracker (Mobile Eye ASL - Applied Science Laboratories, Bedford, MA, USA) with a sample frequency of 30 Hz and calibrated using the 9-point calibration method with 1° accuracy over the obstacle area. Gaze data were analyzed using Results Plus GM™ software (ASL - Applied Science Laboratories, Bedford, MA, USA). There was only one defined area of interest (obstacle). A fixation was counted when the

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participants' gaze remained inside this area of interest for at least 100 ms. Kinematic and gaze data were synchronized offline using an external trigger (light-emitting diode (LED) lamp). This light was positioned in participants' right lower visual field (45 degrees) at the start position. Participants were asked to fixate their gaze on the lamp and start walking only when the lamp's LED was turned on.

Head pitch angle

Head pitch angle was only analyzed for 9 HC and 17 PD patients (ON and OFF) because we only identified this variable would provide important information about the participants' visual behaviour during this task after running a subset of the participants. The head's rotation angle in the sagittal plan (head pitch angle) was calculated using two markers (5 cm apart from each other) that were attached laterally to participants' head (eye-level) and vertically to the eye-tracker's goggles' frame. Head pitch was calculated as the angle between a vertical line (parallel to the vertical axis)(Marigold & Patla, 2008). The average and the maximum head pitch angle were calculated for each step. The average of the head pitch for each phase was the average of the angle of the three steps in each phase. Larger positive angles represent greater head rotation downwards.

Statistical analyses

In order to examine the effects of medication (OFF vs ON), approach phase (Early vs Late), task (Dual task vs No dual task) and trial (3 trials) on our dependent variables during obstacle approach, a two-way mixed repeated measures analysis of variance (RM-ANOVA) [Medication (OFF vs ON) x Phases (Early vs Late) x Task (Dual task vs No dual task) x Trial (3

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trials)] was used. In order to investigate the effects of medication and task on foot clearances another two-way mixed RM-ANOVA [Medication (OFF vs ON) x Task (Dual task vs No dual task) x Trial (3 trials)] was run.

In order to examine the effects of group (PD OFF vs HC; PD ON vs HC), approach phase and task, two mixed RM-ANOVAS were conducted [Group (PD vs HC) x Phase (Early vs Late) x Task (Dual task vs No dual task) x Trial (3 trials)]. Effects of group and task on foot clearances were analyzed in a separate two-way mixed RM-ANOVA [Group (PD vs HC) x Task (Dual task vs No dual task) x Trial (3 trials)]. The comparisons between PD OFF and HC helped to understand the effects of PD. The comparison between PD ON vs HC was used to understand if the dopaminergic medication helped to normalize behaviours in PD relative to HC when dopaminergic replacement effects (PD OFF vs PD ON) were not significant.

Tukey's post hoc comparisons were conducted when appropriate. Independent sample *t*-tests were conducted to compare neuropsychological and clinical tests between groups. The non-parametric test Kruskal-Wallis was used to compare the accuracy of auditory digit monitoring task (secondary task) between groups in each condition. Pearson's correlations were performed between neuropsychological tests, motor severity and with dependent variables that were different between groups or when interactions involving groups and conditions were found. Differences were accepted when p values were ≤0.050. All statistical analyses were run in STATISTICA 8.0.

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RESULTS

Neuropsychological and clinical tests

The groups had similar ages and similar performance on neuropsychological tests (see Table 11), although patients with PD showed marginally reduced executive functioning/cognitive flexibility as indicated by the TMT B-A (p=0.06). T-tests for independent samples revealed improvement of motor symptoms (UPDRS-III scores) after medication intake (t_{19}=7.12, p<0.001

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Table 12 - Results from RM ANOVAS for gait variables during obstacle approach

GAIT VELOCITY	PD OFF X HC			PD ON X HC				PD OFF x PD ON		
	df	F	P	df	F	P		df	F	P
Group	1	15.5	**.0001**	1	1.3	0.262	Med	1	65.21	**.0001**
Phase	1	145.8	**.0001**	1	37.3	**.0001**	Phase	1	97.24	**.0001**
Task	1	22.3	**.0001**	1	25.11	**.0001**	Task	1	10.81	**.004**
Group x Phase	1	45.4	**.0001**	1	0.27	0.607	Med x Phase	1	59.2	**.0001**
Group x task	1	0.1	0.824	1	0.26	0.615	Med x Task	1	0.02	0.9
Group x Phase x Task	1	0.4	0.516	1	0.04	0.841	Med x Phase x Task	1	0.57	0.46
Phase x Task	1	3.7	0.062	1	2.2	0.146	Phase x Task	1	4.74	**.043**

STEP LENGTH VARIABILITY	PD OFF X HC			PD ON X HC				PD OFF x PD ON		
	df	F	P	df	F	P		df	F	P
Group	1	0.75	0.392	1	0.94	0.338	Med	1	0.01	0.906
Phase	1	28.45	**.0001**	1	24.36	**.0001**	Phase	1	12.42	**.002**
Task	1	0.26	0.611	1	0.37	0.546	Task	1	1.19	0.289
Group x Phase	1	0.07	0.795	1	0.16	0.69	Med x Phase	1	1.28	0.273
Group x task	1	0.79	0.379	1	0.83	0.369	Med x Task	1	0.08	0.776
Group x Phase x Task	1	0.08	0.775	1	0.54	0.466	Med x Phase x Task	1	0.32	0.578
Phase x Task	1	0.1	0.754	1	0.58	0.451	Phase x Task	1	0.69	0.415

STEP TIME VARIABILITY	PD OFF X HC			PD ON X HC				PD OFF x PD ON		
	df	F	P	df	F	P		df	F	P
Group	1	2.49	0.123	1	1.8	0.188	Med	1	0.888	0.358
Phase	1	13.29	**.001**	1	19.63	**.0001**	Phase	1	7.883	**.012**
Task	1	2.18	0.148	1	2.06	0.16	Task	1	5.555	**.030**
Group x Phase	1	0.61	0.44	1	0.05	0.832	Med x Phase	1	0.827	0.375

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Group x task	1	4.07	0.051	1	3.94	0.055	Med x Task	1	0.041	0.842
Group x Phase x Task	1	0	0.949†	1	3.43	0.072	Med x Phase x Task	1	3.467	0.079
Phase x Task	1	0.91	0.347	1	7.09	**.011**	Phase x Task	1	5.394	**.032**

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Self-paced gait characteristics

Gait velocity and step length significantly improved with dopaminergic medication ($p<0.01$). The PD ON participants had significantly shorter steps, $F_{1, 37}=5.13$, $p=.029$ (59.7 cm ±2.5; 67.1 cm ±2.6), and a significantly slower walking speed compared to the HC participants, $F_{1, 37}=7.40$, $p=0.009$ (105.0 cm/s ±5.3 ; 125.4 cm/s ±5.2).

Gait velocity during obstacle approach (PD OFF vs HC / PD ON vs HC)

An interaction between group (PD OFF vs HC) and phase, $F_{1, 37}=45.42$, $p<0.001$, was identified, and post hoc tests revealed that the PD OFF participants walked slower than the HC participants in the late phase, but not in the early phase (see Figure 10). Main effects of phase, $F_{1, 37}=145.83$, $p<0.001$, and task, $F_{1, 37}=22.32$, $p<0.001$, showed that participants walked slower in the late phase compared to the early phase; and slower during the dual task conditions.

When the PD ON participants and the HC participants were compared interactions were not significant, although main effects of phase ($p<0.001$) and task ($p<0.001$) were found. All participants walked slower in the late phase compared to the early phase, and slower when performing the secondary task (see Figure 10).

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Step time variability during obstacle approach (PD OFF vs HC / PD ON vs HC)

A four-way interaction between phase, task, group, and trial, $F_{2, 74}$=3.49, p=0.035, showed that step-to-step time variability in PD OFF participants during the late phase was greater than that observed for the HC participants when performing the secondary task (see Figure 10). This effect was found only in the first trial.

The interaction between group, task and phase was not statistically significant when PD ON was compared with HC (see Table 12). The interaction between task and group was marginally significant (p=0.055). An interaction between phase and task revealed that the dual task increased step time variability only during the late phase for all participants, $F_{1, 36}$=7.09, p=0.011.

Step length variability during obstacle approach (PD OFF vs HC / PD ON vs HC)

When the PD OFF participants and the HC participants were compared, a main effect of phase was found for step length variability, $F_{1, 37}$ = 28.44, p<0.001. This main effect revealed that participants walked with greater step length variability in the late phase compared to early phase.

Comparisons between PD ON participants and the HC participants also revealed a main effect of phase, $F_{1, 36}$=24.36, p<0.001, revealing increased step length variability in the late phase compared to early.

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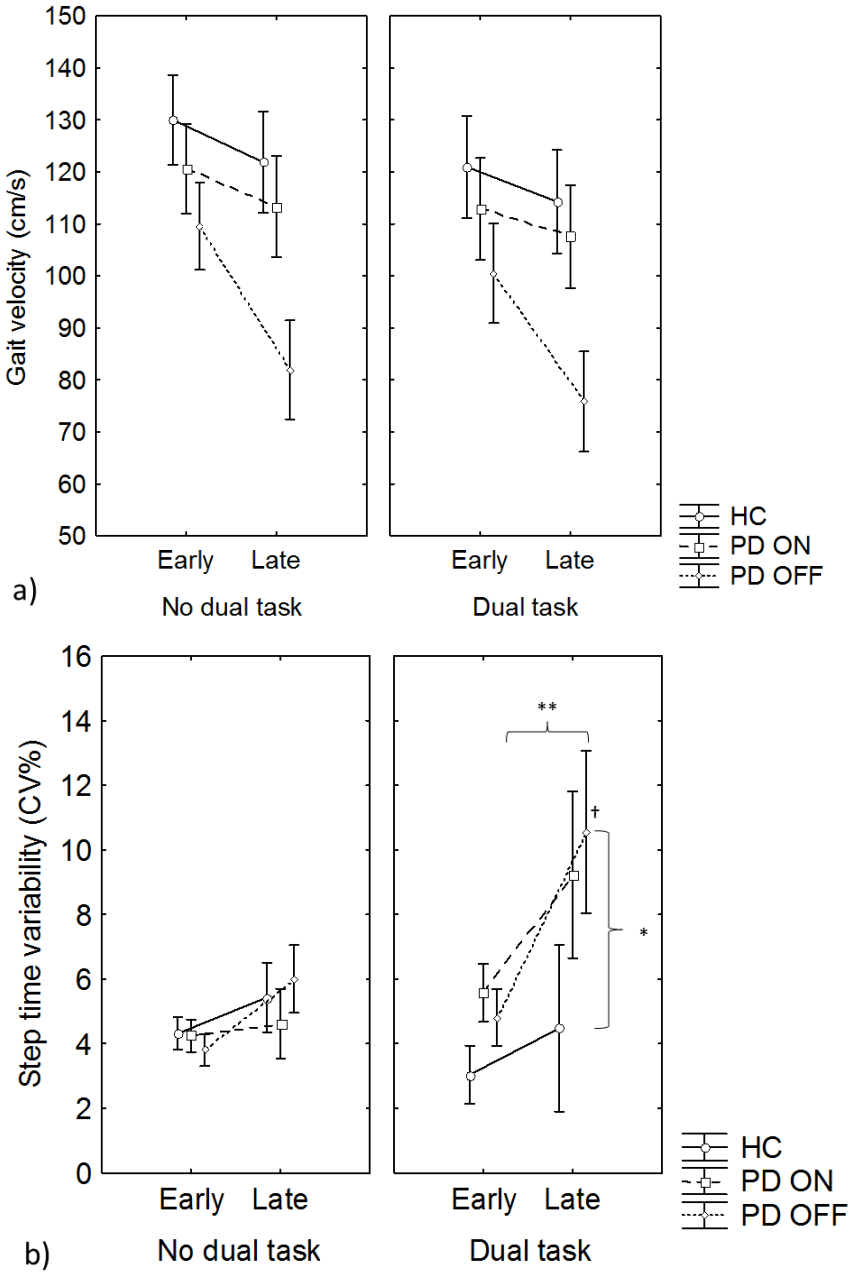

Figure 10a,b – a) Interactions between Phase x Medication; b) Interaction between Phase x Medication x Dual task x Trial (PD OFF and HC comparisons only). Step time variability of PD OFF is higher than healthy controls in the late phase when performing the dual task only in the first trial.

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Medication effects on gait during obstacle approach (PD ON vs PD OFF)

Foot clearances (mean and standard errors) are shown on Table 13. A significant interaction between medication and phase for walking speed, $F_{1, 18}$=59.20, p<0.001, revealed that the PD OFF participants had greater magnitude of deceleration from the early to late phase compared to when they were medicated (see Figure 10). Post hoc tests revealed that walking velocity of the PD OFF and PD ON was slower in the late compared to the early phase. PD OFF walked slower in both phases compared to PD ON. There was no main effect of medication for step time variability, $F_{1, 18}$=0.88, p=0.35. A significant interaction between phase and task, $F_{1, 18}$=5.39, p=0.032, was also found and post hoc tests revealed that patients with PD had greater step time variability in the late phase of the approach compared to the early phase, but only when the patients with PD performed the secondary task. A main effect of phase was found for step length variability, $F_{1, 18}$=12.41, p=0.002 showing that step length variability was higher in the late phase, compared to the early phase.

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Table 13 – Means and standard errors of foot clearances during ON and OFF medication states and task conditions.

GROUP	Task condition	Trail horizontal distance before obstacle(cm)	Lead toe clearance(cm)	Lead horizontal distance beyond obstacle(cm)	Trail toe clearance(cm)	Trail horizontal distance before obstacle variability(cm)	Lead toe clearance variability(cm)	Lead horizontal distance beyond obstacle variability(cm)	Trail toe clearance variability (cm)
HC	No dual task	30.35(2.6)	17.27(1.8)	41.82(3.3)	27.7(2.8)	2.9(0.4)	2.0(0.2)	2.4(0.3)	3.4(0.4)
HC	dual task	29.61(2.6)	16.81(1.8)	40.71(3.5)	25.9(2.7)	3.4(0.5)	1.9(0.2)	3.2(0.5)	3.1(0.4)
PD ON	No dual task	30.69(2.6)	15.2(1.8)	44.34(3.3)	24.9(3.5)	2.3(0.4)	1.5(0.2)	2.0(0.3)	3.5(0.4)
PD ON	dual task	29.89(2.6)	14.9(1.8)	41.25(3.5)	24.2(3.1)	2.5(0.5)	1.6(0.2)	3.1(0.5)	2.6(0.4)
PD OFF	No dual task	32.42(2.6)	15.6(1.8)	38.8(3.2)	23.0(2.3)	3.5(0.4)	1.3(0.2)	2.2(0.3)	3.4(0.4)
PD OFF	dual task	31.2(2.6)	15.1(1.7)	38.9(3.4)	23.5(2.5)	3.3(0.5)	1.8(0.2)	2.8(0.5)	3.6(0.4)

Main effects and interactions are reported in table 14. There were no main effects or interactions foot clearances variability.

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Table 14- Results from RM ANOVA for crossing variables.

Trail horizontal distance prior obstacle	PD OFF X HC			PD ON X HC				PD OFF x PD ON		
	df	F	P	df	F	P		df	F	P
Group	1	0.763	0.388	1	0.017	0.896	Med	1	4.395	0.051
Task	1	2.482	0.124	1	1.469	0.233	Task	1	1.524	0.233
Group x Task	1	0.172	0.68	1	0.008	0.928	Med x Task	1	0.016	0.9
Lead toe clearance	**PD OFF X HC**			**PD ON X HC**				**PD OFF x PD ON**		
	df	F	P	df	F	P		df	F	P
Group	1	1.231	0.274	1	1.779	0.191	Med	1	0.56	0.464
Task	1	1.402	0.244	1	1.201	0.28	Task	1	0.522	0.479
Group x Task	1	0.001	0.971	1	0.016	0.899	Med x Task	1	0.007	0.935
Trail toe clearance	**PD OFF X HC**			**PD ON X HC**				**PD OFF x PD ON**		
	df	F	P	df	F	P		df	F	P
Group	1	3.6	0.06	1	1.2	0.27	Med	1	1.28	0.27
Task	1	3.1	0.08	1	3.1	0.08	Task	1	0.12	0.72
Group x Task	1	2.4	0.12	1	0.78	0.38	Med x Task	1	0.6	0.44
Lead horizontal distance beyond obstacle	**PD OFF X HC**			**PD ON X HC**				**PD OFF x PD ON**		
	df	F	P	df	F	P		df	F	P
Group	1	0.867	0.358	1	0.349	0.558	Med	1	10.15	**.005**
Task	1	0.555	0.461	1	7.852	**.008**	Task	1	3.56	0.075
Group x Task	1	0.629	0.433	1	1.698	0.201	Med x Task	1	6.87	**.017**

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Table 15- Results from RM ANOVA for gaze variables.

Fixations (%)	PD OFF X HC			PD ON X HC				PD OFF x PD ON		
	df	F	P	df	F	P		df	F	P
Group	1	0	0.971	1	1.43	0.239	Med	1	3.29	0.086
Phase	1	7.09	**.012**	1	13.61	**.001**	Phase	1	3.25	0.087
Task	1	19.99	**.0001**	1	49.03	**.0001**	Task	1	57.67	**.0001**
Group x Phase	1	1.72	0.198	1	0.14	0.715	Med x Phase	1	2.33	0.143
Group x Task	1	0	0.968	1	2.48	0.124	Med x Task	1	1.81	0.194
Group x Phase x Task	1	1.48	0.232	1	1.13	0.295	Med x Phase x Task	1	0.03	0.859
Phase x Task	1	0.53	0.473	1	0.33	0.57	Phase x Task	1	5.78	**.027***

Total fixation duration(%)	PD OFF X HC			PD ON X HC				PD OFF x PD ON		
	df	F	P	df	F	P		df	F	P
Group	1	0.1	0.755	1	2.26	0.141	Med	1	3.09	0.095
Phase	1	5.92	**.020**	1	10.81	**.002**	Phase	1	2.34	0.142
Task	1	23.11	**.0001**	1	48.74	**.0001**	Task	1	63.93	**.0001**
Group x Phase	1	1.62	0.211	1	0.3	0.589	Med x Phase	1	1.28	0.272
Group x Task	1	0.04	0.838	1	1.8	0.188	Med x Task	1	1.92	0.182
Group x Phase x Task	1	0.52	0.475	1	1.03	0.318	Med x Phase x Task	1	0.13	0.721
Phase x Task	1	0.01	0.927	1	0.15	0.702	Phase x Task	1	2	0.173

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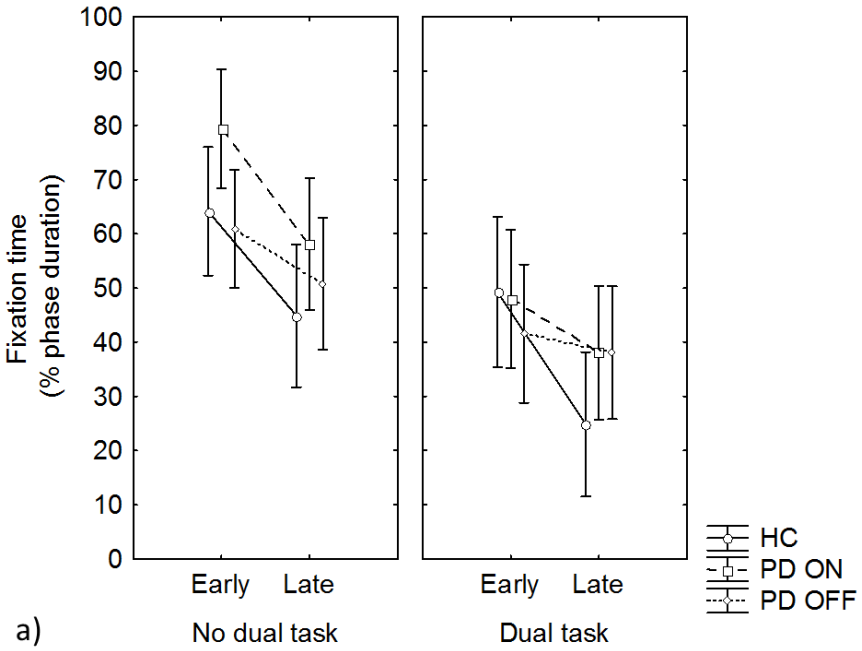

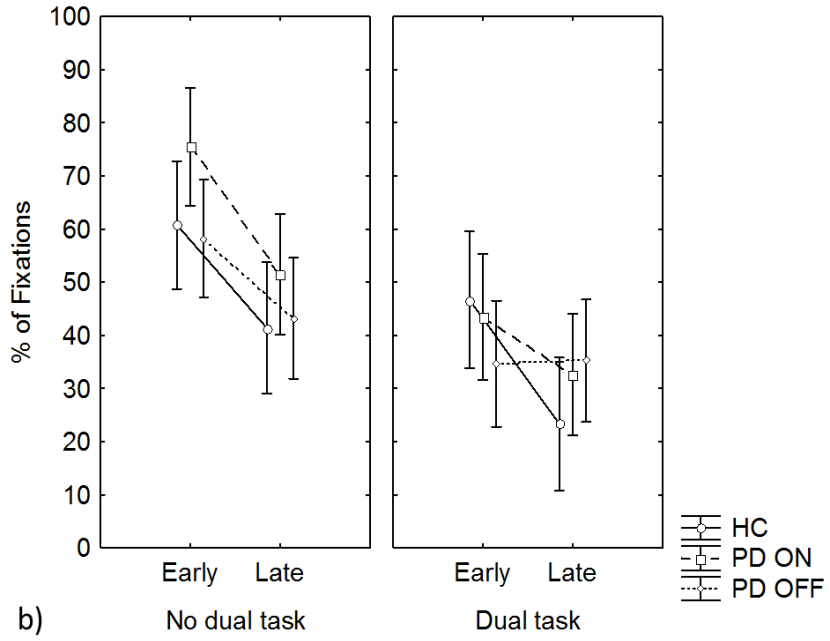

Figure 11a,b – Only a main effect of dual task and phase were found for fixation time (a) and number of fixations (b).

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Gaze behaviour

Patients with PD and the HC patients had similar fixation durations and number of fixations. Both groups of participants fixated longer and more frequently on the obstacle during the early phase compared to the late phase (see Figure 11). Interactions involving groups, task and phase were not significant.

Head pitch

When PD OFF and HC were compared main effects of group, $F_{1, 24}$=5.27, p=0.030, and phase, $F_{1, 24}$=30.82, p<0.001, were found. PD OFF had larger head pitch angles than HC. During the late phase, participants walked with larger head pitch angles compared to early phase. An interaction between phase and group, $F_{1, 24}$=12.83, p=0.001, revealed that PD OFF made larger downwards head movements in the late phase compared to HC who had similar head tilt angles in both approaching phases.

When PD ON and HC were compared, a three-way interaction, $F_{1, 24}$=9.78, p=0.004, between group, phase and dual task revealed that PD ON reduced their downward head movement in the late phase when performing the dual task compared to no dual task conditions just in the late phase. On the other hand, HC had larger head tilt angles during the late phase when performing the dual task compared to late phase when they were not performing the dual task. All main effects and interactions found for Mean Head Pitch were also found for Maximum Head Pitch, hence the results of Maximum Head Pitch are only reported graphically (see Figure 12).

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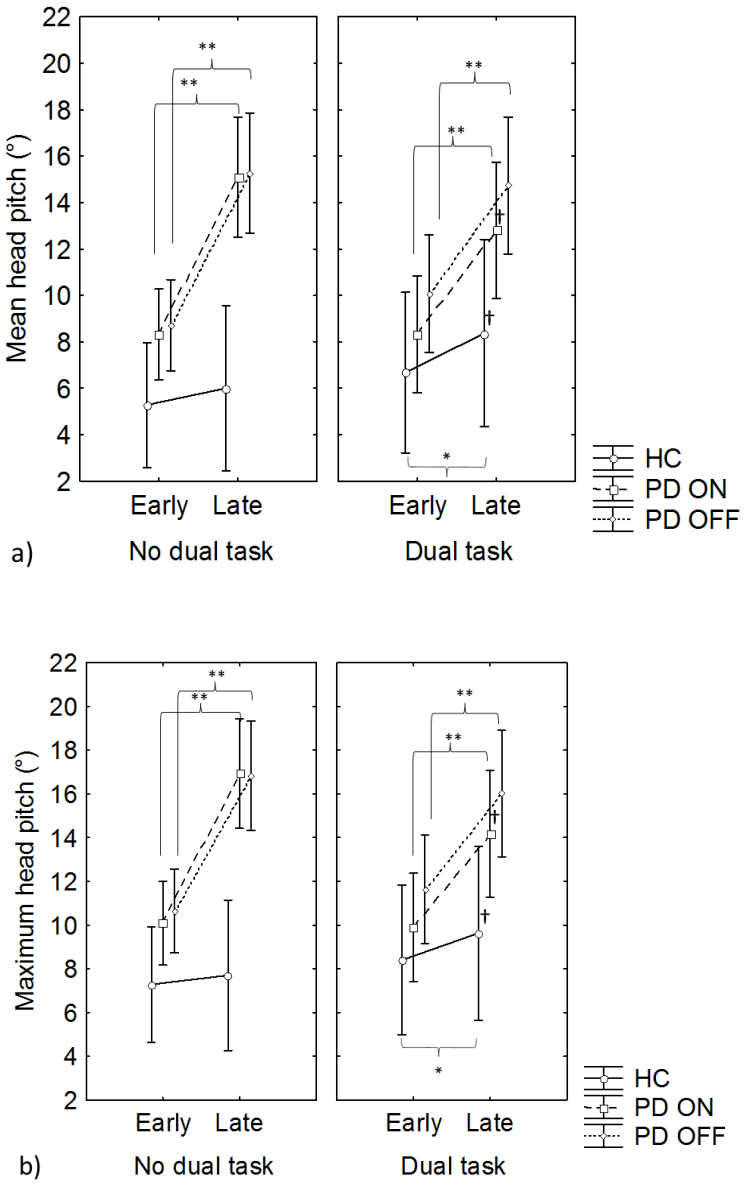

Figure 12 a,b – Interactions between group x phase x dual task for mean (a) and maximum head pitch (b). Higher values mean larger head tilt downward or larger head rotation forwards. †: Individuals with PD have increased head tilt when walking in the late phase compared to early phase. The head tilt, in healthy controls, increased in the late phase compared to the early phase only when they performed the dual task.

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Foot clearances

The results indicated that there were no main effects of group, medication or task for lead toe clearance and trail horizontal distance before the obstacle (see Table 14). An interaction between medication and task was found for lead horizontal distance beyond the obstacle (see Table 14). This interaction revealed that PD ON had shorter lead horizontal distances beyond the obstacle comparable to PD OFF when counting numbers. However, when PD patients were compared to HC there were no significant differences for foot-clearances. Thus, the foot-to-obstacle distances exhibited by individuals with PD patients can be considered unaffected by PD and dual task trials. Finally, the success rate for stepping over the obstacle was also similar between the groups across all the experimental conditions (~99% of success).

Auditory task performance

A medication effect revealed that patients answered more accurately overall during the ON medication state, compared to the OFF state ($F_{1,19}$=4.37, p=0.050; PD ON = 1.4/PD OFF = 1.7). However, there were no significant differences between groups or conditions (seated vs walking) on task performance. Thus the ability to monitor multiple digits is not affected in PD patients.

Correlations

Pearson correlation coefficients were calculated between the gait dependent variables and the scores on the neuropsychological tests, and the UPDRS-III scores (motor scale) when

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interactions involving groups and conditions were found. However, there were no significant correlations between gait variables, neuropsychological tests and clinical scores.

DISCUSSION

Summary

The overall aim of this study was to investigate the contribution of the dopaminergic system to central resources required to plan and control complex gait adaptations to avoid an obstacle. Another aim was to investigate if there were changes in visual strategies associated with cognitive overloading during obstacle approach in PD. The results showed that dopaminergic replacement therapy decreased the abrupt gait deceleration from early to late phases during obstacle approach. Interestingly the dual task only affected gait control (step-to-step time variability) in PD OFF participants in the late phase, compared to HC participants, and only in the first dual task trial. However, ON and OFF comparisons showed that dopaminergic replacement did not reduce the dual task interference on gait of individuals with PD during the late phase. This suggests that dopamine gave little contribution to cognitive processes required to plan complex step adjustments to avoid an obstacle. Finally, visual strategies and foot clearances in PD were similar to healthy participants irrespective of cognitive load and dopaminergic withdrawal.

Dopaminergic contributions to online movement planning in PD

PD participants in the OFF state had a greater magnitude of gait deceleration during the transition from the early to the late phase compared to healthy participants. This abnormal gait

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slowness, during the late phase (last three steps) compared to early phase, might have resulted from the planning complexity of sequential step adjustments to avoid the obstacle (Berg et al., 1994a; Bradshaw & Sparrow, 2001). This result is in line with previous upper limb studies in which bradikinesia (movement slowness) was exacerbated when PD patients performed complex sequential movements, compared to movements having simple sequences (Benecke, Rothwell, Dick, Day, & Marsden, 1986, 1987b). Another explanation for exacerbated gait slowness during obstacle approach is that the central resources allocated to plan gait adaptations might have depleted the resources necessary to control gait in PD. Bond and Morris (2000) showed that gait velocity was abnormally reduced only among PD patients with the secondary goal-directed task(e.g. carrying a tray with glasses compared to no glasses). However, in the current study, the dual task (digit counting while walking) did not differentially influence gait velocity in PD. This suggests that the abrupt gait deceleration from early to late phases, was not caused by distraction or cognitive load to plan foot clearances, otherwise gait velocity of PD patients would have been even more affected by the secondary task (digit counting) than healthy controls. It is likely that a specific deficit in sensorimotor integration might have contributed to an abnormal motor output (slowness). Thus, this abrupt gait deceleration prior obstacle crossing may be interpreted more as an adaptation to overcome impairments in sensorimotor integration, than as a problem to allocate central resources.

Recent imaging studies revealed that inhibitory activity of the *globus pallidus internal/substantia nigra part reticulata* (GPi/SNr) over the *pedunculupontine* (PPN) and mesencephalic locomotor region (MLR), may be exacerbated when individuals with PD need to negotiate complex external stimuli, which results in severe movement slowness (Lewis &

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Barker, 2009a; Shine, Matar, Ward, Bolitho, Gilat, et al., 2013). Furthermore, recent research suggests that abnormal slow walk might be linked to slow sensory processing in older adults (Rosano et al., 2008; Rosano et al., 2012). Therefore, it is likely that the abrupt gait deceleration during obstacle approach, observed in PD OFF, might be a motor response triggered by an overload in sensorimotor processing within the basal ganglia in PD.

Patients with PD also had a greater deceleration, from the early to late phase, in their OFF state (~25%) compared to the ON state (~3%). This result confirms that the abrupt gait deceleration may be related to decreased dopaminergic activity. Dopamine may have improved sensorimotor processing during online planning to avoid an obstacle, since the cognitive load (digit counting) did not exacerbate gait slowness in PD more than in healthy participants. This is in line with a previous study by Almeida et al. (2005) who suggested that dopaminergic replacement therapy improves sensorimotor integration during gait in PD patients.

Interestingly, the influence of the secondary task on gait in individuals with PD was only observed in the step-to-step time variability and in the late phase. Step-to-step time variability may be more sensitive, than gait velocity, to changes in cognitive load during self-paced gait (Hausdorff, Balash, & Giladi, 2003; Yogev et al., 2005). In the current study, the secondary task increased step time variability in PD OFF participants specifically during the late phase (when the demands for planning increased) compared to the early phase. However, when PD patients were in the "ON" state compared to healthy controls, the dual task interference on gait, in the late phase, was not significant. This result replicates previous findings that optimally medicated PD patients with relatively preserved gait characteristics were not affected by the cognitive load

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during obstacle approach (Pieruccini-Faria et al., 2014). Interestingly, in the current study, the dual task interference happened only in the first trial, in the late phase when PD patients were OFF. Experience with the dual task (walking and counting) likely decreased the impact of the secondary task on gait of PD OFF in the late phase. Additionally, PD patients and healthy participants had similar performance in the secondary task (digit counting), even in the first trial of dual tasking, suggesting that PD patients and healthy controls were equally able to attend to the auditory dual task.

It is important to note that the severity of the PD patients in current study was mild. Thus the ability to perform complex cognitive tasks while walking might be spared in our current sample of PD patients. Additionally, PD patients and healthy participants in the current study had similar cognitive scores in the neuropsychological assessments, suggesting normal cognitive capacity. Furthermore, correlations between neuropsychological measures and gait variables were not significant, also supporting the notion that gait changes during the obstacle approach are not linked to a specific cognitive deficit in PD. It might be possible that the dual task interference in the first trial was caused by impaired sensorimotor processing rather than cognitive deficits. This is supported by recent theory suggesting that cognitive processes prevent that distorted sensorimotor signals sent from basal ganglia disturb motor output of individuals with PD (Redgrave et al., 2010). Alternatively, Lewis and Barker (2009a) suggested that sensory, cognitive and limbic signals can be “jammed” within basal ganglia when individuals with PD negotiate complex stimuli, which affects their motor output. Sensorimotor adaptation during obstacle avoidance may have contributed to disentangling or differentiating signals (cognitive, sensory, and limbic) processed by basal ganglia.

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Interestingly, comparisons between PD OFF and PD ON revealed that patients had increased step-to-step variability and slow gait velocity in the late phase compared to early phase when performing the dual task. In other words the dual task did not affect gait in PD OFF more than in PD ON, although patients in both medication conditions were more affected by the dual task in the late phase (compared to early phase). This would suggest that dual task effects on gait of PD patients may not be the result of decreased striatal dopaminergic activity, exclusively. Although only speculative, neurotransmitters other than dopamine might influence cognitive and motor processing in patients with PD. For example, decreased cholinergic activity in patients with PD is linked to deficits in executive functions (Bohnen et al., 2006) and gait (Rochester et al., 2012). Future studies should investigate the contribution of other neurotransmitters to the performance of complex gait tasks in PD.

Gaze behaviour to plan gait adaptations in PD

Gaze behaviours were investigated in order to understand whether individuals with PD used different visual strategies when avoiding obstacles in conditions of increased cognitive load. Interestingly, all participants looked less to the obstacle when they performed the dual task. Averting gaze from obstacle to another location could be a strategy to decrease cognitive load during obstacle approach which could affect gait performance. However, our results do not suggest that individuals with PD used different visual strategies to prevent dual task interference during gait. This result is in contrast to previous studies in which PD patients used different visual strategies to avoid cognitive overload during complex goal-oriented tasks requiring sequential memory-motor transformations and precision (Galna et al., 2012; Ketcham

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et al., 2003). This is also in contrast with previous assumptions that individuals with PD require more visual feedback from the obstacle for successful crossing (Vitorio et al., 2013). The similarity of visual strategies in PD and healthy controls, even when the cognitive load was increased, might suggest that patients employed a maladaptive visual strategy or even the only visual strategy in their repertoire, to avoid an obstacle successfully. It is important to acknowledge that our study investigated gaze behaviour associated with one area of interest (obstacle). Thus it is possible that individuals may have looked to other areas, perhaps close to the obstacle as part of their visual strategy. Therefore, future studies should analyze gaze behaviour of PD patients in more areas in order to understand the importance of other pieces of visual information, other than obstacle, to online movement plan.

Abnormal head tilt in individuals with PD is associated with planning of complex step adjustments

During the final steps prior an obstacle crossing individuals with PD made larger head tilts downwards compared to healthy controls. It is well known that head and eye movements are tightly related. Thus, head movements towards a specific location may suggest that individuals are using more visual information from that specific location. Thus individuals with PD might have attempted to use more visual information from the lower visual field, not necessarily from obstacle, compared to healthy controls. This strategy might have helped patients to correct or to adjust their movement plan accordingly. Additionally, the larger head tilt in healthy individuals when they performed the dual task in the late phase, suggested that head tilts downwards are influenced by the cognitive demand to plan gait adjustments during obstacle approach.

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One could argue that larger downward head movements in PD patients during obstacle approach might have been a postural adaptation to facilitate the propulsion of the body to cross the obstacle. However, a recent study (Stegemoller et al., 2012) demonstrated that PD patients do the opposite by displacing their center of mass backwards during obstacle crossing as a postural strategy to prevent loss of stability when they land their foot beyond the obstacle. This strategy may prevent difficulties to break the center of mass displacement when individuals land their lead foot beyond obstacle. Thus, it is unlikely that individuals with PD were trying to displace their center of mass forward, using head movements. Interestingly healthy individuals adopted similar head tilt behaviour in the late phase when monitoring digits in the audio track. This suggests that abnormal head posture during locomotion in individuals with PD, such as stooped posture, may be centrally mediated in order to help with the planning of complex step adjustments during locomotion.

Limitations

This study has some limitations that need to be acknowledged. The number of steps used to calculate step-to-step time variability is low compared to previous research (Yogev et al., 2005). However, variability between phases using the same number of steps for all groups was consistently compared. Other studies have also calculated step time variability from the same amount of steps (Cowie et al., 2012; Pieruccini-Faria et al., 2014). Another limitation is that it was not possible to know the performance of the secondary task in each phase. It might be possible that the performance of the secondary task in each phase changed as participants approached the obstacle. Poor performance in the secondary task would also indicate that the

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demand for central resources (e.g. cognitive processes, attention) during obstacle approach increased. The eye tracker equipment did not allow calculation of saccades due to low sampling frequency. Downward saccades could play an important role in updating the motor plan of foot-obstacle distances during locomotion(Di Fabio, Zampieri, & Greany, 2003). Future research should investigate the contribution of saccadic eye movements to obstacle avoidance in PD.

CONCLUSION

In summary the current study demonstrates that dopaminergic replacement decreases gait slowness and partially decreased the influence of cognitive load in PD patients when online planning was necessary to avoid an upcoming obstacle during gait. A specific improvement in sensorimotor integration, after dopaminergic replacement, likely contributed to decreased gait slowness during online movement planning. Interestingly, individuals with PD do not adopt different visual strategies or gaze behaviours while planning obstacle avoidance even when the cognitive load was increased. This lack of visual adaptation could potentially contribute to increased risk of falls among PD patients, especially during novel or more demanding gait situations. From a therapeutic point of view, it is important to consider interventions that expose PD patients to complex environments when they are unmedicated. This type of intervention could be particularly important for PD patients who have abrupt motor fluctuations or to those who are less responsive to dopaminergic therapy.

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CHAPTER 5 - GENERAL DISCUSSION

The overall aim of this thesis was to better understand the influence of motor planning on gait control of individuals with Parkinson's disease (PD). Specifically, we attempted to understand if the planning of gait adjustments and foot clearances while walking (online movement plan) to avoid an obstacle exacerbates gait deficits in individuals with PD. In Chapter 1, we hypothesized that an over demand for central neural resources, when individuals with PD are planning obstacle avoidance while walking, could undersupply or interfere with resources required for gait control. A dual task was used to investigate the processing demand created by planning gait adaptations, and the influence this processing had on resources required to control gait in individuals with PD. In Chapter 2, this issue was investigated within the gait spectrum disorder caused by PD both in individuals with less severe (PD-nonFOG), and in individuals with more severe gait impairments known as freezing of gait (PD-FOG). In Chapter 3, the relationship between the load on central resources and sensorimotor processing during the planning and control of gait adaptations was investigated. Finally, in Chapter 4, the influence of dopaminergic replacement therapy on planning resources was investigated.

FOG and online movement planning in PD

In Experiment 1, we attempted to determine if individuals with PD-FOG are more influenced by cognitive load than PD-nonFOG and healthy controls when they plan and control complex step adjustments that are necessary to avoid obstacles. A dual task paradigm, walking while monitoring one or two digits in an audio track, was used to increase cognitive load during gait. The dual task helped to determine if the cognitive load to plan gait adjustments could

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trigger gait disturbances and freezing episodes in individuals with PD when they approached an obstacle. We found that the dual task only influenced gait of PD-FOG when the demand for planning step adjustments increased during the steps closest to the obstacle. Performing the secondary task also increased the number of contacts with the obstacle, but only for PD-FOG. PD-FOG had abnormal planning of horizontal foot-obstacle distances beyond the obstacle (shorter horizontal foot-to-obstacle distance of the lead foot that landed after crossing the obstacle). This abnormal spatial plan correlated with poor executive functioning (i.e., worse attentional set-shifting/cognitive flexibility was associated with worse planning). In addition, their poorer performance on the secondary task (digit counting) also indicated that PD-FOG were allocating greater resources to the gait task compared to PD-nonFOG. These results together showed that the planning and control of complex gait adjustments overload cognitive processing in PD-FOG, which triggers typical gait characteristics known as precursors of FOG episodes, such as timing variability. In addition, the magnitude of impairments in executive functions in PD-FOG contributed to erroneous spatial planning of foot-to-obstacle distances. This result is consistent with previous literature, which has shown that deficits in executive function are linked to FOG (Amboni, Cozzolino, Longo, Picillo, & Barone, 2008; Shine, Naismith, et al., 2013). Thus, an exacerbated deficit in executive function in PD-FOG can compromise the ability to plan complex spatial adjustments between the foot and obstacles. Additionally, the combination of impaired executive functions and the processing demands for planning motor adaptations may have depleted the resources available to control gait in PD-FOG. It appears that PD-FOG's cognitive systems are not able to fully account for increased demand in central resources required to plan and control gait adaptations. It should be noted that individuals with

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PD who experience FOG, compared to those who do not experience FOG, have been shown to have reduced activity in frontal-parietal networks; this suggests that less cognitive resources may be available to process information for PD-FOG, compared to PD-nonFOG (Bartels & Leenders, 2008). These hypoactive areas in PD-FOG are associated with higher-order cognitive processing and sensory processing, which are important to modulate complex actions. Therefore, increased cortical impairments, other than basal ganglia dysfunction, could also explain the impact of cognitive load to plan gait adaptations in PD-FOG.

It is important to acknowledge that deficits in executive functions limit our conclusions because cognition and gait deficits are correlated. Deficits in executive functions are also a marker of cholinergic dysfunction in PD (Bohnen et al., 2006; Bohnen et al., 2010b). Cholinergic decline impairs the functioning of the pedunculopontine nucleus (PPN) which plays a critical role in adjusting motor plans during locomotion. This is supported by recent fMRI study showing that individuals with PD with FOG have abnormal activation of Mesencephalic locomotor region (MLR) while imagining walking (Snijders et al., 2011). Future studies should further investigate the contribution of locomotor networks on complex gait tasks in PD.

Unexpectedly in Experiment 1, PD-nonFOG were not affected by the dual task during obstacle avoidance. This suggests that the resources required to plan gait adjustments did not interfere with gait control of PD-nonFOG more than in healthy individuals. However, it is important to acknowledge that PD patients compensate for deficits in planning and sensorimotor processing by using visual feedback available in the environment (Almeida et al., 2005; Azulay et al., 1999). Differences between individuals with PD and healthy individuals are

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more evident when visual feedback of self-motion is decreased. Removal of visual feedback of self-motion could force PD patients to rely on their impaired sensorimotor processing to achieve optimum motor control, which exacerbates movement disturbances. Additionally, visual feedback of step length decreases the demand on central resources during walking (Baker, Rochester, & Nieuwboer, 2008). This relationship between external feedback (e.g., vision) and cognitive processing in PD has been recently explained by a theoretical model (Redgrave et al., 2010). According to this model, cognitive processes responsible for controlling goal-oriented movements (novel behaviours; non habitual movements) are too overloaded by requirements to compensate for distorted sensorimotor signals in PD. In other words, the cognitive system in individuals with PD can be affected by their impaired sensorimotor processing. Therefore, sensorimotor processing in individuals with PD depletes cognitive resources that are necessary to perform more complex goal-oriented tasks. Thus, Experiment 2 tested whether the impact of movement planning on gait control of individuals with PD would be exacerbated in conditions where visual feedback of self-motion is reduced and conditions where the obstacle is the only source of visual feedback.

Sensorimotor processing and online movement planning in PD

In Experiment 2, we investigated the influence of motor planning resources on gait control in PD-nonFOG during conditions of reduced visual feedback of self-motion and dual tasking (monitoring two digits in an audio track while walking; the same dual task used in Experiment 1). Experiment 2 provided an opportunity to evaluate if deficits in sensorimotor integration increase the chances of disturbances in gait control when PD patients are walking

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and planning gait adaptations during increased cognitive load. It was hypothesized that gait control would be compromised when individuals with PD start to plan complex gait adjustments (late phase) while walking, but only when visual feedback of self-motion is reduced. It was expected that during situations of reduced visual feedback, resources used to plan gait modifications might be shared with resources required to control gait. Thus reduced visual feedback would magnify the impact of planning step adjustments on gait control in individuals with PD. It was also expected that increased dual task interference on gait (or poorer dual task performance) would demonstrate increased load on central resources during conditions of reduced visual feedback.

In order to manipulate visual feedback of self-motion, participants walked and stepped over an obstacle during full vision, in the dark with position cues on lower limbs (small piece of glow-in-the-dark tape attached to their thighs and feet), and in the dark without limb cues. The obstacle was illuminated in the dark (fully covered with glow-in-the-dark tape), and thus equally visible in all conditions. Results from Experiment 2 demonstrated that gait variables of PD patients, such as step time variability and gait velocity, were abnormally affected by reduced visual feedback of self-motion during the steps closer to the obstacle (late phase) compared to steps further from the obstacle (early phase). Specifically, greater gait deceleration and increased step time variability were observed when PD patients walked from the early to late phases during dark conditions. This result agrees with our hypothesis that motor planning affects gait control of PD patients during steps that require planning for complex gait modifications. An important finding is that there were fewer obstacle contacts during the dual task when PD patients had limb position cues that allowed them to see their foot and thigh in

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the dark, compared to when they walked in the dark without limb position cues. This indicates that the central resources of individuals with PD are affected by reduced visual feedback of self-motion. In addition, PD patients had poorer performance on digit monitoring compared to healthy participants, but only when they walked in the dark without glow-in-the-dark tape on their lower limbs. Together, these results indicate that individuals with PD relied on central resources more than healthy controls did during sensorimotor integration. The increased demand in central processing when PD patients walked in the dark may have increased the interference of planning resources on gait control of individuals with PD. Overall, when visual feedback of self-motion was reduced in the dark conditions, gait control (step time variability and gait velocity) was more affected in PD patients than in healthy participants, especially during the closest steps before obstacle crossing (late phase), when planning is critical to avoid an obstacle contact.

Interestingly, gait control exhibited by PD patients in Experiment 2 (during conditions of reduced visual feedback) was similar to the gait behaviours of PD-FOG in Experiment 1, as shown by the greater step time variability in the late phase and more obstacle contacts during dual task conditions. Step time variability is linked to increased cognitive challenge during gait (Hausdorff, Rios, & Edelberg, 2001). This suggests that PD-FOG may require increased central resources for sensorimotor integration compared to PD-nonFOG. Increased step time variability is also linked to increased risk of falling in individuals with PD. Although PD patients in general have a higher risk of falling compared to healthy individuals, severity of gait disorders in individuals with PD (such as FOG) can exacerbate this risk (Bloem, Hausdorff, Visser, & Giladi, 2004). It is possible to conclude from these results that impaired sensorimotor integration in PD

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patients make them more susceptible to trips and falls, especially when planning resources are necessary to make gait adaptations in cluttered environments.

The results of Experiment 2 are consistent with a recent theory about basal ganglia dysfunction, which hypothesizes that impairments in sensorimotor processing in individuals with PD induce patients to use cortical networks that modulate complex goal-oriented behaviours (Redgrave et al., 2010). According to this theory, impaired sensorimotor processing caused by striatal dopaminergic depletion makes individuals use attentional networks to prevent their impaired sensorimotor processing from causing errors in their motor output. Hence, during a condition where individuals with PD are required to integrate sensorimotor information to achieve gait control (e.g., in the dark), a more conscious or attentional control of steps is necessary.

In Experiments 1 and 2, individuals with PD were tested (only) during their "ON" dopaminergic state (when patients are under the effect of dopaminergic medication). Therefore, it is difficult to draw conclusions about the influence of basal ganglia dysfunction on central resources when individuals need to plan and control gait modifications. It is important to understand what processes basal ganglia are modulating when PD patients are walking and planning gait adaptations. The basal ganglia (Alexander, Crutcher, & DeLong, 1990; Graybiel, 1995) and dopamine (Cools, 2006; Hanna-Pladdy & Heilman, 2010; Nutt & Carter, 1984; O'Suilleabhain, Bullard, & Dewey, 2001; Pullman, Watts, Juncos, Chase, & Sanes, 1988; Shin, Kang, & Sohn, 2005) play a critical role in the modulation of sensory, motor, and cognitive processing. Withdrawal of dopaminergic medication might reveal the specific contributions of

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the basal ganglia and dopamine to gait control and resources capacity during gait with obstacle. According to theoretical models, dopamine increases the resource's "reserve" (Lewis & Barker, 2009b) for motor and cognitive processing, making complex motor and cognitive tasks less demanding for these patients. Thus, when dopamine levels are low, the accomplishment of complex gait tasks may be compromised in individuals with PD. Some cognitive and motor tasks may require more "fuel" (more dopamine) than others. For example, previous research suggested that dopaminergic withdrawal exacerbates gait disturbances of individuals with PD, especially when the sensorimotor and cognitive complexity of the task increased (Lord et al., 2010). However, it is not known if dopamine modulates resource allocation and/or the sensorimotor processes required to plan obstacle avoidance. This issue was investigated in Experiment 3.

Another important issue not investigated in Experiments 1 and 2 was the visual strategies used by PD patients to avoid the obstacle. While Experiment 2 demonstrated that PD patients depended more on visual feedback of self-motion than healthy participants to plan and control complex step adjustments, it was not possible to understand how individuals with PD used visual information from the obstacle. As suggested by previous research (Galna et al., 2010; Vitorio et al., 2013), individuals with PD could rely on visual feedback from the obstacle more than healthy participants and, thus use feedback regarding the obstacle's location as a visual cue to plan their gait adjustments. It is well known that visually guided movements are not affected by basal ganglia dysfunction (Morris et al., 2005; Morris, Iansek, Matyas, & Summers, 1994). Alternatively, visual strategies could have optimized the dual task performance, preventing cognitive overload and gait impairments while PD patients walked

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toward an obstacle. According to previous research, PD patients prevent overload in visuospatial working memory by looking less frequently at multiple spatial locations before executing sequential movements (Ketcham et al., 2003). Another recent study showed that PD patients reduce saccadic movements when they have to walk through a doorway while performing a cognitive dual task (memorizing a sequence of numbers while walking) compared to when they do not perform the dual task (Galna et al., 2012). Therefore, gaze strategies may be important to decrease the impact of cognitive overloading on motor performance in individuals with PD. The gaze analysis used in Experiment 3 helped to determine the contribution of visual strategies used by individuals with PD to plan foot clearances. Additionally, we sought to investigate if dopaminergic replacement and increased cognitive load influenced their visual strategy.

Dopaminergic dysfunction and online movement planning in PD

Experiment 3 was an attempt to evaluate the influence of dopaminergic withdrawal on central resources of individuals with PD during the planning and control of complex step adjustments, which are required to step over an obstacle. Specifically, Experiment 3 investigated the effect of cognitive load generated by a dual task (the same task used in Experiments 1 and 2) when individuals approached an obstacle before ("OFF") and after ("ON") taking their regular dopaminergic medication. PD patients were tested in both the "OFF" and "ON" medication state (each participant was tested twice). In this experiment, participants' eye movements were monitored by an eye tracker in order to understand whether their visual

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strategies to avoid an obstacle were mediated by dopamine and by increased demand in central resources.

This experiment showed that when PD patients were "OFF" medication, step time variability was increased during the dual task, but only in the late phase. This effect was only found in the first trial. However, dopaminergic replacement therapy (PD OFF x PD ON comparisons) did not change the impact of cognitive load on gait. The cognitive load was higher for individuals with PD who were OFF medication compared to healthy controls; however, when individuals with PD who were ON medication were compared to healthy controls, there were no differences. In addition, PD patients who were OFF medication had an abrupt gait deceleration from the early to the late phase, compared to healthy controls and PD patients who were ON medication, regardless of the dual task condition. However, dopaminergic medication withdrawal did not affect foot clearances or digit counting performance. These results indicate that dopamine modulates sensorimotor processing but had little influence on cognitive processes associated with the planning of foot clearances.

In Experiment 3, the abrupt gait deceleration from early to late phases, found only in the PD patients who were OFF medication, is comparable to the gait deceleration observed in Experiment 2 (when PD patients walked in the dark toward an obstacle). However, in Experiment 3, like in Experiment 1 and 2, gait velocity of PD patients and healthy individuals was similarly influenced by the dual task during obstacle approach (both groups had their gait velocity similarly affected by the dual task). This result suggests that gait deceleration between phases is not associated with increased demand in cognitive processes when individuals

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approach an obstacle. Perhaps this abnormal gait deceleration in individuals with PD who are OFF medication, found in Experiment 3, is more associated with impairments in processing or integrating sensorimotor information than with limitations in cognitive processes. Recent neuroimaging research revealed that dealing with external stimuli can overload the cognitive, limbic or sensorimotor basal-thalamic-cortical loops, which increases the inhibitory output from basal ganglia to motor centres (Lewis & Barker, 2009a). Specifically the increased demands in sensorimotor integration during obstacle approach could have increased inhibitory motor output from basal ganglia to locomotor centers when individuals with PD were OFF medication compared to ON medication. These results together suggest that BG impairments in PD affect the ability to process sensory feedback to plan obstacle avoidance, but had little influence on cognitive processing since dual task performance of PD ON and PD OFF were similar. Results from experiment 3 (chapter 4) support the idea that sensorimotor integration during movement planning may consume a great portion of striatal dopamine. Additionally, striatal dopamine for cognitive processing may be more preserved than dopamine for sensorimotor processing, especially in the early stages of the disease. Thus, impairments in other neurotransmitter systems, such as the cholinergic system (Bohnen et al., 2010a), may play an important role in modulating cognitive processing during motor planning in PD patients.

Gaze results showed that there were no group differences for fixation duration or number of fixations on the obstacle position. These gaze behaviours do not confirm previous assumptions that individuals with PD use visual feedback from obstacles differently than healthy controls (Galna et al., 2012; Vitorio et al., 2013). Additionally, these gaze results are also in contrast with previous assumptions that individuals with PD use different visual strategies to

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manage cognitive load during goal-directed movements (Galna et al., 2012; Ketcham et al., 2003). Therefore, PD does not affect how individuals extract visual information from the obstacle. This result suggests that patients might be using maladaptive visual strategies to plan movements.

The results in Experiment 2 compared to Experiment 3 suggested that visual information from peripheral vision (optic flow from the environment) might be more important than foveal vision (obstacle location) for individuals with PD to avoid obstacles. It is possible that individuals with PD need more information about the spatial structure of the environment surroundings than healthy controls to plan gait adjustments and to estimate body displacement. However, we cannot make strong conclusions about the importance of central and peripheral visual information for PD patients since it was not directly manipulated in this thesis. Future studies could investigate the importance of different pieces of visual feedback (central or peripheral) during goal-directed tasks for individuals with PD.

Influence of movement planning on gait control in PD

The experiments in this thesis suggest that during the planning of gait adaptations central resources become overloaded, which affects gait control in individuals with PD more than in healthy controls. Deficits in sensorimotor integration may demand increased central resources in individuals with PD compared to healthy individuals, which increases the impact of motor planning on gait. Basal ganglia and non-dopaminergic pathways may modulate central resources, whereas dopamine may specifically influence sensorimotor integration during motor

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planning in individuals with PD. In sum, online movement planning may increase the number of systems (cognitive, sensorimotor) relying on the same resource pool, which affects locomotion of individuals with PD.

Faulty mechanisms during obstacle avoidance in PD: Targets for intervention

Understanding the role of cognitive load on gait disturbances in PD is a very important topic, in particular the use of a dual-task paradigm as an instrument to study this relationship is an emerging area of research. Importantly, very few studies have investigated the impact of dual tasks during real-world tasks, such as obstacle avoidance in PD. The gait impairments and trips observed in the studies from this thesis are strong reflection of what likely happens when individuals navigate in real-world situations, making this a unique and externally valid protocol. Real-world contexts usually require planning for complex gait adaptations to avoid obstacle contacts. Thus, a better understanding of cognitive, sensory and planning mechanisms during navigation with obstacles and gait adaptation will be extremely relevant for many other aging and neurodegenerative populations as well. Rehabilitation programs and other therapeutic interventions for PD patients could result from the findings of this thesis, but it is also important to consider other populations that present with gait impairments such as geriatric population in general and stroke survivors that might also benefit. Therefore, the gait task developed for this thesis provides an important tool, to better understand how faulty mechanisms involved in planning and gait control can result in greater incidence of trips and falls.

PD patients have increased frequency of falls compared to age matched healthy individuals. Although multifactorial, individuals with PD report that trips and slips are among

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the most common reasons for falls (Balash et al., 2007; Balash et al., 2005). Additionally injuries resultant from falls may lead individuals to hospitalization and reduced functional capacity (e.g. reduced strength, aerobic capacity and coordination). Hence, fall prevention is crucial to stabilize the health status and decrease mortality among individuals with PD. This thesis identifies three faulty mechanisms that could be targeted in therapies to help patients navigate with safety in complex environments. These mechanisms are likely associated with faulty extra-nigral pathways, sensorimotor integration and striatal dopaminergic depletion. Identification of faulty mechanisms is the first step to develop pharmacological and non-pharmacological interventions to prevent falls.

In the first experiment, non-dopaminergic aspects such as declined general cognitive status and impaired attention/executive functions were correlated to gait deficits in PD-FOG, whereas disease severity was not. These cognitive impairments are markers of cholinergic rather than dopaminergic deficit in PD (Bohnen et al., 2006). Thus, non-dopaminergic deficits appear to have influenced the planning to avoid an obstacle in individuals with FOG, specifically in the late phase and during obstacle clearance itself. Recent research has shown that severe gait impairments in PD may result from pronounced damage to the cholinergic system (Bohnen et al., 2007; Bohnen et al., 2010b). Degeneration of cholinergic neurons in the pedunculopontine nucleus (PPN) may disrupt postural control and gait in PD (Muller et al., 2013). The PPN works as an interface between supra-spinal and spinal locomotor networks. This region plays an important role in making adaptations in the postural tonus to initiate or to stop gait (Pahapill & Lozano, 2000).

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Declined cognition may compromise the ability to perform complex goal-oriented gait tasks that strongly rely on attentional networks. Hence improving cognition in PD patients may have a positive impact on gait behaviour in PD. For example, cognitive remediation therapy using action observation combined with physical practice decreased FOG severity in gait tasks that elicit FOG episodes (Pelosin et al., 2010). Another recent study showed that FOG severity decreased when individuals are systematically exposed to complex environments that are known to trigger FOG episodes (Plotnik et al., 2014). It has also been shown that locomotor training, using virtual reality, improves both obstacle negotiation and executive functions in PD (Mirelman et al., 2011). These cognitive-motor therapies may stimulate brain areas that encode kinematic characteristics of movement (i.e. inferior frontal gyrus) and goal/object description (i.e. inferior posterior parietal cortex). Together these studies suggest that cholinergic stimulation combined with cognitive-motor training, may an effective strategy to improve obstacle avoidance in PD.

It should also be noted that cholinesterase inhibitors have been shown to decrease the incidence of falls in PD (Chung, Lobb, Nutt, & Horak, 2010). A more recent drug trial observed positive effects of methylphenidate (a cholinergic agonist) on step length and cadence during activities of daily life in individuals experiencing FOG (Moreau et al., 2012), however methylphenidate did not decrease the influence of dual-task on gait in freezers (Delval et al., *in press*). These studies together suggest that the cholinergic system (specifically in PD-FOG) may not be contributing to a cognitive issue, since the ability to deal with multiple tasks simultaneously during gait does not improve. Thus, it may be prudent to consider what other

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mechanisms (other than cognition) the cholinergic system might be involved in, to lead to these gait improvements.

One possible mechanism that may be cholinergic in nature is sensorimotor integration, and based on the findings from experiment 2 (chapter 3) impaired sensorimotor integration appears to have affected planning in individuals with PD, since they show slower velocities and increased step time variability (in the late phase), as well as more obstacle contacts compared to healthy controls. These differences were only apparent when walking in darkness, but with normal vision these group differences disappeared. Sensory feedback integration is necessary to update an ongoing movement plan, however individuals with PD may present limitations to process proprioceptive feedback (Konczak et al., 2012; Maschke, Gomez, Tuite, & Konczak, 2003), which has been proven to affect gait control (Almeida et al., 2005). Therefore, in the absence of visual feedback, attention should be used as a strategy to improve or enhance the sampling of somatosensory feedback during strenuous locomotor contexts. Hence, a viable intervention may be to teach individuals with PD to focus their attention on relevant somatosensory feedback to perform challenging gait adaptations (e.g. lower limbs position). For example, exercise programs can teach PD patients to focus attention to sensory feedback when they perform a variety of complex body movements (Sage & Almeida, 2009). This type of cognitive-physical intervention improves gait during more challenging gait situations (e.g. gait with turns) whereas self-paced gait remained unchanged. Therefore, complex gait navigation in individuals with PD could be improved by exercises combining attention and sensory manipulations.

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Chapter 4 provides evidence that a dopaminergic mechanism is likely involved in the planning of obstacle clearance behaviours. Specifically, the results of this chapter support that dopamine contributes to sensorimotor integration when individuals are planning for an upcoming obstacle. Specifically, dopaminergic withdrawal resulted in similar gait deficits as when patients walked with reduced visual feedback (e.g. optic flow) toward an obstacle. Thus, it seems likely that the BG may mediate sensorimotor integration for planning, with a specific role in integrating proprioceptive feedback with vision.

In terms of therapeutic interventions, and as supported by a recent literature review arguing that "somatosensory deficits are one in which disease-related dopaminergic denervation leads to a loss of response specificity, resulting in transmission of noisier and less-differentiated information to cortical regions" (Conte, Khan, Defazio, Rothwell, & Berardelli, 2013), cuing strategies may be very important in PD. Provision of external cues helps patients to focus attention on relevant sensory information thereby improving motor performance in PD. Cognitive strategies mentioned above, such as focusing attention to steps or lower limbs may be useful for patients to navigate in complex environments, where the salience of sensory information is reduced. Since it is well known that sudden motor fluctuations effects locomotor performance of patients, gait therapies should be performed also when patients are OFF medication whenever possible. This therapeutic strategy could teach patients to overcome their gait impairments when medication is not effective, or when individuals begin to experience frequent wearing off.

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Overall, this dissertation reveals that sensorimotor deficits may be the core mechanism causing gait impairments during obstacle avoidance. Dopaminergic dysfunction is likely the main contributor to faulty sensorimotor deficits in PD, however careful consideration of the role of the cholinergic system in sensorimotor processing should be a focus of future research. To improve or stabilize sensorimotor problems it will be imperative to consider combinations of pharmacological and cognitive remediation interventions that target both the dopaminergic and cholinergic pathways. These therapeutic strategies will optimize planning resources and therefore prevent falls in PD. However, caution is necessary when making conclusions about the contributions of the cholinergic system during planning and control of gait adaptations since we did not directly evaluate the cholinergic system in this thesis. More studies are necessary to understand the specific contributions of cholinergic dysfunction and obstacle avoidance deficits in PD.

Limitations

An important limitation of the current thesis was the inability to quantify the performance on the secondary task during each phase of the walking task. An analysis of secondary task performance during each phase could provide more information regarding the cognitive load associated with each approaching phase (early and late) and obstacle crossing task. In general, participants reported in each experiment that it was very difficult to keep track of the digits during the last steps, which corresponds to the late phase and crossing the obstacle. Thus, it is possible that the performance of the secondary task was worse when participants were closer to the obstacle and during obstacle crossing. Future studies could use

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dual task paradigms that allow the investigation of not only the effects of a secondary task on gait, but also the performance on the secondary task during the approach and crossing phases.

Another limitation is the inability to isolate planning and control using the obstacle paradigm. This dissociation is difficult since planning and control are interwoven neural networks. Thus, it is difficult to know whether gait abnormalities during obstacle avoidance in individuals with PD were caused by deficits in mechanisms of planning, or they were caused by deficits in control; this is especially problematic during obstacle approach. However, according to neurophysiological studies in animals brain lesions in areas that are important when individuals are planning actions only affect gait control in the last few steps prior obstacle crossing (Andujar, Lajoie, & Drew, 2010; Lajoie & Drew, 2007). Thus, gait abnormalities during an obstacle approach may indicate deficits associated with motor planning and not with execution or control of actions. Future brain imaging studies could further investigate this issue in PD patients.

Future directions

There are important questions that should be explored in future studies utilizing the gait protocol of this thesis. Since our results suggest that cholinergic dysfunction would influence gait with obstacles in PD-FOG, patients could be tested before and after cholinergic medication intake. Since cholinergic dysfunction affects the brain stem, stimulation of the PPN could be used to understand the specific contribution of this locomotor region for complex gait navigation in individuals with severe gait deficits. Additionally the use of Transcranial Magnetic Stimulation would be helpful to understand the contribution of specific cortical areas

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associated with movement planning, such as the supplementary motor area and parietal areas in PD. Electroencephalography (EEG) could be used to verify the existence of abnormal activity in different cortical areas associated with planning and/or movement execution. Together these approaches will lead us to a greater understanding of the mechanisms that underlie movement control deficits in PD.

CONCLUDING REMARKS

The results of these experiments demonstrate that motor planning to cross an obstacle overtax resources creating gait disturbances in individuals with PD. One possible reason for the influence of motor planning on gait control is that sensorimotor integration during gait requires more resources for individuals with PD. To put this more plainly, motor planning and sensorimotor integration may use the same pool of resources in individuals with PD, which affects their motor output. As a result, gait control becomes worse when individuals with PD are walking and planning foot clearances, as performing concurrent cognitive tasks either depletes and overload their available resources. Dopamine may have important contribution to sensorimotor integration processes, however had little contribution to cognitive processes that underlie the planning of complex step adjustments. Since dopaminergic replacement partially normalizes planning resources, additional therapeutic strategies (pharmacological, cognitive and physical) might be necessary to improve gait adaptability of PD patients.

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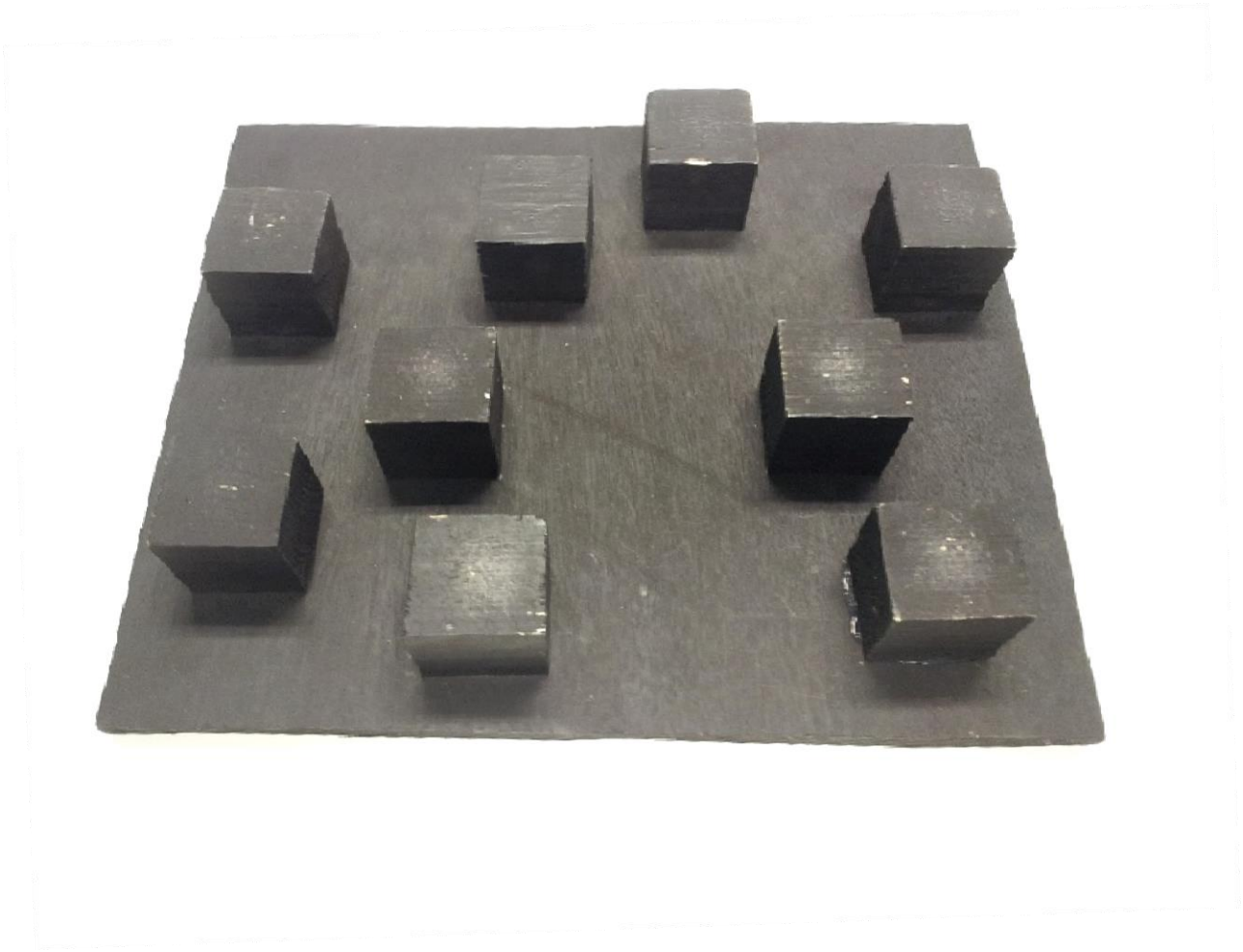
APPENDICES

Appendix A – Corsi block test



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Appendix B – Mini-Mental State (3MS)

Appendix: The Modified Mini-Mental State (3MS)

Subject _____ yr_____ /mo_____ / d_____ Examiner _____

Normal or Dx _____ Age /yrs_____ Edu /yrs_____ M_____ F _____

3MS _____ /100

MMS _____ /30

3MS	MMS		
		DATE AND PLACE OF BIRTH Date: year _____ month_____ day _____ Place: town _____ state_____	
__	5		
__	3	REGISTRATION (No. of presentations: _____) SHIRT, BROWN, HONESTY (or: SOCKS, BLACK, MODESTY) (or: SOCKS, BLUE, CHARITY)	
__	7	MENTAL REVERSAL *5 to 1*	
__	5	Accurate	2
		1 or 2 errors/misses	0 1
		DLROW	0 1 2 3 4 5
__	9	FIRST RECALL	
__	3	Spontaneous recall	3
		After "Something to wear"	2
		"SHOES, SHIRT, SOCKS"	0 1
		Spontaneous recall	3
		After "A color"	2
		"BLUE, BLACK, BROWN"	0 1
		Spontaneous recall	3

3MS	MMS		
__	10	FOUR-LEGGED ANIMALS (30 seconds) 1 point ea.	
__	6	SIMILARITIES	
		Arm-Leg	
		Body part; limb; etc	2
		Less correct answer	0 1
		Laughing-Crying	
		Feeling; emotion	2
		Other correct answer	0 1
		Eating-Sleeping	
		Essential for life	2
		Other correct answer	0 1
__	5	REPETITION	
__	1	"I WOULD LIKE TO GO HOME/OUT"	2
		1 or 2 missed/wrong words	0 1
		"NO IFS___ANDS___OR BUTS___"	0 1 2 3
__	3	READ AND OBEY "CLOSE YOUR EYES"	
__	1	Obeys without prompting	3
		Obeys after prompting	2
		Reads aloud only (spontaneously or by request)	0 1
__	__	WRITING (1 minute)	

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After "A good personal quality" 2

"HONESTY, CHARITY, MODESTY" 0 1

15 5 TEMPORAL ORIENTATION

Year

Accurate 8

Missed by 1 year 4

Missed by 2-5 years 0 2

Season

Accurate or within 1 month 0 1

Month

Accurate or within 5 days 2

Missed by 1 month 0 1

Day of month

Accurate 3

Missed by 1 or 2 days 2

Missed by 3-5 days 0 1

Day of week

Accurate 0 1

5 5 SPATIAL ORIENTATION

State 0 2

County 0 1

City (town) 0 1

Hospital/office building/home? 0 1

5 2 NAMING

(MMS: Pencil ___ Watch ___)

Forehead ___ Chin ___

Shoulder ___

Elbow ___ Knuckle ___

5 1

(I) WOULD LIKE TO GO HOME/OUT

(MMS: Spontaneous sentence: 0 1)

10 1 COPYING TWO PENTAGONS (1 minute)

	Each Pentagon
5 approximately equal sides	4 4
5 unequal (>2;1) sides	3 3
Other enclosed figure	2 2
2 or more lines	0 1 0 1

	Intersection
4 corners	2
Not 4-corner enclosure	0 1

3 3 THREE-STAGE COMMAND

___ TAKE THIS PAPER WITH YOUR LEFT/RIGHT HAND

___ FOLD IT IN HALF, AND

___ HAND IT BACK TO ME

9 SECOND RECALL

(Something to wear)	0 1 2 3
(Color)	0 1 2 3
(Good personal quality)	0 1 2 3

(Teng EL, Chui HC. A Modified Mini-Mental State (3MS) Examination. Journal of Clinical Psychiatry 1987;48:314-318. Copyright Physicians Postgraduate Press. Reprinted with permission.)

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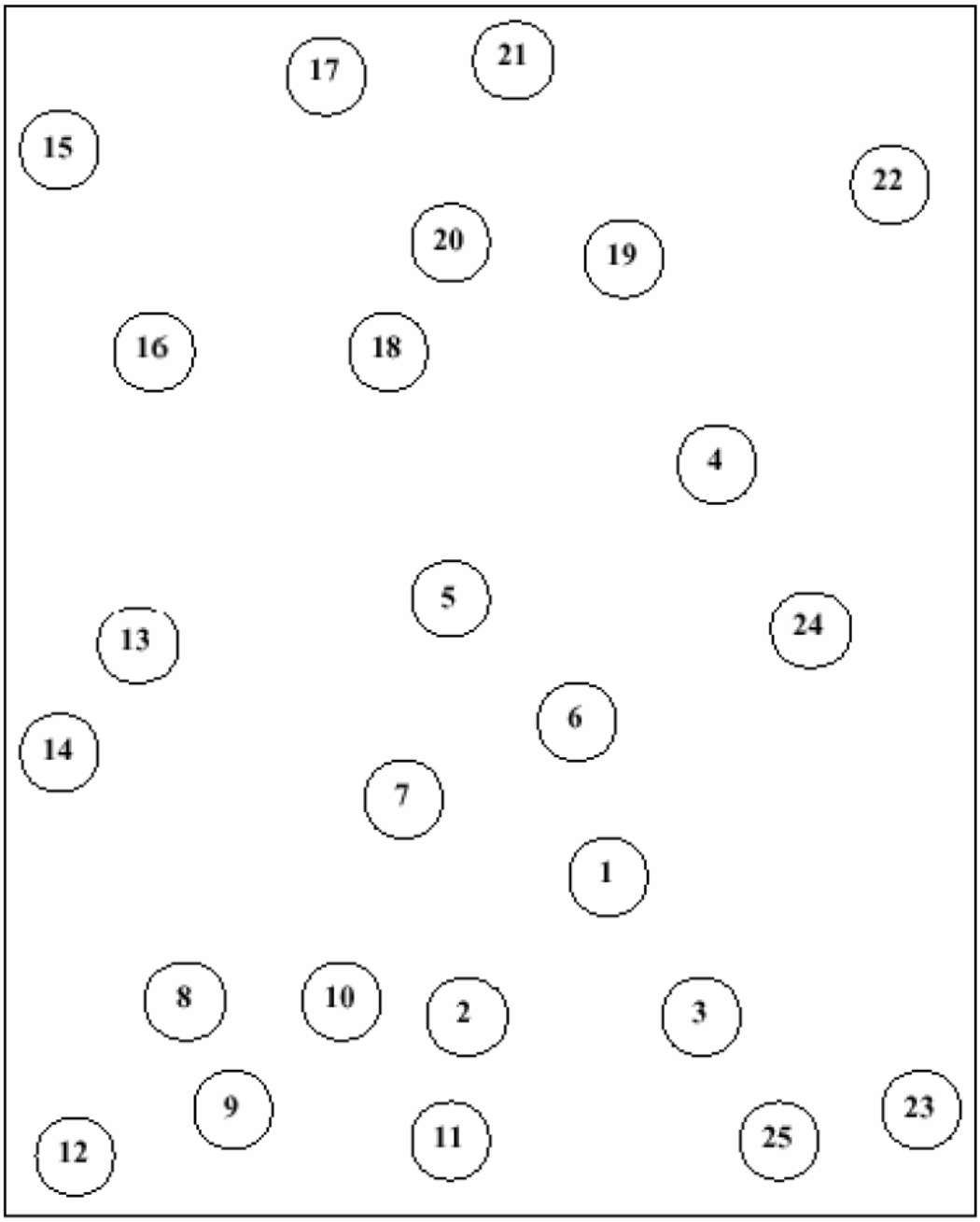
Appendix C - Trail Making Test Parts A and B

Trail Making Test Part A

Patient's Name: _____ Date: _____



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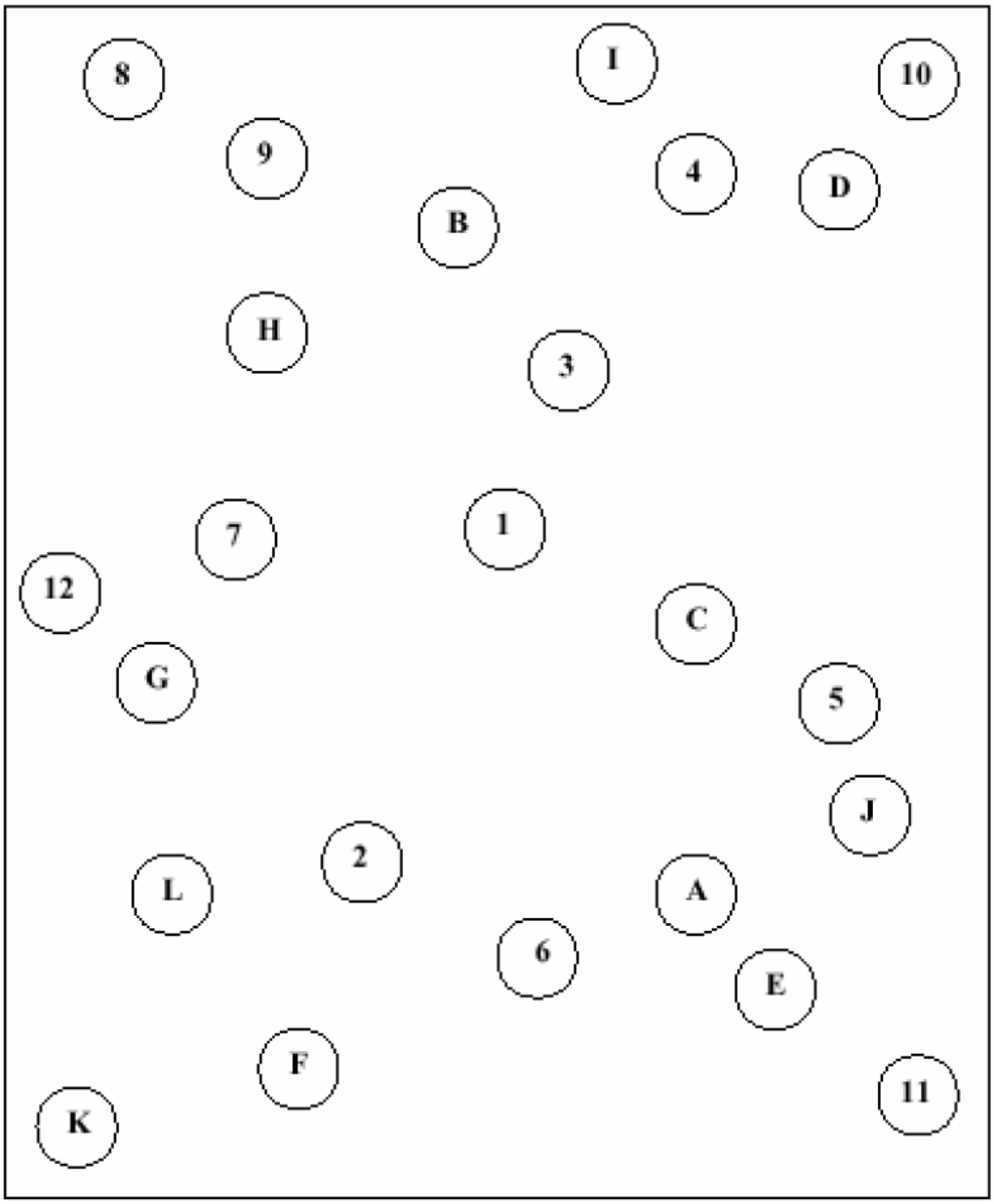
Trail Making Test Part B

Patient's Name: _____ Date: _____



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Appendix D – Digit span forward and backward

11. Digit Span (Optional)

DISCONTINUE RULE:
After scores of 0 on both trials of any item. For both Digits Forward & Backward, administer both trials of each item even if Trial 1 is passed.

RECORDING:
All responses verbatim

SCORING RULE:
0–1 pt. for each response

Digits Forward

Item/Trial	Response	Score 0 or 1
1 Trial 1	1 – 7	
Trial 2	6 – 3	
2. Trial 1	5 – 8 – 2	
Trial 2	6 – 9 – 4	
3. Trial 1	6 – 4 – 3 – 9	
Trial 2	7 – 2 – 8 – 6	
4. Trial 1	4 – 2 – 7 – 3 – 1	
Trial 2	7 – 5 – 8 – 3 – 6	
5. Trial 1	6 – 1 – 9 – 4 – 7 – 3	
Trial 2	3 – 9 – 2 – 4 – 8 – 7	
6. Trial 1	5 – 9 – 1 – 7 – 4 – 2 – 8	
Trial 2	4 – 1 – 7 – 9 – 3 – 8 – 6	
7. Trial 1	5 – 8 – 1 – 9 – 2 – 6 – 4 – 7	
Trial 2	3 – 8 – 2 – 9 – 5 – 1 – 7 – 4	
8. Trial 1	2 – 7 – 5 – 8 – 6 – 2 – 5 – 8 – 4	
Trial 2	7 – 1 – 3 – 9 – 4 – 2 – 5 – 6 – 8	

Forward Total Score
Range = 0 to 16

Digits Backward

Item/Trial	(Correct Response)/Response	Score 0 or 1
1 Trial 1	2 – 4 (4 – 2)	
Trial 2	5 – 7 (7 – 5)	
2. Trial 1	6 – 2 – 9 (9 – 2 – 6)	
Trial 2	4 – 1 – 5 (5 – 1 – 4)	
3. Trial 1	3 – 2 – 7 – 9 (9 – 7 – 2 – 3)	
Trial 2	4 – 9 – 6 – 8 (8 – 6 – 9 – 4)	
4. Trial 1	1 – 5 – 2 – 8 – 6 (6 – 8 – 2 – 5 – 1)	
Trial 2	6 – 1 – 8 – 4 – 3 (3 – 4 – 8 – 1 – 6)	
5. Trial 1	5 – 3 – 9 – 4 – 1 – 8 (8 – 1 – 4 – 9 – 3 – 5)	
Trial 2	7 – 2 – 4 – 8 – 5 – 6 (6 – 5 – 8 – 4 – 2 – 7)	
6. Trial 1	8 – 1 – 2 – 9 – 3 – 6 – 5 (5 – 6 – 3 – 9 – 2 – 1 – 8)	
Trial 2	4 – 7 – 3 – 9 – 1 – 2 – 8 (8 – 2 – 1 – 9 – 3 – 7 – 4)	
7. Trial 1	9 – 4 – 3 – 7 – 6 – 2 – 5 – 8 (8 – 5 – 2 – 6 – 7 – 3 – 4 – 9)	
Trial 2	7 – 2 – 8 – 1 – 9 – 6 – 5 – 3 (3 – 5 – 6 – 9 – 1 – 8 – 2 – 7)	

Backward Total Score
Range = 0 to 14

Total Score
Range = 0 to 30

(Sum Forward Total Score & Backward Total Score)

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Appendix E – UPDRS-III (items 18-31)

Full Name :			Date : Drugs with ( ) or without ( )	
1. Mentation			23. *Finger Tapping:* right	
2. Thought - perception			left	
3. Depression			24. *Palm Movements:* right	
4. Motivation/Initiatives			left	
Subset 1-4 (max=16)			25. *Pronation/supination movements of hands:* right	
5. Speech			left	
6. Salivation			26. *Legs Agility:* right	
7. Swallowing			left	
8. Handwriting			27. Arising from Chair	
9. Food cutting			28. Posture	
10. Dressing			29. Gait	
11. Hygiene			30. Postural Stability	
12. Recumbent in bed			31. Body Bradykinesia	
13. Fallings			**Subset 18-31 (max=18)**	
14. Freezing			**Total scores: 1-31 (max=176)**	
15. Walking			32. Dyskinesia (duration)	
16. Tremor			33. Dyskinesia (disability)	
17. Sensory symptoms			34. Dyskinesia (pain)	
Sybset 5-17 (max=52)			35. Early Morning Dystonia	
18. Speech			36. «Offs» (predictable)	
19. Facial Expression			37. «Offs» (unpredictable)	
20. *Resting tremor:* face, lips, chin)			38. «Offs» (sudden)	
Hands: right			39. «Offs» (duration)	
left			40. Anorexia, nausea, vomiting	
Foots: right			41. Sleep disturbances	
left			42. Symptomatic orthostasis	
21. *Action tremor:* right			**Subset 32-42 (max=23)**	
left			**Total scores: 1-42 (max=199)**	
22. *Rigidity:* neck			*Blood pressure:* sitting position	
Upper limb: right			supine position	
left			standing position	
Lower limb: right			*Pulse:* sitting position	
left			standing potition	
			Body weight:	

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CURRICULUM VITAE

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EDUCATION

2009 - 2014 **PhD in Psychology – Cognitive neuroscience**

Dissertation defense: October 30th 2014

PhD dissertation title: *Influence of planning resources on gait control in Parkinson's disease*

Area: Cognitive neuroscience at Wilfrid Laurier University, Waterloo, ON, Canada.

2004 – 2006 **Master of Science in Human Movement**

Dissertation defense: August 14th 2006

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Master of Science dissertation title: *Influence of levodopa on kinematics of the gait with obstacles in Parkinson's disease*

Area: Biodynamic of Human Movement at University of Sao Paulo State (UNESP), Rio Claro/SP, Brazil.

1999 – 2002 **Bachelor in Physical Education**

University of Sao Paulo State (UNESP), Rio Claro/SP, Brazil.

WORK EXPERIENCE

2014 – Teaching undergraduate psychology students at Wilfrid Laurier University – Canada – Ontario:

- Course: Research in Perception.

2014 – Research Assistant at Movement Disorders Research and Rehabilitation Centre – Wilfrid Laurier University.

2006 – 2009 - Teaching undergraduate physical education students at Estacio de Sa University, Sao Paulo, Ourinhos-Brazil:

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- Motor Control & Learning
- Motor and physiological development during life span
- Adapted Physical Activity

2006 – 2009 - Coordinator of exercise programs for senior individuals with physiological and physical restrictions at Estacio de Sa University, Sao Paulo, Ourinhos - Brazil.

TRAINEE EXPERIENCES

2009 – 2014

Sun Life Financial Movement Disorders Research and Rehabilitation Centre – MDRRC (Waterloo, Ontario, Canada);

2004 – 2006

Gait and Posture Laboratory Physical and cognitive assessments – LEPLO (University of Sao Paulo State/Brazil);

2002 – 2003

Teaching exercise for Parkinson's disease people (University of Sao Paulo State /Brazil);

2001 – 2003

Teaching exercise for senior individuals – PROFIT (University of Sao Paulo State /Brazil);

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AWARDS AND NOMINATIONS

- PhD thesis nominated to compete for the *award of excellence* at Wilfrid Laurier University – 2014.
- "Dr. Aftab Patla award" as the second best clinical scientific work at International Society for Posture and Gait Research (ISPGR)/Gait and Mental Function – Norway (July 2012) (Poster presentation).
- PhD Full Scholarship – 2009-2013
- MSc Scholarship – 2004-2006

PUBLISHED MANUSCRIPTS

- **Pieruccini-Faria F,** Ehgoetz Martens K A, Silveira C R A, Jones, J A, Almeida Q J (*in press*) Interactions between cognitive and sensory load while planning and controlling complex gait adaptations in Parkinson's disease*, BMC Neurology*
- Vitorio R, Lirani-Silva E, **Pieruccini-Faria F**, Moraes R, Gobbi LT, Almeida QJ. (2014) Visual cues and gait improvement in Parkinson's disease: Which piece of information is really important? *Neuroscience*. 277C:273-280.
- **Pieruccini-Faria F**, Jones JA, Almeida QJ. (2014) Motor planning in Parkinson's disease patients experiencing freezing of gait: the influence of cognitive load when approaching obstacles. *Brain & Cognition.*87:76-85.

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- Bhatt, H., **Pieruccini-Faria**, F., & Almeida, Q. J. (2013). Dynamics of turning sharpness influences freezing of gait in Parkinson's disease. *Parkinsonism & Related Disorders, 19*, 181-185.
- Ehgoetz Martens, K. A., **Pieruccini-Faria, F.,** & Almeida, Q. J. (2013). Could sensory mechanisms be a core factor that underlies freezing of gait in Parkinson's disease? *PLoS One, 8*, e62602.
- Ehgoetz Martens, K. A., **Pieruccini-Faria, F.**, Silveira, C. R., & Almeida, Q. J. (2013). The contribution of optic flow to freezing of gait in left- and right-PD: Different mechanisms for a common phenomenon? *Parkinsonism & Related Disorders, 19*, 1046-1048.
- **Pieruccini-Faria, F.**, Vitorio, R., Almeida, Q. J., Silveira, C. R., Caetano, M. J., Stella, F., Gobbi, S., & Gobbi, L. T. (2013). Evaluating the acutecontributions of dopaminergic replacement to gait with obstacles in Parkinson's disease. *Journal of Motor Behaviour, 45*, 369-380.
- **Pieruccini-Faria F**, Menuchi MRTP, Vitório R, Gobbi LTB, Stella F, Gobbi S. Kinematic parameters for gait with obstacles among elderly patients with Parkinson's disease, with and without levodopa: a pilot study. *Brazilian Journal of Physical Therapy.* 2006;10(2):233-239.
- Sánchez-Arias, M. D., Silveira, C. R., Caetano, M. D., **Pieruccini-Faria, F.**, Gobbi, L. T., & Stella, F. (2008). Preditores espaço-temporais do andar para testes de capacidade funcional em pacientes com doença de Parkinson *Brazilian Journal of Physical Therapy*, *12*(5), 359-365.

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- Stella F, Gobbi LT, Gobbi S, Oliani MM, Tanaka K, **Pieruccini-Faria F.** Early impairment of cognitive functions in Parkinson's disease. *Arquives of Neuropsyquiatry.* Jun 2007;65(2B):406-410.

CONFERENCE PRESENTATIONS

- Silveira C.R.A., Bell-Boucher D., **Pieruccini-Faria F.**, Roy E.A., Almeida Q.J. Is freezing of gait in Parkinson's disease associated with changes in gaze behaviour? 2014 ISPGR World Congress, Vancouver, Canada, 2014.
- **Pieruccini-Faria, F**; Jones, J.A.; Almeida, Q.J. (2014) How does dopaminergic dysfunction in Parkinson's disease influence planning for stepping over multiple obstacles during gait? Insights from gaze behaviour. International Society for Posture and Gait Research (ISPGR) – Vancouver - (July 2014). Poster presentation.
- **Pieruccini-Faria, F;** Ehgoetz Martens K.A.; Silveira C.R.A.; Jones J.A.; Almeida Q.J. (2013) Predominant left basal ganglia degeneration influences gait of "freezers" in PD. Israel, Dead sea.
- **Pieruccini-Faria, F;** Ehgoetz Martens K.A.; Silveira C.R.A.; Jones J.A.; Almeida Q.J. (2013) Freezing of gait symptoms in Parkinson's impairs vision for perception but not action: evidence from gait with obstacles. World Parkinson's disease conference, Montreal, Canada (October 1-4). Poster presentation
- **Pieruccini-Faria, F**. ; Jones J.A.; Almeida Q.J. (2013) Impact of visual feedback and cognitive restrictions to the planning of an adaptive step during gait in Parkinson's disease. NASPSA 2013 (June 13-17), New Orleans-USA, (Oral presentation).

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- **Pieruccini-Faria, F.** ; Jones J.A.; Almeida Q.J. (2012) Attentional modulation of foot placements when approaching an obstacle in Parkinson's patients with freezing of gait. SCAPPS conference, Halifax, Canada; Oral presentation.
- **Pieruccini-Faria F.**; Jones J.A; Almeida A. What visual source is more important for toe clearances and stability regulation during obstacle crossing? – International Society for Posture and Gait Research (ISPGR)/Gait and Mental Function – Norway - (July 2012). Poster presentation.
- **Pieruccini-Faria F.**; Jones J.A; Almeida A. Influence of dual task and freezing of gait on obstacle crossing behaviour of patients with Parkinson's disease – Movement disorder society conference – Dublin - (July 2012). Poster presentation.
- **Pieruccini-Faria F.;** Jones J.A; Almeida A. (2012) Motor planning is affected by cognitive load in Parkinson's patients with freezing of gait when approaching obstacles – International Society for Posture and Gait Research (ISPGR)/Gait and Mental Function – Norway (July 2012) (Poster presentation).
- Ehgoetz Martens, K. A., **Pieruccini-Faria, F.,** Bloem, B., Almeida, Q. J. Effects of supramaximal dopaminergic replacement on freezing of gait when passing through doorways (2012) - International Society for Posture and Gait Research (ISPGR)/Gait and Mental Function, Trondheim. Oral Presentation.
- Ehgoetz Martens, K. A., **Pieruccini-Faria, F.,** Ellard, C. & Almeida, Q. J. Investigating the relationship between veering in gait and proprioceptive feedback in L-PD and R-PD (2011) Canadian Society for Psychomotor Learning and Sport Psychology (SCAPPS) Winnipeg, Manitoba. Oral Presentation.

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