The effects of physical exercise on cognition of individuals with Parkinson's disease

by

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A thesis

presented to the University Of Waterloo

in fulfilment of the

thesis requirement for the degree of

Doctor of Philosophy

in

Kinesiology

Waterloo, Ontario, Canada, 2016

Authors Declaration

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

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

Statement of Contributions

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

Abstract

Despite motor symptoms being the hallmark of Parkinson's disease (PD), cognitive decline has been shown to affect a large proportion of individuals with PD throughout the course of disease progression. Deficits in cognition have been associated with exacerbated motor dysfunction (i.e. gait), difficulties performing activities of daily living, and decreased quality of life among individuals with PD. The pattern of cognitive decline in PD is heterogeneous and not limited to disruptions in the basal ganglia-thalamo-cortical loops or dopamine depletion. Consequently, the treatment of these deficits is a major challenge. Since the capability of pharmacological therapies to treat cognitive deficits is limited, the combination of pharmacological and non-pharmacological strategies is encouraged. Among non-pharmacological strategies, physical exercise has shown some potential as a complementary strategy for the treatment of cognitive decline in PD. The general aim of this thesis was to investigate the effects of physical exercise on cognition in individuals with PD. The primary goal of Study 1 was to establish the thesis theoretical and methodological frameworks. Specifically, Study 1aimed to investigate the influence of PD on three cognitive processes (i.e. energization, task-setting, and monitoring) mediated by distinct frontal lobes areas that are anatomically connected to the basal ganglia. Three reaction time tasks were used to achieve this aim. Results from Study 1 showed that individuals with PD have selective deficits in monitoring. Importantly, these deficits were not alleviated by dopaminergic medication, confirming the need for complementary therapies to treat cognition in PD. Hence, Study 2 and Study 3 examined the acute (15- and 40-min post a single exercise session) and chronic (12-week exercise program) effects of aerobic exercise on energization, task-setting, and monitoring. Findings from these studies showed neither acute nor chronic effects of exercise on these cognitive processes. In order to address critical gaps in the

literature, Study 3 also compared the effects of aerobic and goal-based exercises to a non-exercise control group on five different cognitive domains (attention/working memory, executive functions, memory, language and visuospatial processing) in cognitively normal and impaired individuals with PD. Results showed that only aerobic exercise improved executive functions in cognitively normal and impaired individuals with PD. In addition, Study 3 revealed that cognitively impaired individuals in the non-exercise control group showed worsening in cognition at post-test. Finally, Study 4 evaluated the effects of aerobic and goal-based exercises on cognition and gait, and examined whether changes in cognition could predict changes in gait after exercise. Findings from this study showed that aerobic and goal-based exercises improved cognition and dual-task gait in cognitively impaired individuals with PD. However, exercise-induced changes in cognition were associated with changes in gait only after aerobic exercise. In conclusion, this thesis showed that cognitive processes regionally organized within the frontal lobes did not improve after acute or chronic exercise stimulation in PD. However, aerobic exercise was shown to improve executive functions in both cognitively normal and impaired individuals with PD. Worsening in cognitive function found in the non-exercise control group over 12 weeks suggests that exercise may prevent cognitive decline in PD. Changes in cognition were positively associated with changes in gait in PD after aerobic exercise. Therefore, this thesis demonstrates that aerobic exercise may be a powerful complementary treatment of cognitive deficits in PD.

Dedication

This thesis is dedicated to all individuals with Parkinson's disease participating in research at the Movement Disorders Research and Rehabilitation Centre, Wilfrid Laurier University.

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Chapter 1

General Introduction

1.1 Parkinson's disease

Parkinson's disease (PD) is a neurological disease characterized by the degeneration of

dopaminergic neurons in the *substantia nigra pars compact* (SNc) of the basal ganglia.

Considered one of the most common neurodegenerative disorders, its incidence is approximately

16-19 cases per 100,000 individuals (Twelves et al., 2003), increasing for every decade of life

beyond the 60th decade, and affecting men more than women (Van Den Eeden et al., 2003).

Since disease biomarkers are yet to be identified, the diagnosis of PD is clinical and based on

four cardinal symptoms: resting tremor, rigidity, bradykinesia (slowness and decreased

movement amplitude), and postural instability. In addition, asymmetric manifestation of

symptoms and responsiveness to dopaminergic therapy allow differentiating PD from other

parkinsonian syndromes (Hughes et al., 1992). Although the cause of PD is unknown

(idiopathic), post-mortem studies have shown that neural degeneration results primarily from

accumulation of the protein alpha-synuclein inside the neurons (i.e. Lewy bodies and Lewy

neurites). A current pathological model of PD progression suggests that this accumulation of

alpha-synuclein starts in neurons in the brain stem (pre-symptomatic stages), then progresses to

neurons in the midbrain including the SNc (onset of motor symptoms), and finally reaches

cortical neurons (dementia) (Braak et al., 2003a, Braak et al., 2003b). The progression of alpha-

synuclein pathology through these anatomical regions has been associated with the manifestation

and progression of both motor and non-motor symptoms of PD. While the treatment of PD is primarily focused on motor symptoms, non-motor symptoms are often undiagnosed and undertreated despite their high prevalence in individuals with PD.

Among non-motor symptoms, deficits in cognitive function have been reported as one of the main contributors to a decreased quality of life by individuals with PD (Barone et al., 2009). Deficits in cognitive function are observed in early (mild impairment) as well as late (dementia) stages of PD progression. A recent longitudinal study involving newly diagnosed and drug naïve individuals with PD found that, at diagnosis, 42.6% of individuals presented with mild cognitive impairment (Domellof et al., 2015). Following a 5-year follow up period, it was demonstrated that 30% of individuals with normal cognition at baseline had transitioned to mild cognitive impairment, while 51% of those with mild cognitive impairment at diagnosis had converted to PD dementia. With a longer follow up period, Williams-Gray et al. (2013) showed that by the 10-year mark from diagnosis 46% of individuals with PD had developed dementia in their cohort. Thus, given the high prevalence of cognitive decline in individuals with PD, the treatment of these deficits should be an important component of the management of PD.

1.2 Deficits in cognitive function in PD

Previous research has demonstrated that deficits in cognitive function in PD are heterogeneous and not limited to dopaminergic dysfunction (Dubois et al., 1990, Bohnen et al., 2006, Kehagia et al., 2010). The heterogeneity of cognitive deficits in PD has been investigated in post-mortem studies linking the progression of alpha-synuclein pathology and the manifestation of cognitive symptoms. These studies support the existence of three disease phenotypes in which the manifestation of cognitive impairment differs in time course and may be

linked to different patterns of cortical neuropathology in addition to dopaminergic damage in the basal ganglia (Halliday and McCann, 2010). Besides dopaminergic depletion, PD has been shown to affect noradrenergic, serotonergic, and cholinergic functions (Kehagia et al., 2010). For example, cholinergic dysfunction was found to be more severe in demented PD patients than those with Alzheimer's disease (Bohnen et al., 2003). With respect to performance on neuropsychological tests, research has shown that cognitive decline in PD is mainly characterized by deficits in executive functions, visuospatial processing, and memory (Aarsland et al., 2010). While deficits in visuospatial processing and memory have been identified as strong predictors of PD dementia (Williams-Gray et al., 2009, Domellof et al., 2015), deficits in executive functions are very common among individuals with PD (Taylor et al., 1986, Owen et al., 1992, Aarsland et al., 2010, Sollinger et al., 2010, Kudlicka et al., 2011). Therefore, deficits in executive functions received greater focus in the current thesis.

1.2.1 Executive functions deficits in PD

Impairments in executive functions such as working memory, set-shifting, planning, and inhibition are well documented in PD (Taylor et al., 1986, Kudlicka et al., 2011, Dirnberger and Jahanshahi, 2013). Executive functions are defined as ''those capacities that enable a person to engage successfully in independent, purposive, self-serving behavior'' (Lezak et al., 2004). Executive functions have also been referred to as the ability to plan, initiate and monitor goal-directed behaviour (McKinlay et al., 2010) required when novel plans of action are formulated and conducted (Owen, 2004). Since deficits in executive functions tests are often observed following frontal lobe damage, the terms *"executive dysfunction"* and *"frontal lobe dysfunction"* are commonly associated. Although previous research has shown that cognitive deficits observed in individuals with PD are similar to those found in individuals with frontal lobe lesions (Owen

et al., 1992, Owen et al., 1993, Owen, 2004), these deficits have been attributed to the disruption of basal ganglia-thalamo-cortical circuitries involving frontal lobe areas rather than impaired frontal functioning per se.

Neuroanatomical studies have shown that the basal ganglia are structurally and functionally connected (via thalamus) with frontal areas of the brain that are known to participate in the processing of executive functions (e.g. dorsolateral prefrontal cortex and anterior cingulate cortex) (Alexander et al., 1986, Middleton and Strick, 2000b, a). The disruption of these called fronto-striatal circuitries was demonstrated by Owen et al. (1998) based on a decrease in activity in the basal ganglia (specifically the globus pallidus internus) when individuals with PD performed a planning task, in contrast to greater activation in healthy individuals. The authors concluded that decreased levels of dopamine disrupt the outflow of information from the basal ganglia to frontal areas. Furthermore, Lewis et al. (2003) showed that, during a working memory task, activation in the basal ganglia (specifically the caudate nucleus) as well as frontal areas were decreased in cognitively impaired individuals with PD.

However, it is important to note that the association between *"executive dysfunction"* and impaired frontal lobe functioning has been a topic of debate (Stuss, 2011). One aspect of this debate relates to the lack of a formal definition of executive functions and the use of neuropsychological tests to its assessment. Studies have suggested that neuropsychological tests used to measure executive functions are complex in nature and may lack construct validity (Jurado and Rosselli, 2007). Testa et al. (2012), for example, demonstrated that correlations between executive functions test variables are weak, suggesting some independence between executive functions skills and the multifactorial nature of neuropsychological measures. Therefore, identifying the "sources" of impairment in executive functions tasks is a challenge

that restricts the ability to define the underlying mechanisms of cognitive deficits. Furthermore, Stuss and Alexander (2007) argued that the activation of a certain area during neuroimaging paradigms does not imply a critical role of the area to the processing of a defined function. Alternatively, it was suggested that the evaluation of individuals with focal lesions in the frontal lobes would allow determining the role of specific frontal lobe areas in cognitive function. Following a series of studies, these authors demonstrated that distinct areas of the frontal lobes are involved in specific cognitive processes that operate in simple as well as complex tasks, and across different cognitive domains (e.g. executive functions, memory, and language) (Stuss et al., 2002, Stuss et al., 2005, Alexander et al., 2007). These processes were defined as the abilities: [1] to initiate or sustain any response (i.e. energization), [2] to set a stimulus-response relationship (i.e. task-setting), and [3] to monitor performance over time for quality control and adjustment of behaviour (i.e. monitoring). Interestingly, the frontal areas found to be critical to the identified processes (superior medial, left lateral, and right lateral, respectively) are known to be anatomically and functionally connected to the basal ganglia (Stuss, 2011). Therefore, investigating the contributions of the basal ganglia to cognitive processes mediated by specific frontal lobe areas may allow a better description of the neural networks underlying these processes. It might also allow a better understanding of the relationship between these processes and patterns of cognitive impairment found in individuals with PD. Finally, whether these cognitive processes are modulated by the dopaminergic system also warrants further research.

1.3 Cognition and motor dysfunction in PD

Given that cognitive deficits may be observed throughout the course of the disease progression, it is evident that motor and cognitive dysfunction may co-exist in PD. Importantly,

associations between cognitive and motor impairments suggest that deficits in cognition may exacerbate motor dysfunction in individuals with PD. Previous research has demonstrated that individuals with PD with cognitive impairment have worse postural instability and gait dysfunction (PIGD) than those without cognitive impairment (Sollinger et al., 2010). In addition, it has been shown that individuals with predominant PIGD symptoms have a faster rate of decline in both cognitive and motor function than those with predominant tremor symptoms (Burn et al., 2006). This selective association between cognitive impairment and PIGD subtype suggests that the progression of cognitive and mobility deficits may share similar underlying mechanisms. This notion has been supported by findings that cholinergic dysfunction is associated with cognitive deficits (Bohnen et al., 2006) as well as with increased number of falls (Bohnen et al., 2009) in individuals with PD.

More specifically, studies have shown that deficits in attention and executive functions are associated with impaired gait in individuals with PD, especially during dual-task walking (Rochester et al., 2004, Yogev et al., 2005, Lord et al., 2010). In contrast to research in older adults with mild cognitive impairment (Montero-Odasso et al., 2014), performance in memory tests were not associated with changes in gait in PD. These findings suggest that specific (rather than general) cognitive functions are associated with gait disturbances in PD. Poor performance on tests assessing executive functions has been associated with a reduction in speed and increased step-to-step variability when individuals with PD perform dual-task walking (Yogev et al., 2005). According to Yogev and colleagues (2005), the unique relationship between executive functions and step-to-step variability suggests that gait rhythmicity and variability may become attention-demanding in PD. In other words, these associations may reflect the reliance of individuals with PD on cognitive resources to control gait due to decreased automaticity (Iansek

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et al., 2013). Hence, the treatment of cognitive deficits may not only have implications for cognition per se but also influence gait dysfunction in PD, since cognitive decline may decrease the ability to compensate for the lack of gait automaticity in PD. However, to date there have been no studies examining whether improvements in cognition can contribute to better gait control in PD.

1.4 Treatment of cognitive deficits in PD

The relevance of cognitive deficits to the lives of people with PD has been demonstrated by a recent study where the need for research investigating the effectiveness of treatments for PD mild cognitive impairment and PD dementia was ranked among the top 10 research priorities from the perspectives of individuals with PD, carers and healthcare professionals (Deane et al., 2014). However, due to its multifactorial underlying mechanism, the treatment of cognitive impairment in PD is an enormous challenge.

According to Emre et al. (2014), there is currently no standard or proven pharmacological treatment for mild cognitive impairment in PD. The gold standard treatment for PD motor symptoms (levodopa) has been shown to selectively influence tasks sensitive to frontal lobe functioning (Gotham et al., 1988). For example, levodopa was found to improve performance on a task assessing attentional flexibility (switching between two tasks) and to impair performance on a task assessing reversal learning (task contingences are reversed after learning) (Cools et al., 2001a). Therefore, it is proposed that while the levels of dopaminergic medication used to treat motor symptoms may be beneficial to cognitive tasks involving the dorsolateral prefrontal cortex (attentional flexibility), it may overload ventrolateral prefrontal areas (reversal learning) and lead to worsening in performance (Cools et al., 2001a). In contrast to PD mild cognitive impairment,

the treatment of cognitive deficits in PD dementia has specific guidelines which include the administration of acetylcholinesterase inhibitors. However, the increased number of drugs to treat motor, cognitive, and psychiatric problems in these individuals may result in severe side effects and decreased quality of life. Thus, it has been proposed that the management of cognitive decline in PD needs to be anchored into the combination of both pharmacological and non-pharmacological treatment strategies in mild and severe stages (Emre et al., 2014).

Although evidence supporting the efficacy of non-pharmacological strategies to treat cognitive decline in PD is limited, these strategies may play a role in preventing or delaying the development of deficits in cognitively intact patients as well the conversion of PD mild cognitive impairment to PD dementia. Regarding the few studies available, a recent review suggested that these investigations lack sufficient sample sizes, description of randomization methods, blinding assessment, appropriate control groups, clearly defined cognitive outcomes, assessment of long term effects, and translation into everyday function (Hindle et al., 2013). Therefore, it is imperative that non-pharmacological trials follow strict scientific methods in order to be considered alongside pharmacological interventions for the treatment of cognitive deficits in PD.

1.4.1 Physical exercise as a complementary non-pharmacological strategy

Among non-pharmacological strategies, studies investigating the effects of physical exercise on cognition have shown positive results in people with PD. Although the underlying mechanisms of how exercise improves cognition are not fully understood, it has been suggested that exercise may increase the levels of neurotrophic factors (e.g. brain-derived neurotrophic factors and insulin-like growth factor-1) that are important for neuronal growth and survival, synaptic efficacy, and neural plasticity (Cotman and Berchtold, 2002). Given that PD is a progressive neurodegenerative disorder, it has been proposed that increased levels of

neurotrophic factors as a result of exercise may influence the progression of PD by preventing

neurons from dying as well as strengthening the activity of remaining neurons (Ahlskog, 2011).

In healthy older adults, exercise has been shown to improve performance in multiple

cognitive domains (Colcombe and Kramer, 2003), decrease risk of dementia (Hamer and Chida,

2009), increase brain volume specifically in the hippocampus (Erickson et al., 2011) and pre-

frontal areas (Colcombe et al., 2006), and increase task-related brain activation (Colcombe et al.,

2004). Although there is a growing body of evidence showing that different types of exercise

and/or the combination of exercise modalities may have positive effects on cognition, the

majority of large randomized controlled trials in healthy individuals have used aerobic training

as the treatment strategy (Colcombe et al., 2004, Colcombe et al., 2006, Erickson et al., 2011).

The fascinating outcomes from these studies support the notion that improvements are driven by

neurophysiological changes (i.e. plasticity) which are independent of training specificity (in

contrast to cognitive training) and may contribute to long lasting effects.

To date, there is a small number of exercise controlled trials targeting cognitive decline in

PD, despite the consensus in the literature that this area of research has vast potential (Ahlskog,

2011, Petzinger et al., 2013). While only one study investigated the *acute effects* of exercise

specifically on executive functions (Ridgel et al., 2011), studies have primarily evaluated the

chronic effects of exercise on cognition in PD. Of these few studies, positive results using

different exercise strategies have begun to be established (Tanaka et al., 2009, Cruise et al.,

2011, McKee and Hackney, 2013, Uc et al., 2014). In line with previous research in healthy

older adults (Colcombe and Kramer, 2003), improvements in cognition were found primarily in

the executive functions domain (Tanaka et al., 2009, Cruise et al., 2011, Ridgel et al., 2011, Uc

et al., 2014). In addition, improvements in spatial cognition were found in one study (McKee and

Hackney, 2013). Therefore, these studies have demonstrated that the use of exercise as a complementary strategy to treat cognition in PD has great potential. However, there were several limitations in previous investigations that prevent establishing exercise as a treatment for cognitive decline in PD.

Firstly, even though improvements in cognition have been attributed to improvements in aerobic capacity, only two studies to date (Uc et al., 2014; Duchesne et al., 2015) have stringently evaluated the effects of aerobic exercise alone (i.e. not confounded by other components). However, even these studies did not compare their effects to other exercise modalities or a PD control group. A current review by Petzinger et al. (2013) suggested that aerobic as well as goal-based exercise (i.e. focused on increasing the quality of movement) may act upon motor and cognitive pathways that are affected by PD promoting neural plasticity. Since previous exercise programs (e.g. multimodal and adapted Tango) involved both goal-based and aerobic components, it remains unknown which component was critical to the improvements in cognitive function found in these studies. Secondly, the majority of studies have failed to define a theoretical framework that rationalized their selected executive functions measures. This has largely hampered the ability to interpret and compare previous findings (Kudlicka et al., 2011, Hindle et al., 2013). Thirdly, studies have left out other cognitive domains such as language, memory, and visuospatial processing which are strongly associated with increased risk of PD dementia. This is imperative to progress the understanding of whether exercise can influence cognitive functions other than executive functions and whether exercise can delay or even prevent the onset of PD dementia. Finally, most studies have excluded individuals with cognitive impairment, which has limited the ability to differentiate the effects of exercise on PD

with and without cognitive decline. In sum, future research must address these limitations in order to effectively progress exercise as a complementary therapy for cognitive decline in PD.

1.5 Research problem

It has been established that cognitive impairment affects a large proportion of individuals with PD throughout the course of disease progression. The pattern of cognitive decline in these individuals is heterogeneous and not limited to disruptions in the fronto-striatal loops or dopamine depletion. In fact, impairments in cognitive functions mediated by posterior brain areas were found to be strong predictors of dementia in PD. Moreover, given the associations between poor cognitive function and gait disturbances, it is likely that cognitive deficits contribute to motor dysfunction in PD. However, the treatment of these deficits is a major challenge. Since the capability of pharmacological therapies to treat cognitive deficits is limited, the combination of pharmacological and non-pharmacological strategies is encouraged. Among non-pharmacological strategies, physical exercise has shown some potential as a complementary strategy for the treatment of cognitive decline in PD. Nonetheless, there are several research gaps that require further investigation. From a theoretical point of view, previous investigations have lacked a theoretical framework with respect to the definition of executive functions and the rationale for executive functions measures. From a treatment point of view, the acute effects of exercise on cognition are practically unknown and it remains unclear which exercise modality is critical to chronic effects on cognition found in individuals with PD. It is even less clear what the effects of exercise on cognition are in individuals with normal compared to those with impaired cognitive function. Lastly, it is unknown if changes in cognitive function may influence motor dysfunction in individuals with PD, especially gait.

1.5.1 Specific aims and hypotheses

Study 1 (Chapter 2): Since theoretical and methodological aspects regarding executive functions deficits in PD limit current understanding of how this disease affects cognition, the first study of this thesis aimed to investigate whether cognitive processes argued to be regionally organized within the frontal lobes are affected by PD and whether these processes are modulated by dopamine. Given the anatomical links between the basal ganglia and the frontal areas found to be critical to each cognitive process, it was hypothesized that individuals with PD would show impairments in all processes while in the OFF medication state compared to healthy individuals. Dopaminergic medication was expected to improve cognitive processes in PD.

Study 2 (Chapter 3): Considering the scarce literature regarding the acute effects of exercise on cognition in PD, the second study of this thesis aimed to define the effects of a single bout of aerobic exercise on cognitive processes mediated by the frontal lobes. Based on findings in healthy young and older adults showing greater frontal activity (assessed using fNIRS) and improvements in behavioural outcomes after a single bout of exercise, it was hypothesized that individuals with PD would show improvement in the target cognitive processes following exercise.

Study 3 (Chapter 4): The third study aimed to evaluate the chronic effects of exercise on cognitive processes mediated by the frontal lobes as well as on tests assessing five different cognitive domains (i.e. attention/working memory, executive functions, memory, language, and visuospatial processing). More specifically, this study compared the effects of aerobic and goal-based training in order to disentangle which exercise component is critical to improvements in cognitive function in PD. Finally, this study investigated the effects of exercise on individuals with and without cognitive impairments. It was hypothesized that aerobic exercise would be

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more beneficial to cognitive function than goal-based training. It was also expected that exercise would improve all cognitive processes mediated by the frontal lobes and multiple cognitive domains; however, a greater improvement was predicted in the executive functions domain. Lastly, it was postulated that both PD patients with and without cognitive impairment would benefit from exercise.

Study 4 (Chapter 5): The forth study aimed to examine whether exercise-induced improvements in cognitive function could lead to better gait control in people with PD. It was hypothesized that, if cognitive impairment exacerbates gait dysfunction in individuals with PD, then improvements in cognition as a result of exercise should alleviate gait deficits in these individuals.

Chapter 2

Deficits in cognitive processes mediated by the frontal lobes are selective in Parkinson's disease

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Abstract

The aim of the present study was to evaluate whether 1) the associated basal ganglia degeneration in Parkinson's disease (PD) affects specific cognitive processes mediated by distinct frontal areas, namely the abilities to initiate and sustain a response (energization), to set a stimulus-response relationship (task-setting), and to monitor performance over time for quality control and adjustment of behaviour (monitoring); 2) these processes are modulated by dopamine; 3) PD clinical features would be associated with deficits in these cognitive processes. Twenty-one PD and 21 age-matched healthy participants completed three reaction time (RT) tasks which progressively increased in complexity (Simple RT, Easy Choice RT, Complex Choice RT). Individuals with PD were assessed in two separate sessions while in their OFF and ON medication state (counterbalanced order). Results showed that only deficits in monitoring were identified in individuals with PD while in the OFF medication state, as supported by an abnormal foreperiod effect in the Easy Choice RT task (trend p=0.07) and increased total number of errors (p=0.036) in the Complex Choice RT task. When individuals with PD were in the ON medication state, an increase in RT variability was found in the Easy Choice RT (p=0.033). These findings suggest that monitoring is selectively affected by PD. Moreover, rather than alleviating deficits in monitoring, dopaminergic medication had detrimental effects on cognition in PD.

Keywords: Parkinson's disease, basal ganglia, frontal lobes, dopamine, cognition

2.1 Introduction

Parkinson's disease (PD) is a chronic neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra pars compact of the basal ganglia. Despite motor symptoms being the hallmark of PD, studies have demonstrated that deficits in cognition are highly prevalent among people with PD (Domellof, Ekman, Forsgren, & Elgh, 2015; Williams-Gray, Foltynie, Brayne, Robbins, & Barker, 2007; Williams-Gray et al., 2013). More specifically, individuals with PD commonly show deficits in tasks that strongly rely on frontal lobe functioning (Aarsland et al., 2010; Bouquet, Bonnaud, & Gil, 2003; Dujardin, Degreef, Rogelet, Defebvre, & Destee, 1999; Dujardin et al., 2013; Owen et al., 1992), such as those assessing executive functions (Dirnberger & Jahanshahi, 2013; Kudlicka, Clare, & Hindle, 2011; Taylor, Saint-Cyr, & Lang, 1986). Deficits in executive functions tests are suggested to result primarily from frontal lobe dysfunction, but it is important to recognize that a disruption to the circuitries between the frontal lobes (e.g. dorsolateral prefrontal cortex) and basal ganglia (especially the caudate nucleus) might account for these deficits in PD (Lewis, Dove, Robbins, Barker, & Owen, 2003; Owen, Doyon, Dagher, Sadikot, & Evans, 1998). Hence, it is important to understand the interactions between the frontal lobes and basal ganglia, since there is potential to identify appropriate treatments for executive functions deficits in PD.

Nonetheless, the use of executive functions tests to evaluate the relationship between the basal ganglia and specific frontal lobe areas is problematic. Executive functions tests are complex in nature and may require reliance on multiple brain areas for successful performance. In addition, given that a formal definition of executive functions has yet to be established, researchers have argued that neuropsychological tests used to assess executive functions may lack construct validity (whether a test measures a specific construct) (Jurado & Rosselli, 2007).

Therefore, the use of assessment methods with greater specificity to clarify brain-behaviour correlates underlying executive functions deficits in PD is critical.

Previous research has shown that outcomes from different executive functions tests are weakly correlated with each other, suggesting a level of independence between different executive skills (e.g. working memory, set-shifting, planning, and inhibition) as well as a multifactorial nature of executive functions tests (Testa, Bennett, & Ponsford, 2012). While independence between executive skills suggests that deficits in executive functions can be selective rather than general (affecting certain skills but not others), the multifactorial nature of executive functions tests suggests that various executive and non-executive components of a task may contribute to successful performance. For example, a classic test in which individuals with PD show impaired performance is the Wisconsin Card Sorting Test (WCST). Although the WCST was originally designed to evaluate abstract reasoning and the ability to shift cognitive strategies, it has been suggested that successful performance in this test requires strategic planning, organized searching, utilizing feedback to shift cognitive sets, directing behaviour toward achieving a goal, and modulating impulsive responses (Heaton, Chelune, Talley, Kay, & Curtiss, 1993). Thus, due to the numerous components involved in this task, it is difficult to determine what specific deficits contribute to impaired performance of those with PD as well as to demonstrate specific links between brain function and behaviour. In order to overcome some the of the controversy surrounding the concept and assessment of executive functions and advance current knowledge on how fronto-striatal deficits contribute to cognitive decline in PD, one alternative is to examine cognitive processes found to be mediated by distinct frontal lobe areas which are anatomically and functionally connected to the basal ganglia.

In a series of studies that investigated the functions of the frontal lobes based on individuals with well-defined frontal lesions, it was consistently demonstrated that at least three cognitive processes are regionally organized within frontal areas (Alexander, Stuss, Picton, Shallice, & Gillingham, 2007; Picton, Stuss, Shallice, Alexander, & Gillingham, 2006; Stuss et al., 2005; Stuss, Binns, Murphy, & Alexander, 2002). These cognitive processes were mainly attentional and found to operate in simple (e.g. Simple reaction time (RT)) as well as complex tasks (e.g. WCST), and across different cognitive domains such as executive functions, memory, and language. The first cognitive process was defined as the ability to initiate or sustain any response (i.e. energization), which was significantly impaired in individuals with lesions in the superior medial areas of the frontal lobes, including the anterior cingulate cortex. Deficits in this process were mainly characterized by slowness in response (i.e. increased RT) that was even greater in complex tasks compared to simple tasks (i.e. Simple versus Choice RT). The second process was defined as the ability to set a stimulus-response relationship (i.e. task-setting), in which individuals with lesions in the left lateral areas of the frontal lobes, including the left ventrolateral and dorsolateral pre-frontal cortices, were consistently impaired. Task-setting deficits were characterized by increased number of false positive errors when participants had to selectively respond to target and non-target stimuli and increased number of errors in the initial stages of a task (i.e. when individuals were still establishing the stimulus-response relationship). The third process was described as the ability to monitor performance over time for quality control and adjustment of behaviour (i.e. monitoring). The monitoring process was shown to be impaired in individuals with lesions in the right lateral areas of the frontal lobes, including the right ventrolateral and dorsolateral prefrontal cortices. Deficits in this process were associated with impaired ability to anticipate stimulus occurrence (i.e. abnormal foreperiod effect), poor

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timing control during a finger tapping task (increased variability), and increased errors of all types (i.e. false positive, false negative, and omissions). Although the frontal areas found to be critical to each cognitive process are known to be linked to the basal ganglia, it remains unknown whether individuals with PD show deficits in energization, task-setting, and monitoring.

The aims of the present study were to investigate whether 1) the cognitive processes of energization, task-setting, and monitoring are impaired in individuals with PD; 2) dopaminergic therapy influences these processes; and 3) a relationship exists between the severity of PD symptoms and these processes. Since it was hypothesized that all of the aforementioned processes would be affected by basal ganglia networks, it was expected that individuals with PD would show deficits in all processes and that these impairments would be alleviated by dopaminergic medication. It was also hypothesized that individuals with PD with greater disease severity would show greater impairment in the cognitive processes compared to those with milder severity. Finally, since asymmetric basal ganglia degeneration is a characteristic of PD, it was hypothesized that severity of motor symptoms in each side of body would be associated with hemisphere specific cognitive processes (left hemisphere: task-setting; right hemisphere: monitoring).

2.2 Methods

The present study was approved by the University of Waterloo and Wilfrid Laurier University research ethics boards. Informed consent was obtained from all individuals prior to participation.

2.2.1 Participants

Twenty-one non-demented individuals with PD (15 male/6 female) and 21 age-matched healthy control participants (HC) (9 male/12 female) were recruited from the Movement Disorders Research and Rehabilitation Centre database at Wilfrid Laurier University (Waterloo, Canada). All participants were fluent in English. Clinical assessment involved the evaluation of participants' cognitive status (Montreal Cognitive Assessment - MoCA), depression signs (Geriatric Depression Scale - GDS), and handedness (15-item Waterloo Handedness Questionnaire). Motor symptoms severity of PD participants was evaluated using the motor subsection of the Unified Parkinson's disease Rating Scale (UPDRS-III) (Fahn & Elton, 1987) by a movement disorders specialist. The OFF state assessment was performed after a minimum of 12 hours withdrawal of dopaminergic medication, whereas the ON state assessment was performed when patients were optimally medicated (approximately one hour after medication intake - see Table 2 Supplementary Material). The OFF and ON procedures occurred in two separate days that were at least one week apart. The medication state in which participants were in the first and second experiment sessions was counterbalanced between participants. None of the participants had undergone surgical procedure to alleviate PD symptoms (e.g., deep brain stimulation). Exclusion criteria included uncorrected vision or colour blindness, and history of neurological conditions other than PD. Participants' demographic and clinical information is shown on Table 1.

Table 1 Participants' demographic and clinical information (Study 1)

Group	Age (years)	Sex	Hand.	Educ.	MoCA	GDS	UPDRS-OFF	UPDRS-ON	UPDRS-R	UPDRS-L
HC n=21	70 (8.18)	9M/12F	20R/1L	16.47 (4.77)	27.85 (1.49)	4.33 (3.67)	-	-	-	-
PD n=21	67.09 (10.41)	15M/6F	20R/1L	15.52 (2.74)	26.66 ⱡ (2.33)	5.85 (5.44)	30.05 (10.89)	21.67* (9.49)	9.07 (3.55)	12.87* (4.8)

Legend: Hand. – Handedness; Educ. – Years of education; MoCA – Montreal Cognitive Assessment; GDS – Geriatric Depression Scale; UPDRS – Unified Parkinson's disease Rating Scale; UPDRS-R – sum of UPDRS scores for upper and lower limbs in the right side of the body; UPDRS-L – sum of UPDRS scores for upper and lower limbs in the left side of the body; ⱡ p=0.055; * p<0.001

Cognitive processes assessment

Three tasks from the *Feature Integration Test* (Stuss et al., 2002) were used in this study: Simple RT, Easy Choice RT, and Complex Choice RT. In the Simple RT task, participants had to make a single button response to every occurrence of a single stimulus. In the Easy and Complex Choice RT tasks participants were asked to press one button with their index finger in response to a target stimulus pre-defined by one (shape, Easy RT) or three (shape, colour, line filling, Complex RT) features and a second button response with their middle finger to all other non-target stimuli. Increases in task demand (i.e., the number of features to be identified and integrated) would require the mental operations of the previous task and the addition of other processes. For all tasks, the stimulus was randomly presented at interstimulus intervals varying between 3 s and 7 s (there were equal numbers of each interstimulus interval). The stimulus stayed on the screen for 2 seconds or until a response was made; participants were instructed to respond as quickly as possible. In Simple RT, the stimulus was a square that was presented 50 times after 3 practice trials. For Easy Choice RT, the target was defined by a simple shape (one of a square, cross or triangle) and occurred on 25% of 102 trials preceded by 10 practice trials (the non-targets were the remaining shapes). For Complex Choice RT, the target was defined by a combination of one of the four shapes, one of four colours (red, yellow, blue, or green) and one of four line fillings (horizontal, vertical, or forward or backward slanting) on 25% of 102 trials, preceded by 10 practice trials. The non-targets in the Complex RT task could either share zero, one, or two features with the target stimulus. The stimuli were dark grey or coloured on a black background on a computer monitor, with a screen measuring 47.5cm (width) x 30cm (height). The monitor refresh rate was set at 75 Hz. Participants were positioned approximately 55cm

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from the monitor. Each task was programed using MEL2 (Psychology Software Tools, Inc.), and responses were made on a Serial Response Box (Psychology Software Tools, Inc.) with five buttons (numbered 1-5 from left to right) aligned horizontally.

Executive functions assessment

Executive functions were assessed using the Wisconsin Card Sorting Test (WCST). Following the procedures described by Stuss and Alexander (2007), the WCST was administered three times which differed in the amount of information given to participants. First, participants were assessed using the standard procedures for the WCST (Milner, 1963). Sixty-four additional cards were administered twice more in succession with differing instructions. In the second round (64A), participants were informed about the sorting criteria (colour, shape, and number), while in the third round (64B), participants were told that the first sorting criterion was colour and that the criterion would switch after ten consecutive correct responses. While overall performance on the WCST was assessed in the standard test format (percentage of correct responses, number of categories completed, and number of set loss errors), the influence of cognitive processes on performance in the WCST was evaluated comparing the number of set loss errors in the standard and the 64B form of test administration. Set loss error was defined as an error following at least three consecutive correct responses, one of which being an unambiguous correct response to demonstrate that the participant experienced the correct sorting criterion. Set loss errors in the standard test format may be attributed to trial and error strategy used by the participant while establishing the sorting criteria and might be related to task-setting process. Conversely, set loss errors in the 64B format may be attributed to impaired monitoring process, since in this format participants were explicitly told what were the criteria, which criteria was the first one, and when criteria were switched (Stuss et al., 2000).

2.2.3 Outcome measures and Statistical Analysis

The main dependent variables in the current study were RT and errors. For all tests, the first two trials and trials faster than 150ms were excluded from the analysis. In addition, slow trials were eliminated if they were 4 standard deviation slower than the group average RT, leading to an exclusion of less than 2% of the trials (Stuss et al., 2005; Stuss et al., 2002). RT analysis was composed by overall RT, RT variability (coefficient of variation= standard deviation/mean *100), RT by stimulus type (i.e. target and non-targets), and RT for short (3 and 4 seconds) and long (6 and 7 s) inter-stimulus intervals. Total number of errors was calculated for all choice RT tasks. Error analysis also involved the comparison of different types of error, naming false positives (calling a non-target as a target) and false negatives (calling a target as non-target), and omissions (no response).

Independent t-tests were used to test differences between the PD OFF and HC for RT and RT coefficient of variation. For Easy and Complex Choice RT, Repeated Measures ANOVAs were used to compare RT between groups for each stimulus type. While in Easy Choice RT there were two stimulus types (target or non-target), in Complex Choice RT there were four stimulus types depending on the number of features shared with the target (0, 1, 2, or 3; where 3 is the actual target). In addition, Repeated Measures ANOVAs were used to test differences in RT between groups for short and long inter-stimulus intervals in the Simple RT and Easy Choice RT tasks. Repeated Measures ANOVAs were used to tests differences in accuracy between groups across error types (FP vs FN vs O) in both choice RT tasks.

Pairwise t-tests were used to compare RT and RT coefficient of variation between PD participants in the OFF and ON states. Repeated Measures ANOVAs were used to test differences in RT between medication states for each stimulus type and for short and long inter-

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stimulus intervals. Repeated Measures ANOVAs were also used to compare error measures between medication states. Since one participant with PD did not take any medication, 20 individuals with PD who completed both OFF and ON assessments were used when comparing the effect of dopaminergic treatment in the outcome measures.

The independent measures used to evaluate the relationship between RT and error measures with clinical features of PD were the total motor UPDRS score and the sum of the UPDRS scores from each side of the body including upper and lower limbs (UPDRS-Right and UPDRS-Left). One-tailed Pearson correlations were used to test the relationship between dependent (RT and error) and independent (total UPDRS, UPDRS-Right, and UPDRS-Left) measures. For this analysis, only PD participants' outcome measures in the OFF state were used as a representation of the parkinsonian brain functioning without the interference of the dopaminergic treatment.

Independent t-tests were used to compare percentage of correct responses, number of categories completed, and number of set loss errors of individuals with PD and HC in the standard format of the WCST. In addition, Repeated Measures ANOVA was used to compare set loss errors in the standard and 64B formats of the WCST.

Tukey post-hoc was used to examine significant differences and alpha level was kept at $p < 0.05$. All statistical analyses were performed on SPSS$^{®}$ version 22 software.

2.3 Results

2.3.1 Demographics and clinical information

PD and HC participants were matched for age, handedness (WHQ), years of education, and depressive state (GDS). With respect to participants' general cognitive status (MoCA), group differences approached significance (p=0.055), with individuals with PD having lower scores than HC. It is important to note that general cognitive status of individuals with PD was assessed while in the OFF medication, and this may have contributed to lower scores in the MoCA. Nonetheless, mean score of PD participants was still above the cut-off score for this test.

Motor severity scores (UPDRS-III) were significantly lower (i.e. improvement) when individuals with PD were in the ON medication state (p<0.001). Lastly, participants showed greater disease severity in the left- compared to the right-side of the body (inferring more severe right basal ganglia degeneration) (p<0.001).

2.3.2 PD OFF vs HC: Contributions of the basal ganglia to cognitive processes

Reaction time

Overall RT was different between PD OFF and HC (F(1,40)=6.19; p=0.017; η_p^2=0.13) in the Simple RT task, showing that the PD OFF group had slower RT than the HC group. For the choice RT tasks, no differences in RT were found between PD OFF and HC participants in both Easy and Complex choice tasks. The variability in RT was not different between PD OFF and HC in any task. Figure 1 shows participants' mean RT across tasks.
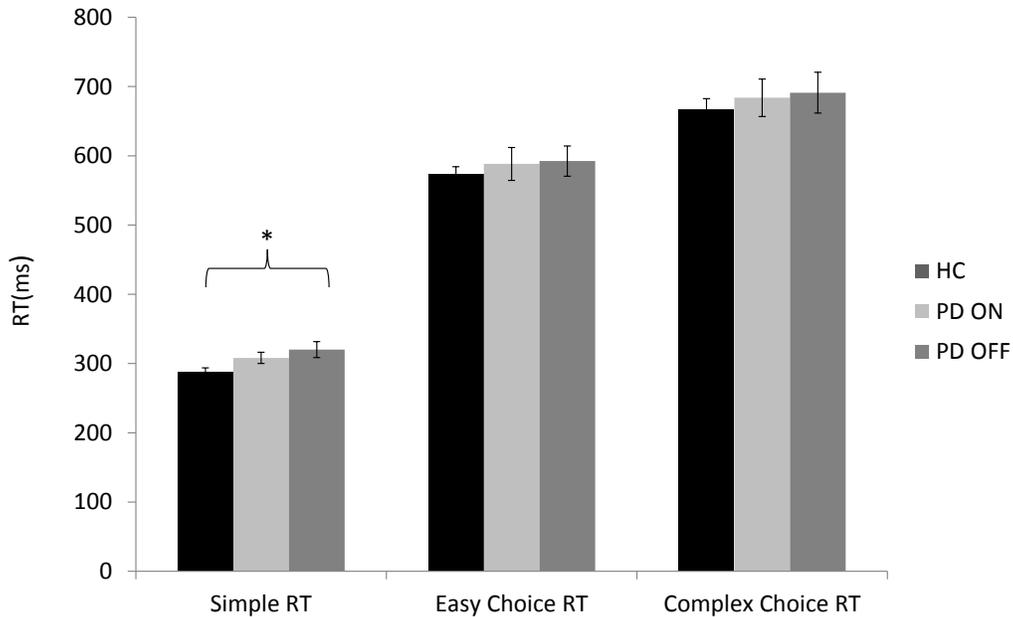
Figure 1 Differences in mean RT between individuals with PD in the OFF state and HC were only observed in the Simple RT task.

When RT was analyzed separately for each stimulus type, a main effect of stimulus type in the Easy Choice RT task (F(1,40)=13.15; p=0.001; η_p^2 =0.24) showed that both PD OFF and HC had similarly slower responses for the target stimuli compared to non-targets. In the Complex Choice RT task, a main effect of stimulus type (F(3,120)=51.04; p=0.000; η_p^2 =0.56) showed both PD OFF and HC groups responded slower when the stimulus was the actual target (p<0.001) or a non-target sharing two common features with the target (p<0.001) compared to non-targets with none or one feature in common with the target.

The influence of the inter-stimulus interval length on participants' RT was examined comparing RT for short and long inter-stimulus intervals. In the Simple RT task, a main effect of inter-stimulus interval showed that both PD OFF and HC demonstrated a normal foreperiod

effect (F(1,40)=59.01; p=0.000; η^2_p =0.59) which is a decrease in RT when inter-stimulus interval

was longer compared to shorter. In the Easy Choice RT task, a main effect of inter-stimulus

interval (F(1,40)=13.18; p=0.001; η^2_p =0.24) showed that PD OFF and HC decreased RT when

inter-stimulus interval was longer compared to shorter; however, a group by inter-stimulus

interval interaction approached significance (F(1,40)= 3.30; p=0.07; η^2_p =0.076). The

examination of this result in Figure 2 reveals that while HC had a normal foreperiod effect, PD

OFF participants showed no discrepancy in RT between short and long inter-stimulus intervals

(i.e. abnormal foreperiod effect).
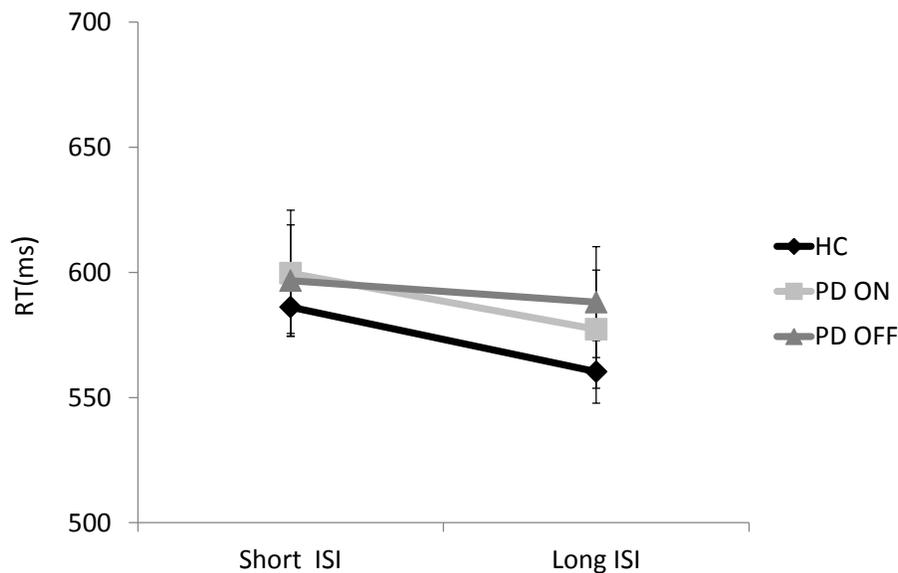
Figure 2 HC showed a normal foreperiod effect (decrease in RT as inter-stimulus interval
increased), while PD participants in the OFF state did not show the same effect in the Easy
Choice RT task.

Accuracy

A main effect of group (F(1,40)=4.62 p=0.038 η_p^2=0.10) showed that PD OFF had a greater number of errors of all kinds compared to HC in the Complex Choice RT task (Figure 3). No main effect of error type or interaction between error type and group were found for the Complex Choice RT task. For the Easy Choice RT no main effect of group or interaction between group and error type were found.
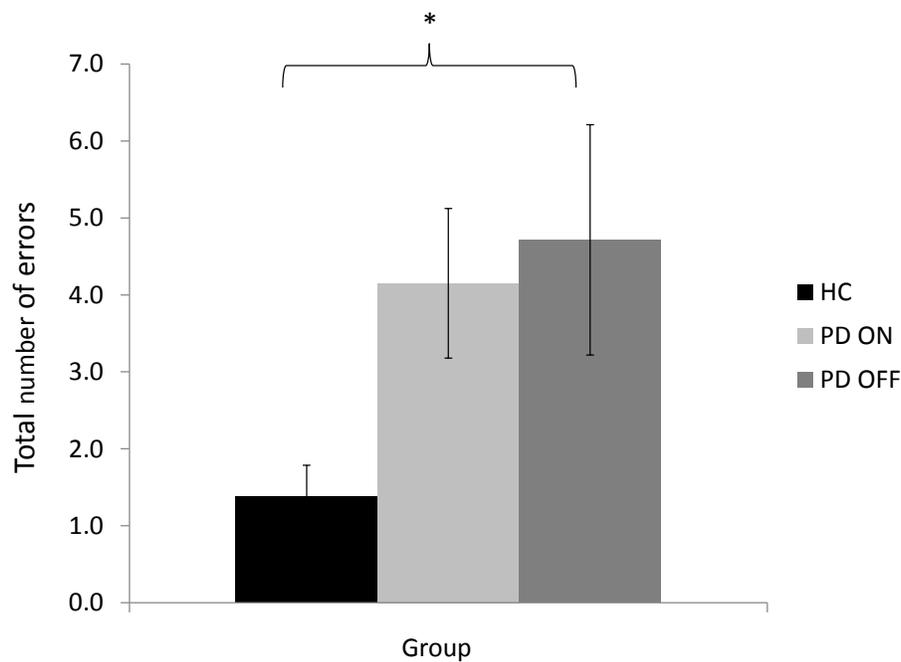
Figure 3 Individuals with PD in the OFF state had greater number of errors than HC in the Complex Choice RT task.

In order to examine whether PD patients with greater deficits in executive functions would show greater deficits in cognitive processes, secondary analyses were run where individuals with PD were divided based on the number of categories achieved in the standard format of the WCST (median split). Given that PD participants with better executive functions

were younger (M=60.6 years) than those with worse executive functions (M=73.0 years) and HC (M=70.0 years), age was included as a covariate in all analyses. A main effect of group in the Simple RT task (F(2,38)=5.18; p=0.010) showed that PD patients with worse executive functions had slower overall RT than HC (p<0.05). In addition, an interaction between group and RT by inter-stimulus interval (F(2,38)=3.21; p=0.05) revealed that only PD patients with worse executive functions had an abnormal foreperiod effect (no difference in RT for short and long inter-stimulus intervals). Finally, a main effect of group in the Complex Choice RT task (F(2,38)=3.71; p=0.034) showed that PD patients with worse executive functions had greater total number of errors than HC participants (p<0.05). Thus, results from this subgroup analyses demonstrated that deficits in cognitive processes were more pronouced in PD patients with worse executive functions, while no differences were found between PD patients with better executive functions and HC.

2.3.3 PD OFF vs PD ON: Does dopamine modulate cognitive processes mediated by the frontal lobes?

Although dopaminergic medication did not significantly change overall RT in Simple as well as choice tasks (Easy Choice RT and Complex Choice RT), differences in RT variability within the PD group while OFF and ON medication states were found in the Easy Choice RT task (F(1,19)=5.30; p=0.033; η_p^2=0.21). This result showed that after taking their regular dose of dopaminergic medication individuals with PD became more variable in their responses. There was no effect of dopaminergic medication on RT for stimulus type or length of inter-stimulus interval.

For the error measures, there were no main effects of medication state or interactions between medication state and error type for both choice RT tasks.

2.3.4 Relationship between cognitive processes and the severity of PD symptoms

Correlation analyses showed that PD OFF overall RT in the Simple RT task was positively correlated with motor disease severity (r=0.42; p=0.03), where slower RT was associated with greater motor disease severity. In addition, PD OFF RT variability in the Simple RT task was positively correlated with motor disease severity (r=0.38; p=0.045), showing that greater variability was associated with greater motor disease severity. Neither associations between disease severity scores and RT in the choice tasks nor associations between unilateral symptom severity and hemisphere-specific outcome measures were found.

2.3.5 Executive Functions Assessment (WCST)

There were no differences between groups in the standard format of the WCST (128 cards). The comparison of set-loss errors between groups in the standard and 64B conditions revealed a main effect of task (F(1,39)=11.41 p=0.002 η_p^2=0.22) , where both PD and HC participants had fewer set loss errors in the 64B condition compared to the standard condition. This result demonstrated that both groups decreased set-loss errors after receiving greater amount of information about the test structure (64B).

2.4 Discussion

The aims of the present study were to investigate whether [1] energization, task-setting, and monitoring were impaired in individuals with PD, [2] these processes were modulated by the

dopaminergic system, and [3] associations between cognitive processes and the severity of PD symptoms exist. Results showed that individuals with PD were impaired specifically in monitoring (abnormal foreperiod effect and increased number of errors of all kinds), but not energization (slower RT only in the Simple task) or task-setting. Contrary to the original hypothesis that dopamine would alleviate deficits in these processes, individuals with PD had worse performance as shown by an increase in RT variability after dopaminergic medication intake (ON state) compared to OFF state. Finally, overall RT and RT variability were associated with motor disease severity scores (UPDRS-III) only in the Simple RT task.

2.4.1 Contributions of the basal ganglia to cognitive processes

Although it was expected that all cognitive processes would be impaired in individuals with PD, results showed that individuals with PD in the OFF state had worse performance than HC participants only in the outcome measures representing the ability to monitor performance over time for quality control (i.e. monitoring). This was shown by an abnormal foreperiod effect and increased number of errors of all kinds. A normal foreperiod effect is characterized by a decrease in RT as a function of increase in time preceding stimulus occurrence (i.e. inter-stimulus interval). Previous research in animal models of PD has showed that striatal dopamine depletion can abolish this effect (Brown & Robbins, 1991), thus suggesting that the dopaminergic system mediates the ability to use temporal information to predict or anticipate stimulus onset. Interestingly, Jurkowski, Stepp, and Hackley (2005) attributed impaired foreperiod effect in PD to a disrupted time keeping mechanism specifically during voluntary tasks. Nonetheless, Picton et al. (2006) argued that while the basal ganglia has a critical role in time keeping, right lateral frontal areas (especially the dorsolateral prefrontal cortex) are responsible for monitoring the passage of time. Therefore, findings from this study may suggest

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that monitoring deficits found in individuals with PD could result from an impaired network processing time information involving (but not limited to) the basal ganglia and right lateral pre-frontal areas. The involvement of right lateral frontal areas in the deficits observed in PD OFF is supported by the greater number of errors of all kinds in the Complex Choice RT task compared to HC, since previous research found that lesions in right frontal areas led to increased number of errors of all kinds in the same task (Stuss et al., 2002). This behaviour was attributed to an inability of individuals with right frontal lesions to note the error and adjust behaviour to avoid errors in consecutive trials. Finally, the notion of these deficits being associated with impaired networks in right hemisphere is further supported by the fact that individuals with PD in the current study had more severe symptoms in the left side of the body, inferring greater right basal ganglia degeneration.

With respect to group differences in overall RT, findings from this study were limited to the Simple RT task. This was in contrast with the study's hypothesis that basal ganglia degeneration could disrupt circuitries between these structures and superior medial frontal areas (including the anterior cingulate cortex) that mediate energization. Similarly to patients with superior medial frontal lesions, it was expected that PD OFF would show slower reaction time than healthy participants across tasks and especially in tasks with greater cognitive processing demands (i.e. Easy and Complex RT). Since individuals with PD in the OFF state were slower than HC participants in the Simple task but not in the choice tasks, this slowness could be attributed to sensorimotor rather than cognitive deficits in PD. This suggestion was further supported by a correlation between RT and UPDRS-III scores only in the Simple task, where individuals with more severe motor impairments had slower Simple RT. This result coincides with Evarts, Teravainen, and Calne (1981) who showed differences between individuals with PD

and healthy controls during simple RT but not during choice RT. Most importantly, these authors demonstrated that speed of movement and speed of response initiation may be independently impaired in individuals with PD, with the first being more "profoundly and consistently affected" (page 183). The authors concluded that choice RT did not seem to be distinctly impaired in individuals with PD, but also acknowledged that task choice could have influenced their results. Previous research has showed that deficits in RT may be task dependent in PD. For example, greater deficits in choice RT were found in individuals with PD in tasks involving attentional flexibility compared to other choice RT tasks (Dujardin et al., 2013). Taken together, results from previous investigations and the current study do not support the notion of slowness of response being due to impaired energization process in PD.

2.4.2 Does dopamine modulate cognitive processes mediated by the frontal lobes?

Interestingly, the only effect of dopaminergic medication found in the current study was an increase in RT variability in the Easy Choice RT task. Since increased RT variability is argued to reflect inconsistency in attention regulation (Stuss, Murphy, Binns, & Alexander, 2003), this finding suggests that dopaminergic medication had a detrimental effect on cognitive function of individuals with PD. Previous research has suggested that dopamine levels used to alleviate motor symptoms may overload areas within the pre-frontal cortex that still have normal levels of dopamine (Cools, Barker, Sahakian, & Robbins, 2001; Gotham, Brown, & Marsden, 1988). For example, Gotham and colleagues (1988) showed that individuals with PD had worse performance on a conditional learning task (i.e. participants had to learn associations between different visual stimuli) while in the ON medication state compared to OFF. Moreover, Owen (2004) suggested that dopamine levels that positively affect cognitive functions processed in the dorsolateral areas may overload ventrolateral areas in the prefrontal cortex. Thus, it is likely that

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dopaminergic treatment used to decrease motor symptoms in this sample may have overloaded some pre-frontal areas and resulted in greater inconsistency in attentional control.

Although it was hypothesized that dopaminergic medication would positively influence performance of PD participants in all RT tasks, neither RT nor accuracy were different between medication states. Jahanshahi, Brown, and Marsden (1992) have showed that dopaminergic medication did not affect Simple or Choice RT in individuals with PD, but it positively influenced movement time. Given that in the current study movement demands were minimal, it is possible that this may have influenced the ability to detect effects of dopaminergic medication in RT outcomes. Furthermore, since no differences in choice RT were found between PD OFF and HC, it could be that RT performance of PD participants was at ceiling and therefore not affected by medication intake. On the other hand, dopaminergic medication did not change response accuracy despite PD participants being less accurate in the Complex Choice RT task. Riekkinen, Kejonen, Jakala, Soininen, and Riekkinen (1998) found that while dopaminergic medication significantly improved reaction and movement time of individuals with PD in Simple and Choice RT tasks, accuracy measures seemed to be sensitive to dysfunctions of the noradrenergic system. Thus, although beyond the scope of the present study, it is important to acknowledge that dopaminergic dysfunction is not the sole mechanism of cognitive impairment in PD (Kehagia, Barker, & Robbins, 2010) and that other neurotransmitters such as noradrenaline and acetylcholine (Bohnen et al., 2006; Dubois, Pilon, Lhermitte, & Agid, 1990; Riekkinen et al., 1998) also contribute to frontal-like deficits observed in individuals with PD.

2.4.3 Relationship between cognitive processes and PD clinical features

Associations between the severity of PD symptoms and cognitive outcome measures were not found in the choice RT tasks, where cognitive demand was higher compared to the

Simple task. These findings corroborate previous research showing lack of correlation between cognitive outcomes and motor disease severity (Bouquet et al., 2003). This might suggest that slowness and variability in performing simple movements are not related to cognitive dysfunction in PD.

2.4.4 Cognitive processes and executive functions in PD

Results from the WCST did not reveal differences in executive functions as reflected in this test between PD and HC participants. In addition, it was found that PD and HC participants were similarly influenced by provision of extra information about test structure, leading to a decrease in set-loss errors from standard to 64B conditions. The lack of group differences in executive functions was unexpected, and it shows that PD participants in this study had relatively preserved cognitive function as measured by this standard neuropsychological test. Most importantly, the expected difference in set loss errors between PD and HC in the 64B condition as a result of monitoring deficits was not identified. It is relevant to note that deficits in monitoring found in this study were modest, therefore they may not have been severe enough to influence performance in a multifaceted test such as the WCST. Moreover, these results indicate that the assessment of cognitive processes may be sensitive to even sudden changes in cognition in individuals with PD.

Limitations of this study include a small sample size considering the well-known intra- and inter-individual variability found in PD. Future studies with larger samples would be able to explore the spectrum of cognitive deficits found among individuals with PD. Moreover, it should be noted that the HC group did not underwent testing procedures at two time points in the same manner as PD participants did (ON and OFF sessions). However, we attempt to control for

practicing effects by counterbalancing the order of medication state in the first session across PD participants. Lastly, it is acknowledged that different theories exist regarding the role of frontal areas in cognitive processing, thus results and interpretations from this study are focused on the investigation of one of these proposed models.

In conclusion, this study shows that PD selectively affected monitoring. In addition, it shows that monitoring deficits did not improve with dopaminergic medication. Conversely, dopaminergic medication had detrimental effects (i.e. increased variability) on cognitive processing of individuals with PD. Finally, deficits in cognitive processes were not associated with disease severity, demonstrating that the progression of cognitive and motor severity in PD may have different underlying mechanisms and trajectories.

Supplementary Material – Chapter 2

Table 2 PD participants' individual severity scores in the OFF and ON medication states, withdrawal time and time of medication intake, levodopa equivalent dose (LED), and medication type

Case	Age	Sex	UPDRS OFF	UPDRS ON	Time OFF (min)	Time ON (min)	LED	Medication
1	80	M	49	40	900	100	500	Levodopa/Carbidopa
2	83	M	40	31	750	260	900	Levodopa/Carbidopa
3	57	M	34	31	750	345	750	Levodopa/Carbidopa
4	54	F	10	6	870	150	375	Levodopa/Carbidopa
5	60	M	40	32	690	345	775	Levodopa/Carbidopa; Rasagiline
6	62	M	43	26	945; 765	60	642.5	Levodopa/Carbidopa; Ropinirole
7	61	F	30	29	930	60	375	Levodopa/Carbidopa
8	79	M	38	27	765	150	850	Levodopa/Carbidopa; Rasagiline
9	87	M	16	11	915	105	1000	Levodopa/Carbidopa
10	71	M	27	*drug naïve*	-	-	-	-
11	65	M	18	15	900	180	375	Levodopa/Carbidopa
12	71	F	41	36	1640	30	160	Ropinirole; Amantadine
13	58	M	22	15	540	150	850	Levodopa/Carbidopa; Rasagiline
14	69	M	36	21	*de novo*	170	475	Levodopa/Carbidopa; Rasagiline
15	65	F	27	21	920	110	1296.75	Levodopa/Carbidopa/Entacapone

16	80	M	26	16	975	135	1000	Levodopa/Carbidopa
17	53	F	21	14	795	170	500	Levodopa/Carbidopa
18	77	M	26	14	1080	180	500	Levodopa/Benserazide
19	64	M	37	25	1260	100	1045	Pramipexole; Levodopa/Carbidopa; Rasagiline
20	56	M	15	10	1080	195	562.5	Levodopa/Carbidopa
21	57	F	37	17	600	45	1250	Levodopa/Carbidopa

Legend: Time OFF – number of minutes since the last dose of medication; Time ON – number of minutes after medication intake

Table 3 Mean and standard deviation of overall RT and RT variability (coefficient of variation) for Simple, Easy Choice, and Complex Choice RT tasks

Group	SRT	ECRT	CCRT	SRT CV	ECRT CV	CCRT CV
HC (n=21)	287.47 (28.39)	573.09 (50.49)	667.43 (68.72)	19.16 (6.28)	20.59 (3.19)	22.69 (3.76)
PD OFF (n=21)	320.16 (53.09)	592.33 (100.58)	691.09 (135.31)	18.26 (4.96)	20.03 (3.13)	23.96 (3.25)
PD ON (n=20)	308.16 (36.61)	588.28 (106.28)	683.76 (120.80)	20.02 (5.01)	22.21 (3.33)	22.90 (4.52)

Legend: SRT – Simple Reaction Time; ECRT – Easy Choice Reaction Time; CCRT – Complex Choice Reaction Time; CV – Coefficient of Variation

Table 4 Mean and standard deviation of RT by stimulus type for Easy and Complex Choice RT tasks

Group	ECRT		CCRT			
	Target	*Non-target*	*F0*	*F1*	*F2*	*Target*
HC (n=21)	586.70 (59.60)	568.72 (52.14)	601.31 (67.29)	618.32 (68.60)	716.05 (77.25)	701.05 (96.23)
PD OFF (n=21)	618.11 (112.77)	583.81 (99.913)	626.04 (144.91)	645.09 (129.90)	722.86 (134.20)	741.61 (168.77)
PD ON (n=20)	620.41 (138.14)	579.01 (100.48)	590.27 (110.60)	635.37 (117.18)	714.74 (127.20)	762.70 (167.91)

Legend: ECRT – Easy Choice RT; CCRT – Complex Choice Reaction Time; F0 – non-target stimulus sharing 0 features with the target stimulus; F1 - non-target stimulus sharing 1 feature with the target stimulus; F2 - non-target stimulus sharing 2 features with the target stimulus

Table 5 Mean and standard deviation of RT for short and long inter-stimulus intervals in Simple and Easy Choice RT tasks

Group	SRT		ECRT	
	Short ISI	*Long ISI*	*Short ISI*	*Long ISI*
HC (n=21)	302.68 (27.30)	271.81 (33.14)	586.10 (48.09)	560.27 (57.55)
PD OFF (n=21)	334.15 (52.36)	305.65 (56.81)	596.71 (102.08)	588.11 (101.40)
PD ON (n=20)	321.91 (43.66)	294.78 (35.82)	599.70 (112.46)	577.29 (105.48)

Legend: SRT – Simple Reaction Time; ECRT – Easy Choice Reaction Time; ISI – inter-stimulus intervals

Chapter 3

Acute effects of aerobic exercise on cognitive function in individuals with Parkinson's disease

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Abstract

Deficits in executive functions are highly prevalent in individuals with Parkinson's disease (PD). Yet, these deficits are not fully alleviated by current pharmacological treatments to PD symptoms. Thus, the effects of non-pharmacological therapies on executive functions have been of great interest in PD. Among these non-pharmacological strategies, physical exercise has shown benefits to executive functions in PD. While most studies have focused on the chronic effects of exercise, evidence of the acute effects of exercise on executive functions is limited in PD. The aim of the current study was to investigate the effects of an acute bout of exercise on cognitive processes underlying executive functions in PD. Twenty individuals with PD were assessed in both a Control and an Exercise conditions that occurred on two separate days and in counterbalanced order across participants. In each condition, individuals started performing a simple and a choice reaction time tasks. Subsequently, participants were asked to sit on a cycle ergometer (Control) or cycle (Exercise) for twenty minutes. Participants were asked to repeat both simple and choice reaction time tasks immediately after the Control and Exercise conditions twice: once after 15- and again after 40-minute rest periods. There were no interactions between time of assessment and experimental conditions in the current study. These findings suggest that individuals with PD may not respond behaviourally to a single bout of acute exercise.

Keywords: Parkinson's disease, acute exercise, aerobic exercise, cognition

3.1 Introduction

While Parkinson's disease (PD) is known as a movement disorder, studies have shown that many individuals with PD experience cognitive deficits, especially in executive functions (Aarsland et al., 2010; Cools, Barker, Sahakian, & Robbins, 2001b; Dirnberger & Jahanshahi, 2013; Kudlicka, Clare, & Hindle, 2011; Taylor, Saint-Cyr, & Lang, 1986). Importantly, deficits in executive functions are linked to difficulties performing activities of daily living (e.g. driving) (Crizzle, Classen, & Uc, 2012), exacerbated motor dysfunction (e.g. gait) (Amboni, Barone, & Hausdorff, 2013; Rochester et al., 2004; Yogev et al., 2005), and decreased quality of life among individuals with PD (Barone et al., 2009). Although impaired performance in executive functions tests are often observed following frontal lobe lesions, deficits found in individuals with PD have been attributed to the disruption of basal ganglia-thalamo-cortical circuitries that loop through frontal lobe areas, rather than impaired frontal lobe functioning per se (Owen, Doyon, Dagher, Sadikot, & Evans, 1998). However, research has shown that executive outcomes are variable in their response to the dopaminergic treatment for nigrostriatal-related PD symptoms (Cools, Barker, Sahakian, & Robbins, 2001a; Gotham, Brown, & Marsden, 1988; Kehagia, Barker, & Robbins, 2010; Owen, 2004). Therefore, complementary therapies to treat these deficits have been investigated in PD.

Among non-pharmacological therapies, there is increasing evidence of the benefits of physical exercise to executive functions in PD (Cruise et al., 2011; Murray, Sacheli, Eng, & Stoessl, 2014; Tanaka et al., 2009; Uc et al., 2014). While this growing body of literature is primarily focused on the chronic effects of exercise, studies investigating the acute effects of exercise on cognition are almost non-existent in PD. The first and only study that evaluated the effects of a single bout of exercise on cognition in PD (Ridgel, Kim, Fickes, Muller, & Alberts,

2011) showed significant improvements in executive functions after 30 minutes of *passive* cycling on a motorized cycle ergometer. This was demonstrated with a reduction in the total time to complete part-B of the Trail Making Test, and specifically by a reduction in the time spent on each target (number or letter) prior to a shift. Yet, an important limitation of this study was the lack of a control condition in which participants did not undergo the experimental manipulation (passive cycling).Thus, it remains unclear whether positive results were due to passive cycling or practice effects associated with repeating the task for a second time. In addition, it is important to note that the mechanisms underlying the effects of passive exercise on cognition are not well understood. In contrast, studies investigating the mechanisms underlying acute effects of exercise on cognition in healthy individuals have mostly used *active* exercise. However, the acute effects of *active* exercise on cognition have yet to be investigated in PD.

In neurological healthy young and older adults, behavioural effects following an acute bout of (*active*) exercise have been observed through decreases in reaction time (RT), especially in tasks requiring greater executive control (Hyodo et al., 2012; Kamijo et al., 2009; McMorris & Hale, 2012; Tsai et al., 2014; Yanagisawa et al., 2010). Importantly, improvements in behavioural response have been explained by studies using electrophysiological measures (i.e. P300 latency and amplitude) suggesting that an acute bout of aerobic exercise can increase cognitive processing speed as well as improve allocation of cognitive resources (Hillman, Snook, & Jerome, 2003; Kamijo et al., 2009; Tsai et al., 2014). In addition, neuroimaging studies have demonstrated that improvements in behavioural responses were associated with greater activation of prefrontal areas in young and older adults (Hyodo et al., 2012; Yanagisawa et al., 2010). Thus, it has been argued that an acute bout of exercise may selectively influence executive functions as a result of increased frontal lobe activation. In this context, it could be

hypothesized that exercise may improve drive from frontal areas into fronto-striatal loops and potentially improve cognitive processing in individuals with PD.

Perhaps the most critical aspect to be overlooked in previous investigations is that a clear rationale for the choice of assessment tasks is rarely provided. While it may seem reasonable to suggest that the sensitivity of executive functions tasks to acute effects of exercise is a complete justification, one may find a wide variety of executive functions tests to choose from and selecting the appropriate test to answer specific research questions may be a challenge. Further, because a formal definition of executive functions has yet to be established, researchers have argued that tests assessing executive functions may lack construct validity (whether a test actually measures a specific construct) (Jurado & Rosselli, 2007). In addition, it has been found that outcomes from different executive functions tests are poorly correlated, suggesting that deficits in executive functions may be specific rather than general (Testa, Bennett, & Ponsford, 2012). Lastly, the multifactorial nature of executive functions tests may require the recruitment of several brain areas for successful performance, making it difficult to reveal specific brain-behaviour relationships (Stuss, 2011). Thus, in order to better understand the acute effects of exercise on cognition, the provision of clear rationale for tests selection is a fundamental aspect to be considered.

In the present study the choice of testing procedures was based on lesion studies with frontal lobe patients, which demonstrated that at least three cognitive processes underlying performance in executive functions tests are regionally organized within the frontal lobes. These processes were defined as the abilities [i] to initiate and sustain a response (energization), [ii] to set a stimulus-response relationship (task-setting), and [iii] to monitor performance over time for quality control and adjustment of behaviour (monitoring) (Alexander, Stuss, Picton, Shallice, &

Gillingham, 2007; Stuss & Alexander, 2007; Stuss, Binns, Murphy, & Alexander, 2002).

Deficits in these processes were found to underlie impaired performance in classic

neuropsychological tests assessing executive functions such as phonemic verbal fluency, Stroop

test, and the Wisconsin Card Sorting Test (Stuss & Alexander, 2007). Most importantly, the

frontal lobe areas found to be critical to each cognitive process (superior medial, left lateral, and

right lateral, respectively) are known to anatomically and functionally linked to the basal ganglia

(Alexander, DeLong, & Strick, 1986; Middleton & Strick, 2000a, 2000b). In fact, findings from

this thesis demonstrated that individuals with PD have deficits in monitoring, supporting the

notion that the basal ganglia may be involved in operating at least some of these cognitive

processes (see Chapter 2). Therefore, in order to assess the acute effects of exercise on

energization, task-setting, and monitoring the current study used two RT tasks which were the

same as those used in previous research with frontal lobe (Stuss et al., 2002) and PD patients

while assessing the role of frontal and basal ganglia structures in these processes (see Chapter 2).

By investigating the effects of an acute bout of exercise on cognitive processes regionally

organized within the frontal lobes, this study could provide greater understanding of the selective

effects of exercise on cognitive function of individuals with PD.

Thus, the aim of the present study was to investigate the effects of a single bout of *active*

aerobic exercise on cognitive processes underlying executive functions in PD. The acute effects

of exercise on energization were assessed through the outcome measure overall RT. Since

energization deficits are characterized by slowness in RT, positive effects of exercise on

energization would be characterized by faster RT. The acute effects of exercise on task-setting

were assessed through the outcome measures RT by stimulus type (target vs non-target) and

number of false positive errors. Since deficits in task-setting are characterized by an inability to

establish the criteria defining a target stimulus in order to promptly and accurately select the correct response, then improvements in task-setting would be characterized by faster RT for target stimulus and decrease in false positive errors. The acute effects of exercise on monitoring were assessed through the outcome measures RT by inter-stimulus interval and total number of errors. Given that monitoring deficits lead to inability to anticipate/predict time of stimulus onset and to note an error for appropriate adjustment of behaviour, then positive effects of exercise on monitoring would be characterized by faster RT for long inter-stimulus intervals compared to short as well as decrease in the total number of errors.

3.2 Methods

The present study was approved by the University of Waterloo and the Wilfrid Laurier University research ethics boards. Informed consent was obtained from all individuals prior to participation.

3.2.1 Participants

Participants included 20 male and female adults with confirmed diagnosis of PD, taking appropriate medication, and with medical clearance to exercise. Participants were recruited from the database of the Movement Disorders Research and Rehabilitation Centre (MDRC) at Wilfrid Laurier University (Waterloo, Canada). The follow exclusion criteria were employed: history of neurological diseases other than PD, unstable medical condition, uncontrolled diabetes mellitus, uncontrolled hypertension (BP>140/90), history of heart disease, resting heart rate >100, history of stroke, history of chronic obstructive pulmonary disease, or uncorrected visual impairments (including colour blindness). Participants' demographic and clinical information are displayed in Table 6.

Table 6 Participants' demographic and clinical information (Study 2)

Participants	Age (years)	Sex	Hand.	Educ.	MoCA	GDS	UPDRS III
PD (n=20)	66.55 (10.11)	13M/7F	19R/1L	16.05 (3.61)	27.1 (2.46)	7.35 (5.33)	16.35 (5.89)

Legend: Hand. – Handedness; Educ. – Years of education; MoCA – Montreal Cognitive Assessment; GDS – Geriatric Depression Scale; UPDRS III– Unified Parkinson's disease Rating Scale motor subsection

Participants completed three assessment sessions, in three separate days, and while in their ON medication state. The first session consisted of baseline evaluation of participants' clinical and physical conditions, while the second and third sessions consisted of the experimental conditions when participants' cognitive function was assessed before and after an acute bout of Exercise or a Control condition (Figure 4). The second and third sessions were a week apart and scheduled at the same time. Participants performed Control and Exercise conditions in a counterbalanced order and served as their own controls (cross-over design).

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                    ┌─────────────────────────────┐
                    │  Day 1 – Baseline Assessment │
                    └─────────────────────────────┘
                                    │
         ┌──────────────────────────────────────────────────────┐
         │          Disease Severity (UPDRS III)                 │
         │  Questionnaires (anxiety & depression, handedness)    │
         │         General Cognitive Status (MoCA)               │
         │              Graded Exercise Test                     │
         └──────────────────────────────────────────────────────┘
                                    │
                 ┌──────────────────────────────────────┐
                 │  Days 2 and 3 – Experimental conditions│
                 │        (counterbalanced order)         │
                 └──────────────────────────────────────┘
                                    │
            ┌───────────────────────┴────────────────────────┐
    ┌───────────────┐                                 ┌───────────────┐
    │ Acute Exercise│                                 │    Control    │
    └───────────────┘                                 └───────────────┘
            │                                                  │
  ┌──────────────────────┐                        ┌──────────────────────┐
  │ Simple and Choice RT │                        │ Simple and Choice RT │
  └──────────────────────┘                        └──────────────────────┘
            │                                                  │
  ┌──────────────────────┐                ┌───────────────────────────────────┐
  │20 minutes cycling    │                │20 minutes sitting on cycle        │
  │exercise              │                │ergometer                          │
  └──────────────────────┘                └───────────────────────────────────┘
            │                                                  │
  ┌──────────────────────┐                        ┌──────────────────────┐
  │ t₁: 15 min delay     │                        │ t₁: 15 min delay     │
  └──────────────────────┘                        └──────────────────────┘
            │                                                  │
  ┌──────────────────────┐                        ┌──────────────────────┐
  │ Simple and Choice RT │                        │ Simple and Choice RT │
  └──────────────────────┘                        └──────────────────────┘
            │                                                  │
  ┌──────────────────────┐                        ┌──────────────────────┐
  │ t₂: 40 min delay     │                        │ t₂: 40 min delay     │
  └──────────────────────┘                        └──────────────────────┘
            │                                                  │
  ┌──────────────────────┐                        ┌──────────────────────┐
  │ Simple and Choice RT │                        │ Simple and Choice RT │
  └──────────────────────┘                        └──────────────────────┘
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Figure 4 Assessment flow chart (Study 2)

3.2.2 Apparatus and Experimental Procedures

Baseline evaluation

Upon arrival, participants were asked to fill out two questionnaires. The first (Geriatric Depression Scale) provided information about participants' depression and anxiety signs and the second (15-item Waterloo Handedness Questionnaire) evaluated participants' hand preference. Subsequently, the severity of PD motor symptoms was assessed by a certified movement disorders specialist using the motor subsection of the Unified Parkinson's disease Rating Scale (UPDRS III) (Fahn & Elton, 1987). Participants' general cognitive status was assessed using the Montreal Cognitive Assessment (MoCA). Finally, participants' aerobic fitness level was assessed through a submaximal graded exercise test on a cycle ergometer.

In order to assess participants' fitness levels and define individual parameters for exercise prescription, a submaximal graded exercise test was completed. In this test, participants started with a 2 minute warm up with no load on the cycle ergometer. Participants began the graded exercise test cycling with a workload of 30 watts at 50 rotations per minute. Then, the workload was increased every minute (15 watts/per increment unit) until participants achieved testing termination criteria. The protocol was terminated if two of the following criteria were achieved: participant's heart rate reached 70% of the age-predicted maximal heart, respiratory exchange ratio (RER) was greater than 1.1, participant rate of perceived exertion (RPE) was greater than 16, or participant asked to stop. The equation to predict maximal heart rate was [208-(0.7* age)] (Tanaka, Monahan, & Seals, 2001) and [164-(0.7*age)] for individuals on β-blockers (Brawner, Ehrman, Schairer, Cao, & Keteyian, 2004). Gas exchange (levels of oxygen (O_2) and carbon dioxide (CO_2)) was recorded breath-by-breath using an Ergocard Cardiopulmonary Stress Test Metabolic Cart (Roxon medi-tech ltd. St-Leonard, Quebec, Canada). Heart rate was recorded at

rest, continuously during, and after the test using a Polar HR monitor (Lachine, Quebec,

Canada). After the test, HR was monitored until it returned to values close to baseline. Blood

pressure (BP) was measured using an OMRON® 7 series blood pressure monitor at rest (sitting

and standing) and after the completion of the test. VO_2 values at test termination were recorded

and used as a reference of participants' fitness levels. The influence of participants' baseline

fitness levels on cognitive outcomes was examined as a confounding factor, since research has

demonstrated that individuals with higher fitness levels have more efficient cognitive control

than those with lower fitness levels (Colcombe et al., 2004).

Exercise condition

Immediately following the pre-tests of simple and choice RT, participants exercised on a

recumbent cycle ergometer (700 Excite + Recline, Technogym USA©, Seattle, Washington) for

20 minutes at a set intensity of 50% heart rate reserve (HRR). Intensity prescription was defined

based on the Karvonen method which was expressed in the equation Target HR = ([(HRmax -

HRrest)* 0.5)]+HRrest) (ACSM, 2000). Heart rate, workload, and rate of perceived exertion

recordings from baseline graded exercise test were used in order to lead participants to the

desired exercise intensity. Subsequently, participants rested on a comfortable chair for 15

minutes. After the resting period, participants were invited to repeat the simple and choice RT

tasks (t_1). This procedure was also repeated 40 minutes after exercise completion (t_2). Exercise

duration and intensity as well as time of post assessment were chosen based on a meta-analysis

(Chang, Labban, Gapin, & Etnier, 2012), where the largest effects of acute aerobic exercise on

cognition were found after 20 minutes-long sessions of moderate intensity exercise (45% - 55%

HRR; rate of perceived exertion 12-13) and following a post-assessment delay between 11 and

20 minutes. Post-testing assessment at 40 minutes was used to examine whether fatigue played a

role on behavioural response at the first post-test time point (15 minutes), since participants would then have had longer time to recover from exercise.

Control condition

In the Control condition participants started with the simple and choice RT tasks and after the completion of these tests they were invited to sit on the same cycle ergometer in which the Exercise condition was performed for 20 minutes in the company of a trained volunteer. Later, participants sat on a comfortable chair for 15 minutes which corresponded to the resting period during the exercise session. Participants repeated both simple and choice RT tasks 15 minutes (t1) and 40 minutes (t2) after the completion of the Control condition.

3.2.3 Outcome measures

Reaction Time

Simple and Complex Choice RT tasks from the *Feature Integration Test* (Stuss et al., 2002) were used to assess the effects of exercise on energization, task-setting, and monitoring. Detailed information regarding experimental setup, testing procedures, and data processing can be found in Chapter 2 of this thesis.

The stimulus in these tasks was one of the four shapes: square, circle, triangle, or cross. The shapes were dark grey or coloured on a black background. For both tasks, stimuli were randomly presented at interstimulus intervals varying between 3 s and 7 s. Each stimulus stayed on the screen for 2 seconds or until a response was made. Each task was programed using MEL2 (Psychology Software Tools, Inc.), and responses were made on a Serial Response Box (Psychology Software Tools, Inc.) with five buttons (numbered 1-5 from left to right) aligned horizontally.

In the Simple RT task, the stimulus was a grey square presented 50 times after 5 practice trials. Participants were instructed to press button number 1 in the serial response box as fast as possible whenever they saw the square. In the Complex Choice RT task, all shapes (square, circle, triangle, and cross) were presented in random order 102 times (one shape at a time), preceded by 10 practice trials. Each shape was coloured (red, blue, green, or yellow) and filled with a different pattern of internal lines (vertical, horizontal, diagonals to the right, or diagonals to the left). Thus, each stimulus varied in a combination of shape, colour and internal line orientation. A pre-determined target stimulus was defined by a specific combination of these three features (shape, colour, internal lines), while the other combinations were non-targets. The target stimulus occurred randomly on 25% of the trials. Participants were asked to respond to the target stimulus by pressing button number 1 with their right index finger, while they were asked to respond to non-target stimuli by pressing button 2 with their right middle finger on the serial response box. Four stimulus types existed in the Complex Choice RT task depending on the number of features shared with the target (0, 1, 2, or 3; where 3 was the actual target).

3.2.4 Statistical analysis

The dependent variables in the current study were RT and errors. RT analysis was composed of overall RT, RT variability (coefficient of variation), RT by stimulus type (i.e. target vs non-targets), and RT for short and long inter-stimulus intervals (ISI). Total number of errors was calculated for the Complex Choice RT task. Error analysis also involved the comparison of different types of error, namely false positives (calling a non-target as a target) and false negatives (calling a target as non-target). Repeated measures analysis of variance (RM ANOVA) was used to test differences in RT and RT coefficient of variation before and after the acute bout of Exercise and the Control conditions (2 conditions (exercise and control) x 2 times (pre and

post)). RM ANOVA was used to test differences in RT between experimental conditions for short and long ISI exclusively for Simple RT (2 conditions (exercise and control) x 2 time (pre and post) x ISI (short and long). RT at short ISI was calculated based on the mean RT for 3 and 4 seconds ISIs, while RT at long ISI was calculated based on the mean RT for 6 and 7 seconds ISIs. In addition, RM ANOVA was used to compare RT between conditions for stimulus type (2 conditions (exercise and control) x 2 time (pre and post) x stimulus type (F0, F1, F2, target)) exclusively for Complex Choice RT. RM ANOVA was used to compare the total number of errors and error type for Complex Choice RT (2 conditions (exercise vs control) x 2 time (pre vs post) x 2 error types (false positive vs false negative)). Tukey post-hoc was used to examine significant differences and alpha level was kept at $p<0.05$. Given that only 14 out 20 participants in the current study completed post-testing at the 40 minutes time point, these data is presented as complementary analysis including a third level into the time of assessment factor of each RM ANOVA. Finally, since previous research has demonstrated that level of fitness may influence one's response to a single bout of aerobic exercise (Tsai et al., 2014), Pearson correlations were used to test whether changes in RT and accuracy were associated with participants' VO_2 value at test termination.

3.3 Results

3.3.1 Reaction time

The pre and post (t_1) comparison of overall RT in each experimental condition revealed no differences in Simple RT following the Exercise or the Control session (Figure 5 - left). In the secondary analysis that included two post-testing time points, a main effect of assessment time

$(F(2,26)=4.58; p=0.019; \eta_p^2 =0.26)$ was identified. For this main effect, Tukey post-hoc showed

that participants had slower RT at t_2 (40 min delay) compared to pre-test in both Exercise and

Control conditions (p=0.015). For Complex Choice RT, a main effect of assessment time

$(F(1,19)=7.64; p=0.012; \eta_p^2 =0.28)$ showed that participants had faster RT at t_1 compared to pre-

test regardless of experimental condition (Figure 5 - right). The secondary analysis including two

post-testing time points also revealed a main effect of assessment time (F(2,26)=3.79; p=0.035;

$\eta_p^2 =0.22)$, where participants showed faster RT only at t_1 compared to pre-test (p=0.02). There

were no significant difference in RT between t_1 and t_2.
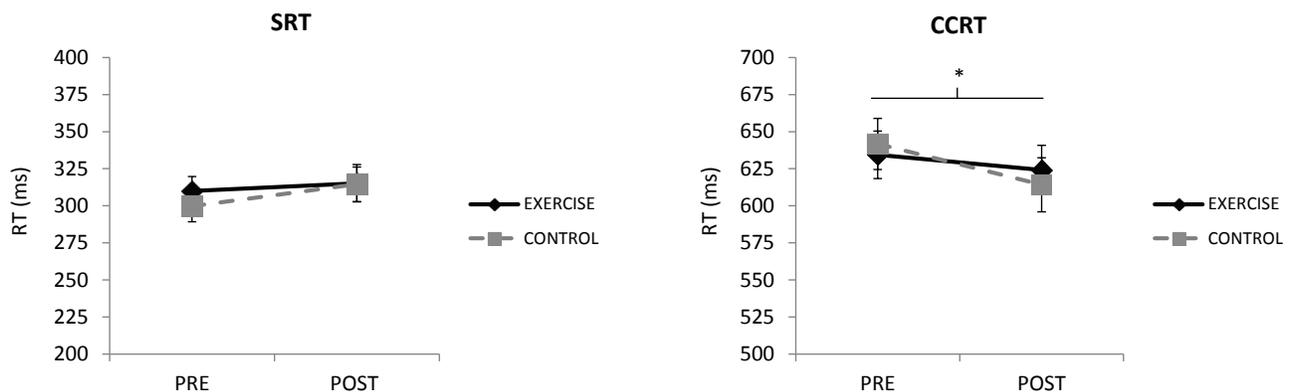
Figure 5 Participants showed no change in Simple RT (SRT) following both experimental
conditions (left). Conversely, they showed faster RT in the Complex Choice RT task (CCRT)
after both Exercise and Control conditions (right).

RT variability did not change from pre to post (t_1) in all experimental conditions for

Simple RT and Complex Choice RT. Secondary analysis with two post-testing time points also

showed no differences in RT variability after 15 minutes (t_1) or 40 minutes (t_2) delays.

The analysis of RT for short and long ISI aimed to demonstrate whether exercise could improve the ability of participants to predict stimulus occurrence. This is characterized by a decrease in RT for long compared to short ISI. Following the same procedures as previous research, this analysis was run for the Simple RT but not Complex Choice RT (Stuss et al., 2002). A main effect of ISI demonstrated that, overall, participants showed the expected reduction in RT for longer ISI compared to shorter (F(1,19)=96.86; p<0.0000; η_p^2 =0.83). An interaction between assessment time and ISI neared significance (F(1,19)= 4.13; p=0.056; η_p^2 =0.17), showing that at post-test (t_1) participants had slower RT during short ISI compared to performance at pre (p=0.006) (Figure 6). No pre and post differences were found in RT for long ISI. Importantly, these findings occurred across experimental conditions, revealing no specific effect of exercise in participants' ability to predict stimulus occurrence. Secondary analysis with two post-testing points also revealed a main effect of ISI (F(1,13)=64.30; p<0.0000; η_p^2 =0.83), where participants showed faster RT for longer compared to shorter ISIs. No significant interactions were found in this secondary analysis.

EXERCISE: RT by ISI

CONTROL: RT by ISI
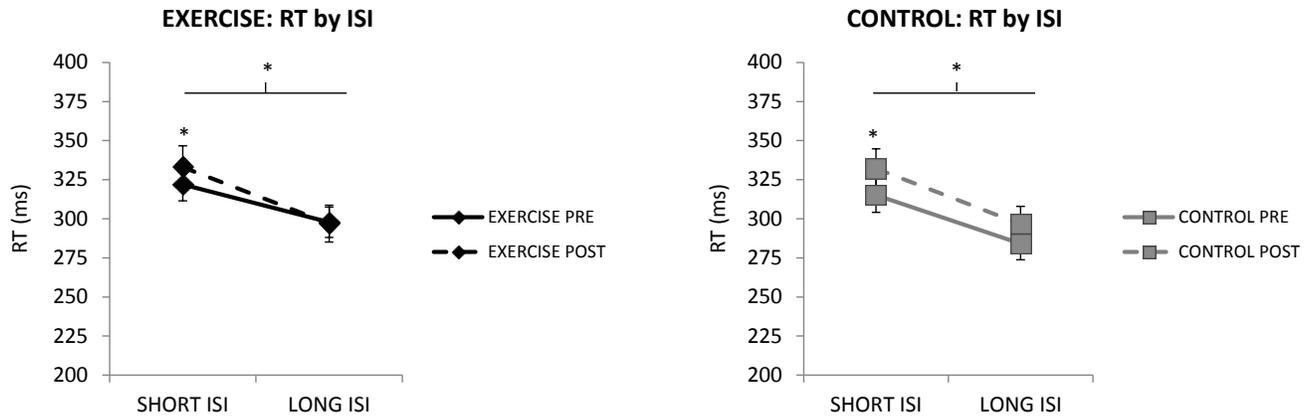
Figure 6 Participants showed faster RT for long ISI compared to short ISI regardless of experimental condition. In addition, participants had slower RT for short ISI at post compared to pre-test in both conditions.

Finally, RT was analyzed with respect to stimulus type for the Complex Choice RT task. A main effect of number of features was found ($F(3,57)=96.67$ $p<0.0000$; $\eta^2_p=0.83$), showing that across experimental conditions participants had faster RT for stimulus sharing none or one feature with the target compared to stimulus sharing two features with target or the target itself ($p<0.0001$) (Figure 7). There was no selective effect of exercise on response to target and non-target stimuli or any effect of assessment time. Secondary analysis with two post-testing time points also showed only a main effect features on RT ($F(3,39)=66.41$; $p<0.0000$; $\eta^2_p=0.83$), once again demonstrating that participants had faster RT for stimuli sharing none or one feature with target compared to stimulus sharing two features with target or the target itself ($p<0.0001$).
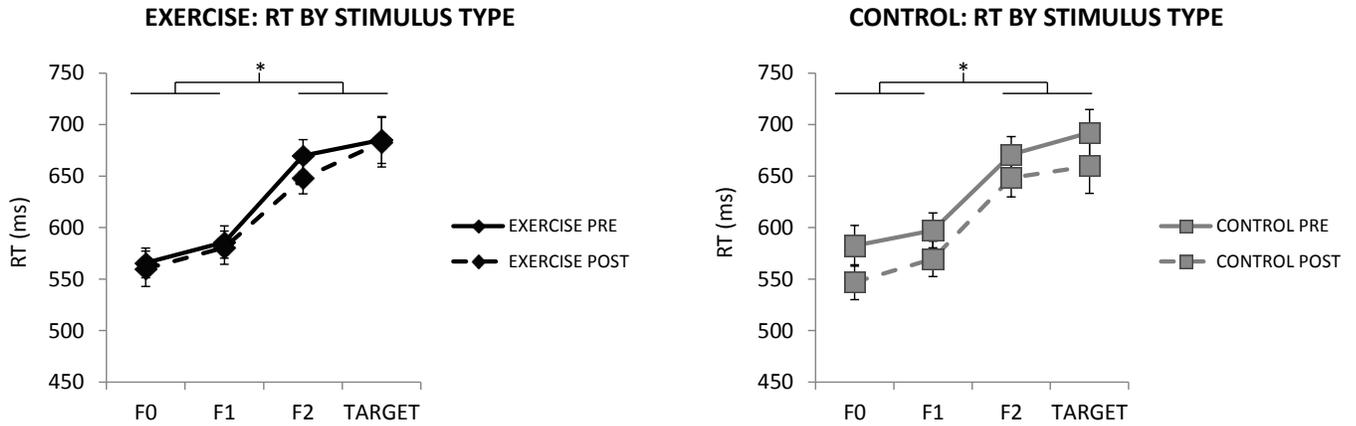
Figure 7 Participants responded faster to non-target stimuli sharing none or one feature with the target compared to stimuli sharing two features or the target itself, regardless of experimental condition or assessment time point.

3.3.2 Accuracy

An interaction between experimental condition and assessment time approached

significance (F(1,19)=4.23; p=0.053; η_p^2 =0.18) for the error measures (Figure 8). Although post-

hoc test did not reveal any statistical difference, mean values suggested that participants were

slightly less accurate following the Exercise condition.

CCRT TOTAL ERROR
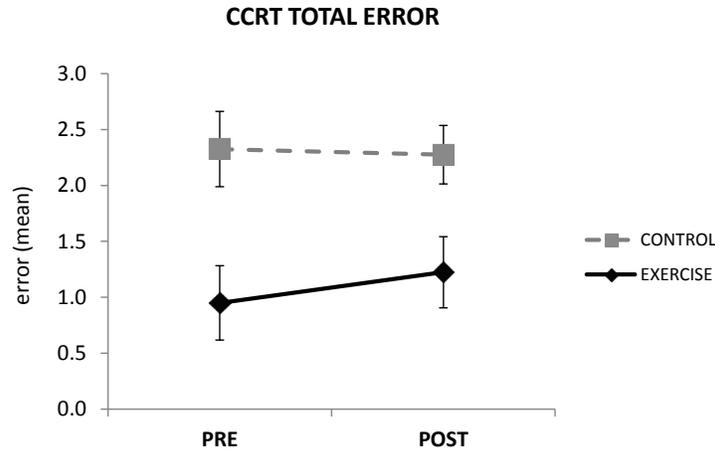
Figure 8 Participants were slightly less accurate following an acute bout of aerobic exercise.

For the secondary analysis with two post-testing time points, an interaction between experimental condition and assessment time ($F(2,26)=3.27$; $p=0.053$; $\eta_p^2=0.20$) approached significance. This interaction showed that in the Exercise condition, participants made less errors after post-test t_2 (40-min) compared to t_1 (15-min) ($p=0.01$). However, there was no difference in accuracy between pre-test and post-test t_2.

3.3.3 Association between cognitive outcomes and fitness level

There were no associations between RT or accuracy and VO_2 values at test termination.

3.4 Discussion

The aim of this study was to investigate the effects of a single bout of *active* aerobic exercise on energization, task-setting, and monitoring cognitive processes in PD. Although it was

expected that participants would show faster RT following an acute bout of exercise, results did not support this hypothesis. Participants also showed slightly worse accuracy 15 min after a single bout of exercise. Although accuracy improved from the first (15 min) to the second (40 min) post-test time points, accuracy levels at 40 min were not different than those at pre-test.

In the current study the effects of a single bout of exercise on cognitive function of individuals with PD was examined using RT tasks with varying complexity levels. These tasks have been previously used to evaluate the effects of localized frontal lobe lesions on three cognitive processes underlying executive functions. Most importantly, the frontal areas found to critical to each cognitive process are known to be anatomically and functionally linked to the basal ganglia through the basal ganglia-thalamo-cortical loops (Alexander et al., 2007; Stuss & Alexander, 2007; Stuss et al., 2002). Given that previous studies with healthy young and older adults have found that a single bout of exercise leads to improvements in RT outcomes (i.e. faster RT) which were associated with increased brain activity in frontal brain areas (Kamijo et al., 2009; Yanagisawa et al., 2010), it was predicted that individuals with PD would show improvements in performance (i.e. faster RT) in the tasks used in the current study after a single bout of exercise. Contrary to this hypothesis, there were no selective effects of exercise on performance. While no changes in RT were found in the Simple RT task, faster RT was observed for the Complex Choice RT task in both experimental conditions. This latter result suggests that rather than a selective effect of exercise on cognition, participants were likely showing practice effects. A secondary analysis with fourteen participants examined the influence of recovery time on all behavioural outcomes and showed similar results. These findings may have important implications to the interpretation of results from Ridgel et al. (2011), given that their study design lacked a Control condition and limited their ability to account for practice effects. The

Control condition in the current study allowed us to demonstrate that improvements in performance did result from practice effects, and therefore suggests that practice effects could also have influenced findings from Ridgel et al. (2011). Although these results were not predicted, the absence of changes in behavioural measures following an acute bout of exercise has been previously reported in healthy individuals using different tasks (Kamijo et al., 2004). Thus, one could suggest that task choice may have influenced the outcomes in the present study.

The tasks used in the current study were carefully selected based on lesion studies that repeatedly showed the effects of localized frontal lobe lesions to each cognitive process. A recent meta-analysis has showed that the effects of an acute bout of exercise on cognition are small, but that this effect may increase depending on task complexity (Chang et al., 2012). Thus, in the current study we had two tasks that were similar in structure, but that varied in complexity. Two tasks that are commonly used in previous investigations are modified versions of the Flanker Task and the Stroop Test (Barella, Etnier, & Chang, 2010; Kamijo et al., 2009; Yanagisawa et al., 2010). A commonality between these tasks is their large reliance on inhibitory control for successful performance. This component was also present in the Complex Choice RT task used in the current study, since participants had to pay attention to three stimulus characteristics in order to correctly respond to target and non-target stimuli. Therefore, it is unlikely that the lack of RT changes in the current study were simply a result of task choice. It is very important to note that the effects of exercise on behavioural measures (null in this case) may not fully reflect the effects of exercise at neurophysiological level. Previous studies have reported changes in neurophysiological measures underlying cognition which were not detected in behavioural measures (Kamijo et al., 2009; Kamijo et al., 2004). Therefore, future studies should examine the

effects of an acute bout of exercise on neurophysiological measures in order to confirm whether

or not individuals with PD are responsive to the effects of a single bout of exercise.

Alternatively, one could argue that individuals with PD were actually not responsive to a

single bout of exercise. Interestingly, previous studies have suggested that the effects of a single

bout of exercise on cognition may result from changes in circulating catecholamine (including

dopamine) and arousal levels (Chang, Etnier, & Barella, 2009). With respect to the latter, studies

have showed that the effects of exercise intensity on cognitive function follow an inverted-U

pattern, suggesting that moderate exercise intensity leads to optimal arousal levels, which in turn

leads to improvements in brain function and behaviour (Kamijo et al., 2009; Kamijo et al., 2004).

Changes in arousal are argued to be mediated by serotonergic, noradrenergic, and cholinergic

activity (Gratwicke, Jahanshahi, & Foltynie, 2015). While the depletion of dopaminergic activity

is a hallmark of PD, there is growing evidence that serotonergic, noradrenergic and cholinergic

activity are also decreased in those with PD (Bohnen et al., 2006; Bohnen et al., 2003; Kehagia

et al., 2010; Muller & Bohnen, 2013; Rochester et al., 2012). Thus, it could be argued that, from

a neurotransmitter point of view, individuals with PD could have limited resources to acutely

respond to the stress caused by exercise on brain activity. On the other hand, given that

improvements in cognition have been found in individuals with PD in chronic exercise studies, it

is possible that chronic exposure to exercise stimulation could lead to improvements in

neurotransmitter activity. These improvements in neurotransmitter activity could result from

increased activity of dopamine receptors (Fisher et al., 2013) and neuroplastic effects driven by

increased levels of neurotrophic factors (Frazzitta et al., 2014; Marusiak et al., 2015). Although

highly speculative, this interpretation may help design future studies to investigate the acute

effects of exercise on individuals with PD and potentially explain the underlying mechanisms of improvements found in chronic exercise studies in this population.

Limitations of this study include a sample of participants with mild disease severity and who had relatively normal cognitive function. Therefore, the results of this study cannot be generalized to all individuals with PD.

In conclusion, the current study showed that an acute bout of exercise did not influence cognitive processes underlying executive functions in individuals with PD at the behavioural level. Future research should examine the effects of an acute bout of exercise on neurophysiological measures in order to confirm whether individuals with PD are responsive or not the immediate effects of exercise on cognition. In addition, future studies using neuroimaging techniques should examine whether an acute bout of exercise can influence activation in the frontal lobes as well as basal ganglia areas in individuals with PD. Finally, in order to define the underlying mechanisms of the presence or absence of response to exercise stimulation, the assessment of neurotransmitter activity is a promising direction.

Supplementary Material – Chapter 3

Table 7 RT Mean and standard deviation during Simple RT task in each experimental condition

	RT		RT CV		RT by ISI			
					Pre		Post	
	Pre	**Post**	**Pre**	**Post**	Short ISI	Long ISI	Short ISI	Long ISI
Exercise	309.99 (43.83)	315.22 (55.99)	19.33 (5.79)	20.16 (4.99)	321.88 (46.38)	297.75 (43.32)	333.01 (61.23)	296.87 (52.59)
Control	299.78 (47.15)	314.49 (52.35)	18.02 (4.17)	19.25 (4.24)	315.11 (49.05)	284.05 (45.60)	332.03 (56.52)	296.61 (50.79)

Legend: RT – Reaction Time; CV – Coefficient of Variation; ISI – Inter-stimulus Intervals

Table 8 Mean and standard deviation during Complex Choice RT task in each experimental condition

	RT		RT CV		RT by Stimulus type							
					Pre				Post			
	Pre	Post	Pre	Post	F0	F1	F2	target	F0	F1	F2	target
Exercise	634.39 (71.52)	624.10 (74.37)	21.11 (2.81)	21.89 (4.39)	565.66 (64.48)	586.00 (70.25)	669.75 (70.04)	685.14 (101.71)	560.02 (77.13)	580.52 (72.23)	647.90 (67.73)	682.88 (107.58)
Control	641.69 (76.90)	614.16 (81.32)	22.48 (3.93)	21.15 (3.13)	582.39 (88.47)	597.34 (75.77)	670.92 (77.91)	692.25 (100.68)	547.04 (75.69)	569.58 (76.86)	648.33 (82.89)	659.88 (119.32)

Legend: RT – Reaction Time; CV – Coefficient of Variation; F0 – non-target stimulus sharing 0 features with the target stimulus; F1 - non-target stimulus sharing 1 feature with the target stimulus; F2 - non-target stimulus sharing 2 features with the target stimulus.

Chapter 4

Aerobic exercise improves executive functions similarly in Parkinson's disease with or without cognitive impairment

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Abstract

Physical exercise has been shown to improve cognitive function in individuals with Parkinson's disease (PD). However, little is known about how difference exercise modalities influence cognition in PD. Research has suggested that aerobic and goal-based exercise may have positive effects on cognition of those with PD. Yet, the isolated effects of these exercise modalities have never been compared in PD. In addition, the focus of previous investigations on examining the effects of exercise mainly on executive functions and the exclusion of PD patients with cognitive impairment in these studies may limit defining exercise as a treatment for cognitive decline in PD. The aim of the present study was to compare the effects of aerobic and goal-based exercise on three cognitive processes and five different cognitive domains in cognitively normal and impaired individuals with PD. Seventy-six individuals with PD were randomly allocated into three groups: aerobic exercise, goal-based exercise, and control. Participants in the exercise groups attended 1-hour sessions 3x/week for 12 weeks, while those in the Control group carried on with their regular activities. Changes in cognitive processes were assessed using reaction time (RT) tasks, whereas changes cognitive domains were assessed using paper-based neuropsychological tests. Participants showed improvement in inhibitory control with the aerobic intervention (p=0.039), irrespective of cognitive status. Conversely, participants with cognitive impairment in the Control group showed slower RT (p=0.003), slower processing speed (p=0.016), and worse set-shifting ability (p=0.0018) at post test. To conclude, this is the first study to show that aerobic exercise is more efficient than goal-based exercise for the treatment of cognitive deficits in PD with and without cognitive impairment.

Keywords: Parkinson's disease, exercise, cognition, dementia

4.1 Introduction

Although motor symptoms are the hallmark of Parkinson's disease (PD), deficits in cognition have been found to be one of the main (non-motor) contributors to decreased quality of life among individuals with PD (Barone et al., 2009). According to Aarsland et al. (2010), approximately 26% of non-demented PD patients have some form of mild cognitive decline, with deficits primarily in the attention, executive functions, visuospatial, and memory domains. Moreover, findings from a longitudinal study demonstrated that 46% of individuals with PD developed dementia by the 10 year-mark from diagnosis (Williams-Gray et al., 2013). Hence, in order to improve quality of life of those living with PD, treatment strategies should not be focused on alleviating motor symptoms alone, but should also aim to improve cognitive function.

The treatment of cognitive deficits in PD is an enormous challenge, since the underlying mechanisms of these deficits are complex and not limited to the disruption of the dopaminergic system (Bohnen et al., 2006; Dubois, Pilon, Lhermitte, & Agid, 1990; Kehagia, Barker, & Robbins, 2010; Williams-Gray et al., 2009). To date, no standard pharmacological treatment has been established for mild cognitive impairment in PD (Emre, Ford, Bilgic, & Uc, 2014), and the gold standard treatment for PD motor symptoms (levodopa) has been shown to have variable effects on cognition (improvement, no change, or worsening) (Cools, Barker, Sahakian, & Robbins, 2001; Gotham, Brown, & Marsden, 1988). While guidelines exist for the treatment of dementia in PD, the increased number of drugs to treat motor, cognitive, and psychiatric problems may lead to severe side effects (Emre et al., 2014). Thus, since current pharmacological therapies are limited in their ability to alleviate cognitive deficits in PD, the combination of pharmacological and non-pharmacological therapies has been encouraged.

Among non-pharmacological strategies, current research suggests that physical exercise may be a promising approach in the treatment of cognitive decline in PD.

Studies investigating the effects of exercise on cognition in PD have revealed positive effects in case series (Nocera, Altmann, Sapienza, Okun, & Hass, 2010; Tabak, Aquije, & Fisher, 2013) as well as larger samples of PD patients (Cruise et al., 2011; David et al., 2015; Duchesne et al., 2015; McKee & Hackney, 2013; Ridgel, Kim, Fickes, Muller, & Alberts, 2011; Tanaka et al., 2009; Uc et al., 2014). A pioneering study by Tanaka and colleagues (2009) showed that a 24-week long multimodal exercise program improved executive functions in individuals with PD compared to a non-exercise control group. Cruise and colleagues (2011) further investigated the effects of exercise on cognition in PD with a 12-week multimodal program employing a larger cognitive assessment battery. It was found that exercise selectively improved executive functions, whereas no changes were observed in memory. Selective effects of exercise on executive functions were also supported by two studies investigating the effects of aerobic exercise on cognition in PD (Duchesne et al., 2015; Uc et al., 2014). Finally, improvements in cognitive domains other than executive functions (i.e. spatial cognition) were demonstrated by McKee and Hackney (2013) after a 12-week program of adapted Tango dancing. Taken together, these findings demonstrate the potential of exercise in the treatment of cognitive decline in PD. However, as recently noted in a literature review (Murray, Sacheli, Eng, & Stoessl, 2014), there are critical aspects in previous investigations that need to be addressed in order to improve the current knowledge of how exercise influences cognition in PD.

The first limitation to be considered is the use of multimodal exercise protocols to examine the effects of exercise on cognition. Although previous investigations have attributed positive changes in cognition to improvements in aerobic capacity, only two studies to date

(Duchesne et al., 2015; Uc et al., 2014) have stringently evaluated the effects of aerobic exercise alone (i.e. not confounded by other components) in PD. However, even these studies did not compare their effects to other exercise modalities or a control group composed by individuals with PD. A current review by Petzinger et al. (2013) suggested that aerobic as well as goal-based exercise (i.e. focused on increasing the quality of movement) may act upon motor and cognitive pathways that are affected in PD, thus promoting neural plasticity. Since previous exercise programs (e.g. multimodal and adapted Tango) involved both aerobic and goal-based components, it remains unknown which one was critical to the improvements in cognitive function found in these studies. In order to address this gap, the effects of aerobic and goal-based exercise were directly compared in the present study.

Another important aspect to be addressed is the absence of a clear rationale for the selection of outcome measures used in previous investigations to evaluate the effects of exercise on cognition. The choice of executive functions tests is often based on their sensitivity to the effects of exercise, as well as their potential to infer the effects of exercise on frontal lobe functioning. Yet, exercise studies have demonstrated that selective components of executive functions improve after exercise rather than an overall improvement in executive functions. For example, Duchesne et al. (2015) assessed the effects of exercise in two different components of executive functions (i.e. inhibition and flexibility) and found that only one of them (i.e. inhibition) improved post-exercise. Although it remains unknown why selective effects of exercise on executive functions occur, research has suggested that differences in these outcomes may result from unique underlying cognitive processes employed by each component of executive functions (Testa, Bennett, & Ponsford, 2012). Thus, it could be hypothesized that the

assessment of distinct cognitive processes could contribute to further understanding the effects of exercise on cognition in PD.

In the present study, three cognitive processes that underlie the performance of executive functions (Stuss & Alexander, 2007) were evaluated through RT tests. These cognitive processes were defined as the abilities to initiate and sustain a response (energization), set a stimulus-response relationship (task-setting), and monitor performance over time for adjustment of behaviour (monitoring) (Stuss, 2006; Stuss et al., 2005; Stuss, Binns, Murphy, & Alexander, 2002). Importantly, the frontal lobe areas found to be critical to each of these processes are known to be anatomically and functionally linked to the basal ganglia (Alexander, DeLong, & Strick, 1986; Middleton & Strick, 2000), and selective deficits in these processes have been observed in individuals with PD (see Chapter 2). Hence, the assessment of energization, task-setting and monitoring may help clarify the effects of exercise on executive functions in PD, as well as provide insight into the brain networks involved in these changes.

It is also important to note that the focus of previous investigations on assessing executive functions in isolation is a limitation in determining the potential of exercise as a therapy to prevent and/or treat cognitive decline in PD. Research has shown that despite deficits in executive functions being highly prevalent in PD, deficits in other cognitive domains such as memory, language, and visuospatial processing are stronger predictors of dementia in PD than deficits in executive functions (Williams-Gray et al., 2009). Thus, in order to determine whether exercise maybe useful to prevent or postpone the onset of dementia in PD, a broader range of cognitive domains should be assessed before and after exercise. In the current study, the effects of exercise were examined in five different cognitive domains: attention/working memory, executive functions, memory, language, and visuospatial processing.

Finally, it remains unknown whether exercise differentially affects those with and without cognitive impairment, since previous studies excluded individuals with PD who had cognitive impairment. Investigating the effects of exercise in these subgroups of individuals with PD may be critical to determine whether exercise can be used as a complementary therapy in more advanced stages of cognitive decline.

In this context, the current study aimed to compare the effects of aerobic and goal-based exercise on three cognitive processes mediated by the frontal lobes and five different cognitive domains in cognitively normal and impaired individuals with PD. It was hypothesized that if the aerobic capacity is critical to cognitive improvement (as found in previous studies), aerobic exercise will be more beneficial than goal-based exercise to enhance cognitive function in individuals with PD. Finally, given that aerobic exercise has been shown to improve cognition of older adults with and without cognitive decline (Baker et al., 2010; Heyn, Abreu, & Ottenbacher, 2004), it was hypothesized that both cognitively normal and impaired individuals with PD would benefit from aerobic exercise.

4.2 Method

The present study was approved by the University of Waterloo and the Wilfrid Laurier University research ethics boards. Informed consent was obtained from all individuals prior to participation.

4.2.1 Participants

Participants included 76 people with confirmed diagnosis of idiopathic PD by a neurologist who were recruited from the Movement Disorders Research and Rehabilitation

Centre (MDRC) database at Wilfrid Laurier University over a 10 month period (Figure 9). In order to enrol in the MDRC database, participants had voluntary contacted the MDRC staff or have been encouraged to participate in research activities at the centre by their clinician. In their first visit participants specify in which type of research studies they would like to participate and whether they are able to commit to single appointments and/or studies with longer duration. Exclusion criteria were defined as follows: history of neurological diseases other than PD, unstable medical condition, uncontrolled diabetes mellitus, uncontrolled hypertension (BP>140/90), history of heart disease, resting heart rate >100, history of stroke, history of chronic obstructive pulmonary disease, or uncorrected visual impairments (including colour blindness). Following a careful screening for eligibility, participants were randomly assigned into three groups: aerobic exercise, goal-based exercise, and control group. Participants were classified into cognitively normal and cognitively impaired based on the Level 1 guidelines from the Movement Disorders Task Force for PD mild cognitive impairment (Litvan et al., 2012) and PD dementia (Dubois et al., 2007). All participants (but four drug naïve) were assessed while in their ON medication state.
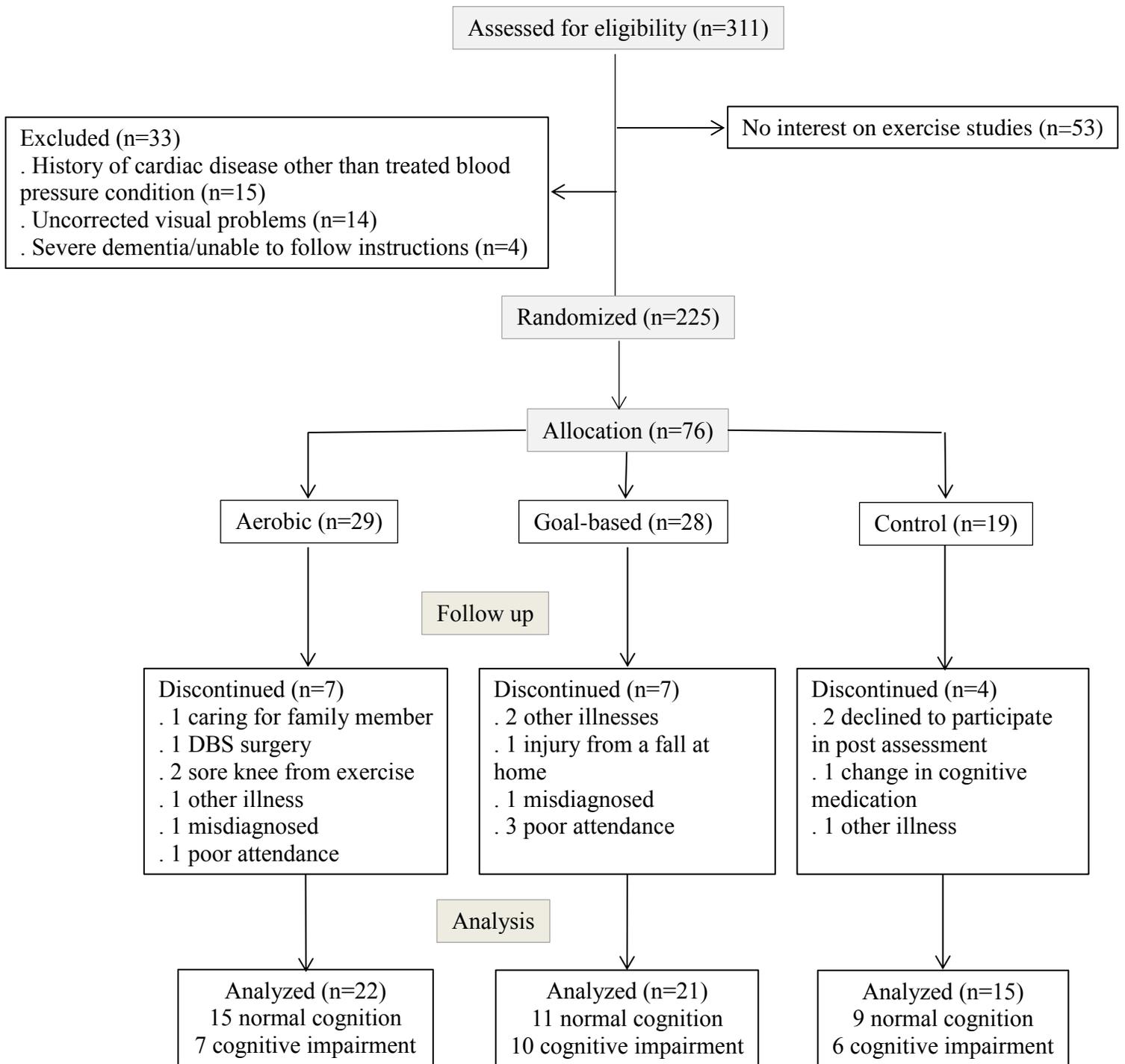
Figure 9 Flow of participants throughout the study (Study 3)

4.2.2 Apparatus and Experimental Procedures

The assessment phase was completed in two separate sessions. The first consisted of the assessment of participants' clinical and functional conditions and the second involved the assessment of participants' cognitive function. These sessions took place on two separate days within two weeks. Alternate forms of neuropsychological tests were used at post-exercise testing if available. Except for the assessment of aerobic capacity and RT tasks, participants were assessed at baseline and at the end of the study by trained evaluators blinded to the treatment arm, but not to pre-post training status.

Demographic and Clinical information

After reading and signing the informed consent form, participants filled out two questionnaires. The first (Geriatric Depression Scale) provided information about participants' depression and anxiety signs, and the second (15-item Waterloo Handedness Questionnaire) evaluated participants' hand preference. Following the completion of the questionnaires, PD participants had the severity of their motor symptoms assessed by a movement disorders specialist using the Unified Parkinson's disease Rating Scale (UPDRS) (Fahn & Elton, 1987), and had their general cognitive status assessed by a trained evaluator using the Montreal Cognitive Assessment (MoCA). Participants' demographic and clinical information is displayed on Table 9.

Table 9 Demographic and clinical information of 58 participants who completed the study (Study 3)

	Aerobic (n=22)	Goal-based (n=21)	Control (n=15)	P value
Demographic information				
Age (years)	70.63 (9.27)	69.76 (8.34)	67.60 (8.34)	0.57
Sex (M/F)	18/3	12/9	11/4	-
Handedness (R/L)	21/1	17/4	14/1	-
Education (years)	14.45(3.26)[a]	14.28 (3.28)[b]	16.66 (2.41)	**0.052**
Clinical information				
GDS	6.22 (5.83)	10.09 (7.94)	5.60 (5.26)	0.7
MoCA	25.22 (4.53)	24.57 (3.99)	25.80 (5.00)	0.71
UPDRS III	25.38 (8.07)	27.64 (9.72)	21.76 (9.20)	0.16
Disease duration (years)	5.95(5.12)	6.09 (4.18)	5.60 (5.69)	0.95
LED	710.63 (425.70)	482.91 (342.67)	759.70 (560.19)	0.12

Legend: GDS – Geriatric Depression Scale; MoCA – Montreal Cognitive Assessment; UPDRS III – Unified Parkinson's disease Rating Scale motor subsection; Disease duration – years since diagnosis; LED – Levodopa Equivalent Dose; a = Aerobic different than Control (p=0.036); b = Goal-based different than Control (p=0.025)

Exercise interventions

Participants were randomly assigned into three groups: aerobic exercise, goal-based exercise, and control group. Those in the exercise groups attended three 1-hour sessions per week for 12 weeks, while participants in the control group were instructed to continue with their regular activities (no restrictions were made regarding the types of activities).

For the aerobic training, recumbent cycle ergometers (700 Excite + Recline, Technogym USA©, Seattle, Washington) were used in order to provide safety and stability during training. The exercise class started with 5 minutes warm up followed by 30-40 minutes of aerobic training and 2 min cool down. Participants initially cycled for 30 minutes and increased duration weekly, with all participants cycling for 40 minutes by week 4. Exercise intensity levels started at 40-50% heart rate reserve (HHR) and increased to 60-70% HRR by week 4. Intensity prescription was defined based on the Karvonen method which is expressed in the equation Target HR = ([(HRmax - HRrest)* (% exercise intensity)]+HRrest) (ACSM, 2000). It is important to note that these parameters were used as guidance and that participants were instructed to give their best effort without feeling unsafe.

For the goal-based training, participants performed a standardized exercise protocol (PD SAFEX™ - without eyes closed condition) that involved walking exercises coordinating upper and lower limbs on a simultaneous or alternating manner, non-progressive muscle-toning exercises using resistance bands and the persons' own body weight, and whole body stretching exercises. A new sequence of exercises was introduced every week in order to increase the level of difficulty progressively.

Participants were excluded from analysis if exercise adherence was less than 80% (29/36 classes) or if 3 classes were missed in a row.

Exercise sessions were led by Kinesiology graduate students (not blinded to study purpose) and participants were assisted by trained volunteers.

4.2.3 Outcome measures

Cognitive processes

In order to assess the effects of exercise on energization, task-setting, and monitoring , participants performed three reaction time (RT) tasks from the *Feature Integration Test (FIT)* (Stuss et al., 2002)*.* These tasks were composed of a Simple RT, an Easy Choice RT, and a Complex Choice RT task. The stimulus in these tasks was one of four shapes: square, circle, triangle, or cross. The shapes were dark grey or coloured (red, yellow, green or blue) on a black background. For all tasks, the stimulus was presented at interstimulus intervals varying between 3 s and 7 s. The stimulus stayed on the screen for 2 seconds or until a response was made. In the Simple RT, the stimulus was a square that was presented 50 times after 5 practice trials. For Easy and Complex Choice RT tasks, a total of 102 trials were performed, preceded by 10 practice trials each. In the Easy Choice RT task, shapes were presented one at a time in random order, but one of them was initially defined as target and the others, consequently, were non-targets. In the Complex Choice RT task, shapes were also presented one at a time in random order, but each stimulus varied in a combination of shape, colour, and internal line orientation, with the target being defined by a specific combination of these three features. Participants were asked to respond to target stimuli by pressing button 1 with their right index finger and to non-target stimuli by pressing button 2 with their right middle finger on a Serial Response Box (Psychology Software Tools, Inc.) with five buttons (numbered 1-5 from left to right) aligned horizontally.

Chronic effects of exercise on energization were assessed through the outcome measure overall RT. Since energization deficits are characterized by slowness in RT, then it was expected that exercise would lead to faster RT. The effects of exercise on task-setting were assessed through the outcome measures RT by stimulus type (target vs non-target) and number of false positive errors. Since deficits in task-setting are characterized by an inability to establish the criteria defining a target stimulus, then it was expected that exercise would lead to faster RT for the target stimulus and decrease in false positive errors. Lastly, the effects of exercise on monitoring were assessed through the outcome measures RT by inter-stimulus interval and total number of errors. Given that monitoring deficits are characterized by the inability to anticipate/predict time of stimulus onset and to note an error for appropriate adjustment of behaviour, then it was expected that exercise would lead to improvements in time expectancy (faster RT for long interstimulus interval compared to short) as well as decrease in the total number of errors.

Cognitive domains

Participants were assessed in five cognitive domains (attention/working memory, executive function, memory, language, and visuospatial function) using paper-based neuropsychological tests. Two tests representing each cognitive domain were chosen according to the guidelines of the Movement Disorders Task Force to evaluate PD mild cognitive impairment (Litvan et al., 2012). Attention and working memory were assessed using the Digit Span (forward and backwards) and the Corsi Block test, executive functions were assessed using the Trail Making Test (parts A and B) and the Stroop test (word, colour, and colour-word conditions), memory was assessed using the Short-form of the California Verbal Learning Test and the Rey-Osterrieth (Rey-O) Complex Figure Test (immediate recall, and delayed recall),

language was assessed using two verbal fluency tasks (phonemic and semantic) and the Short-form of the Boston Naming Test, and visuospatial processing was evaluated using the copy of the Intersecting Pentagons from the Wechsler Memory Scale and the Benton Line Orientation Test.

Aerobic capacity

Oxygen uptake was measured during a submaximal graded exercise test on a cycle ergometer. Participants started with a 2 minute warm up with 30 watts workload on the cycle ergometer. Then, work rate was increased by 15 watts every 1 minute until approximately 10 minutes. Gas exchange was recorded throughout the protocol. For the gas exchange measurements, levels of oxygen (O_2) and carbon dioxide (CO_2) were assessed breath-by-breath using an Ergocard Cardiopulmonary Stress Test Metabolic Cart (Roxon medi-tech ltd. St-Leonard, Quebec, Canada). Heart rate was recorded at rest, continuously during graded exercise test, and after graded exercise test using a Polar HR monitor (Lachine, Quebec, Canada). After the test, HR was monitored until it returned to values close to baseline. Blood pressure (BP) was assessed at rest (sitting and standing), and after the completion of the test until BP returned to values close to baseline. BP measures were taken using an OMRON® 7 series blood pressure monitor. The protocol terminated if two of the following criteria were achieved: participant's heart rate reaches 70% of the age-predicted maximal heart, respiratory exchange ratio (RER) was greater than 1.1, participant rate of perceived exertion (RPE) was greater than 16, or participant asked to stop. The equation to predict maximal heart rate was [208-(0.7* age)] (Tanaka, Monahan, & Seals, 2001) and [164-(0.7*age)] for individuals on β-blockers (Brawner, Ehrman, Schairer, Cao, & Keteyian, 2004). Outcome measures for aerobic capacity included Stage and VO_2 at test termination.

4.2.4 Statistical Analysis

One-way analysis of variance (ANOVA) was used to compare demographic and clinical features across groups at baseline. Although it was recommended at the beginning of the study that all PD medication was kept the same throughout the course of the study, 4 participants in the aerobic group (+66, +120, +160, and - 100 LED change), 4 in the Goal-based group (+33, +200, -400, and -204.25 LED change), and 6 in the Control group (+82.5, +150, +200,+ 240, and +330, -150 LED change) felt the need to do so. Given that the majority of cognitive outcomes in the current study respond poorly to dopaminergic treatment (Kehagia et al., 2010), these participants were kept in the final analysis. However, in order to control for any influence changes in medication could have on the outcomes from the current study, change in LED was included as a covariate in the final analysis. Thus, analysis of covariance (ANCOVA) was used to assess the effects of exercise (pre vs post) across groups (Aerobic vs Goal-based vs Control) while controlling for participants' cognitive status at baseline (normal vs impaired) and changes in LED from pre to post-test. Fisher LSD post-hoc was used to examine significant differences and alpha level was kept at p<0.05.

Statistical analyses were performed on SPSS$^®$ version 22 software.

4.3 Results

4.3.1 Groups' demographic and clinical information at baseline

Groups were matched for age, general cognitive status (MoCA), depression signs (GDS), motor disease severity (UPDRS-III), and disease duration (years since diagnosis), and were

taking similar doses of PD medication (LED). However, group differences were found for years of education (F(2,55)=3.10; p=0.052; η_p^2=0.10), where participants in the Control group had more years of education than those in the Aerobic (p=0.036) and Goal-based (p=0.025) groups.

Results regarding group differences at baseline for all outcome measures are available in the Supplementary Material section of this chapter.

The following sections are focused on describing interactions between time of assessment, group, and/or cognitive status.

4.3.2 Cognitive processes

Reaction time

The assessment of RT pre and post intervention showed no significant differences between groups in the Simple RT task (Figures 10A and 10B). Conversely, an interaction between time of assessment, group, and cognitive status for Easy Choice RT task (F(2,51)=3.47; p=0.038; η_p^2=0.11) revealed that participants with cognitive impairment in the Control group were slower at post-test (p=0.003) (Figure 10D). In addition, an interaction between time of assessment and cognitive status was found for the Complex Choice RT task (F(1,51)=4.43; p=0.04; η_p^2=0.08), showing that participants with cognitive impairment from all groups were slower at post-test (p=0.028) (Figure 10F).
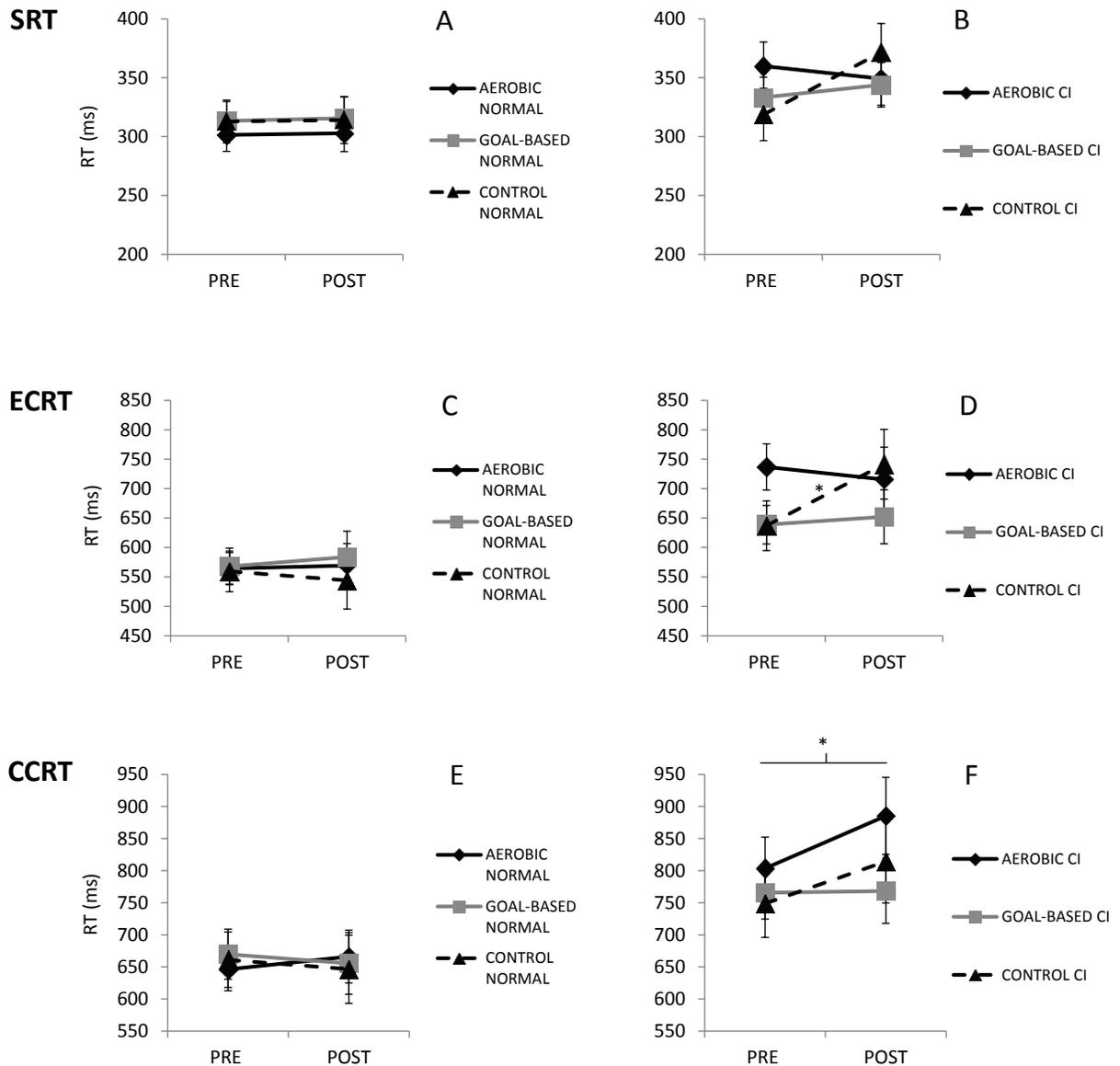
Figure 10 Participants with cognitive impairment (CI) in the Control group showed slowing in RT at post-test in the Easy Choice RT (ECRT) task (D). Participants with cognitive impairment had slower RT at post-test in the Complex Choice RT (CCRT) (F).

There were no interactions for RT variability, RT by stimulus type or RT by inter-stimulus interval.

Accuracy

An interaction between time of assessment, group, and cognitive status was found for the Complex Choice RT task (F(2,51)=3.84; p=0.027; η_p^2=0.13), showing that only PD patients with cognitive impairment in the Aerobic group were more accurate at post-test compared to pre-test (p=0.006) (Figure 11 – right).
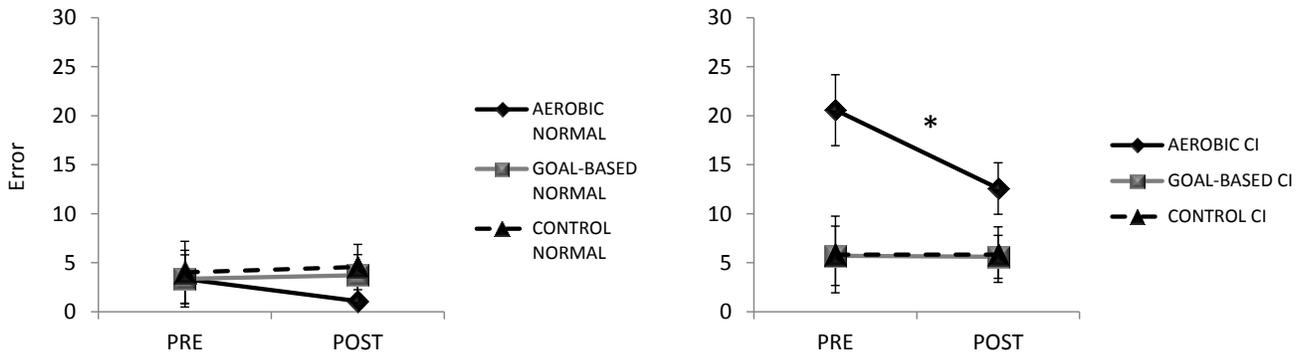
Figure 11 Only participants in the Aerobic group with cognitive impairment (CI) were more accurate at post-test in the Complex Choice RT task (right).

4.3.3 Cognitive domains

The effects of exercise on the executive functions domain were observed for both Stroop and TMT tasks. In the Stroop Test, an interaction between group and time of assessment approached significance for the Colour Word condition (F(2,51)=3.04; p=0.056; η_p^2=0.10). This interaction showed that the Aerobic group named more correct colour/word items at post-test (p=0.039), while performance did not change for the Goal-based and Control groups (Figure 12). No differences between groups were found for the Word and Colour conditions following the intervention.
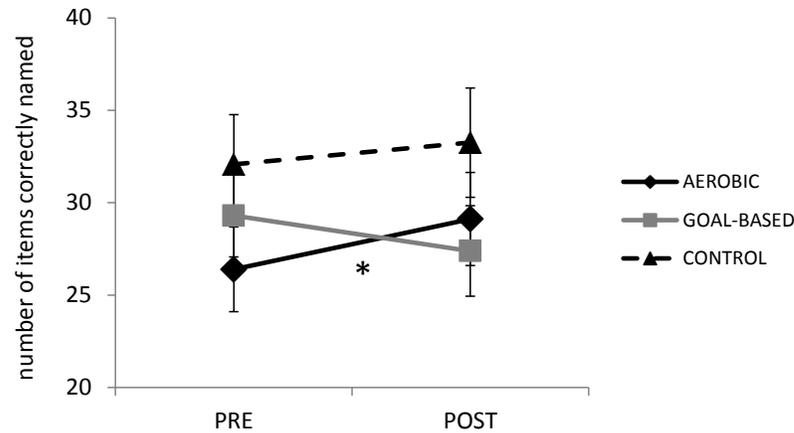
Figure 12 Regardless of cognitive status, participants in the Aerobic group showed improvement in response inhibition (Stroop test) at post-test.

Three individuals in the Aerobic group, 3 in the Goal-based group, and 1 in the Control group were not capable of completing the TMT. With respect to the remaining participants, an interaction between time of assessment, group and cognitive status was marginally significant for the TMT A ($F(2,44)=3.02$; $p=0.058$; $\eta^2=0.12$). This interaction showed that participants with cognitive impairment in the Control group were significantly slower at post-test ($p=0.016$) (Figure 13B). A similar interaction between time of assessment, group, and cognitive status was found for TMT part B ($F(2,44)=3.19$; $p=0.05$; $\eta^2=0.12$), where participants with cognitive impairment in the Control group were significantly slower at post-test ($p=0.0018$) (Figure 13D). Finally, the interaction between time of assessment, group, and cognitive status was marginally significant for TMT B-A ($F(2,44)=2.73$; $p=0.076$; $\eta^2=0.11$), once again showing a worsening in performance for CI participants in the Control group at post-test ($p=0.003$).
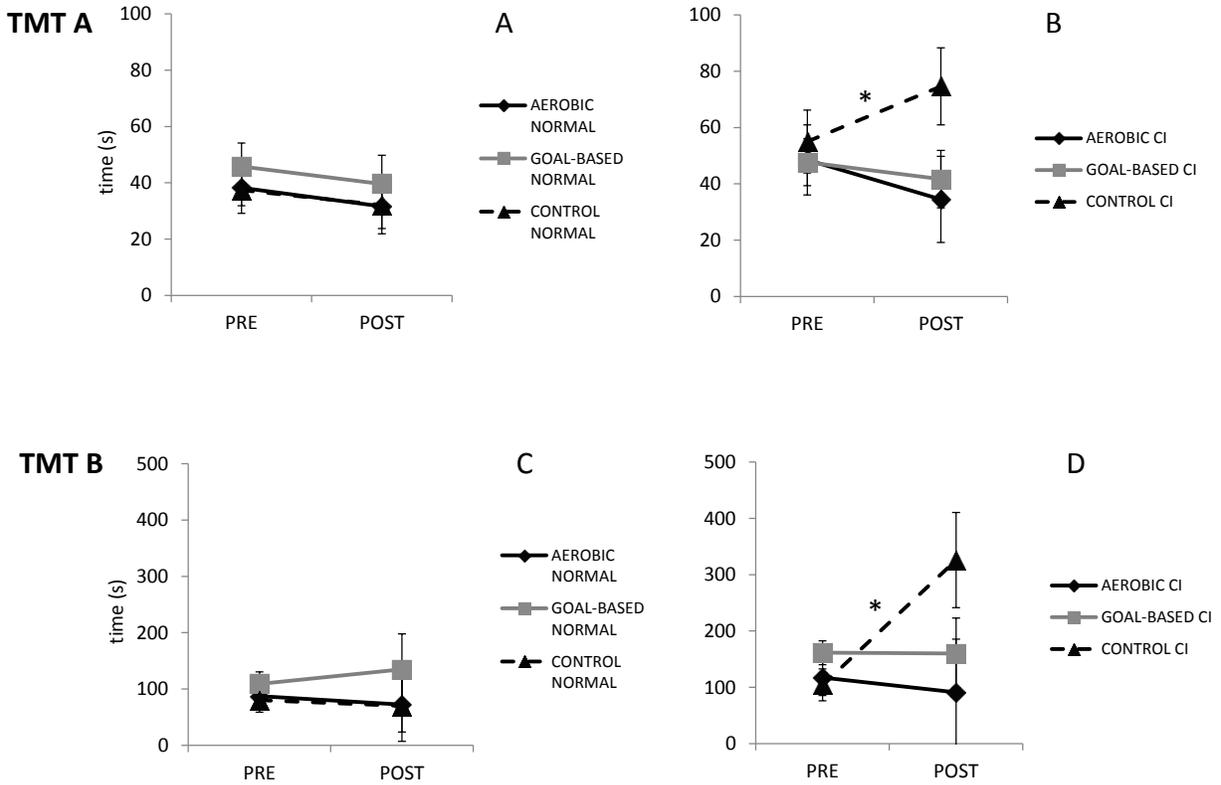
Figure 13 Participants with cognitive impairment (CI) in the Control group were significantly slower at post-test compared to pre-test for both TMT A and TMT B.

In the Working Memory domain, a time by cognitive status interaction was identified for the number of points in the Digit Span forward (F(1,51)=4.11; p=0.047; η^2_p=0.07). This interaction showed that participants with normal cognition from all groups recalled less correct number sequences (worsening) at post-test (p=0.05). No differences between groups or interaction between group and cognitive status were found for Digit Span backwards at pre and post-testing. No differences were found pre and post-test the intervention period for the Corsi Block Test.

In the memory domain, an interaction between time of assessment and cognitive status (F(1,51)=7.22; p=0.009; η_p^2 =0.12) for the CVLT short recall revealed that participants with normal cognition from all groups recalled more words at post-test (p=0.045), while participants with cognitive impairment did not change. There were no differences between groups for the long recall of the CVLT or any condition of the Rey-O complex figure task from pre to post assessments.

Finally, in the visuospatial domain, an interaction between time of assessment and cognitive status was found for the Pentagons task (F(1,51)=10.85; p=0.001; η_p^2 =0.17), showing that participants with cognitive impairment from all groups had worse performance at post-test (p=0.0002). A second interaction between time of assessment, group, and cognitive status was marginally significant for the Pentagons' task (F(2.51)=2.72; p=0.07; η_p^2 =0.09), suggesting that specifically participants from the Control and Goal-based groups had worse performance at post-test (Figure 14 - right).
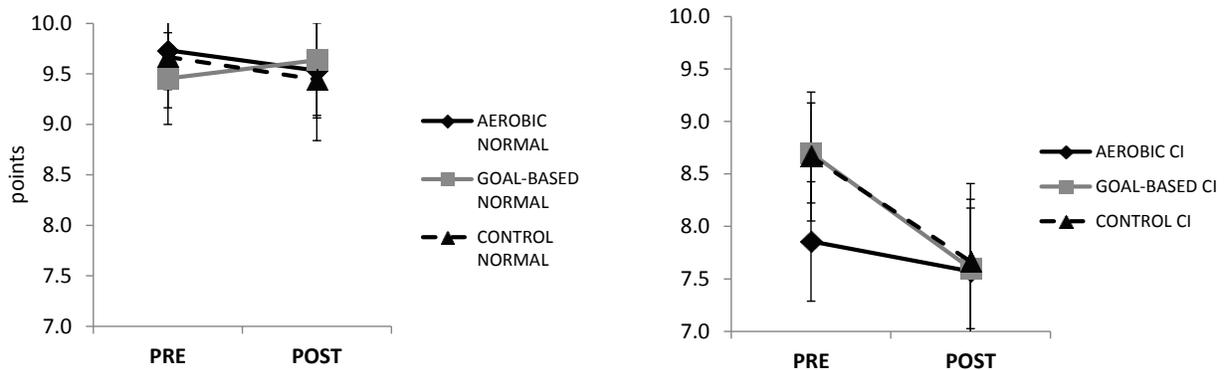
Figure 14 Participants with cognitive impairment (CI) from both Goal-based and Control groups had lower scores in the Pentagons task, while those in the Aerobic group remained at similar levels

There were no differences between groups in the language domain after exercise interventions.

4.3.4 Aerobic capacity

Twenty participants in the Aerobic group (out of 22), 18 participants in the Goal-based group (out of 21), and 14 participants in the Control group (out of 15) completed the graded exercise test at pre and post-test. Reasons for not completing the test included declining to take the test (Aerobic n=2, Goal-based n=2, Control n=1) and technical difficulties (Goal-based n=1).

In order to confirm whether the test termination criteria was comparable across groups at pre and post-testing, HR, RER, and RPE at test termination were examined. When comparing HR, RER, and RPE between groups at pre and post, no main effect of time of assessment, time of assessment by group interaction, or time of assessment by group by cognitive status interaction was found. These results confirmed that the same criteria to terminate the graded exercise test were used during pre and post-test across groups.

An interaction between time of assessment and group (F(2,45)=6.32; p=0.003; η_p^2=0.21) showed that, although all groups completed more stages at post-test (main effect of time of assessment F(1,45)=21.39; p<0.0001; η_p^2=0.32), participants in the Aerobic group were the only ones that completed significantly more stages at post-test (p<0.0001). It is important to note that each stage of the graded exercise test was one minute long and composed by a 15 watts workload increment. Thus, these results showed that at post-test participants in the Aerobic group were able to sustain exercise for longer duration and with greater workload than the other two groups until termination criteria was achieved.

The analysis of VO2 at test termination showed a main effect of time of assessment (F(1,45)=5.39; p=0.024; η_p^2=0.10), where participants from all groups had higher VO2 at test termination at post-test (p=0.017). No interaction between time of assessment and group or interaction between time of assessment, group, and cognitive status were found for this outcome measure.

4.3.5 Severity of PD motor symptoms

With respect to the severity of Parkinsonian motor symptoms, an interaction between group and time of assessment (F(2,51)=4.79; p=0.012; η_p^2=0.15) showed that both Aerobic (p=0.0003) and Goal-based (p=0.0008) groups improved severity scores at post-test, irrespective of cognitive status (Aerobic pre: M=26.51; Aerobic post: M=21.10; Goal-base pre: 27.77; Goal-based post: M=22.38). No difference in severity scores were found for the Control group (Control pre: M=21.93; Control post: M=22.72).

4.4 Discussion

The aims of the present study were to compare the effects of aerobic and goal-based exercise on three cognitive processes and five cognitive domains in cognitively normal and impaired individuals with PD. Neither aerobic nor goal-based interventions improved the processes of energization, task-setting, and monitoring as seen with the RT tasks, however aerobic exercise was found to improve executive functions (i.e. response inhibition) in both cognitively normal and impaired individuals with PD.

In line with previous studies in PD (Duchesne et al., 2015; Uc et al., 2014), aerobic exercise led to improvements in executive functions. In the current study, improvements in executive functions were demonstrated by an increase in the number of items correctly named in the colour-word condition of the Stroop test after aerobic exercise. Importantly, the present study contributes with two new pieces of evidence. This is the first study to disentangle the effects of exercise modality on cognitive functions in PD, showing that aerobic exercise was more effective than goal-based exercise on improving executive functions in individuals with PD. Therefore, the aerobic component of exercise in previous multimodal studies may have played a critical role in changes in cognition. In addition, this is the first study to demonstrate that cognitively normal and impaired individuals with PD can benefit similarly from aerobic exercise. Recent research has shown that moderate to high intensity exercise (primarily aerobic) can lead to increases in serum BDNF levels (Frazzitta et al., 2014; Marusiak et al., 2015), increases in dopamine transporter D2 expression (Fisher et al., 2013) and changes in cortical excitability (Fisher et al., 2008) in individuals with PD. Although these studies were not focused on the effects of exercise in cognition, they provide insight into the potential underlying mechanisms of improvements in executive functions found in the current study.

With respect to the effects of exercise on energization, task-setting, and monitoring, there was no strong evidence to suggest that exercise could improve these processes. However, results showed that cognitively impaired participants from the Control group were significantly slower at post-test in the Easy Choice RT test. A similar slowing in RT for this group was observed in the Simple RT and Complex Choice RT tasks, but these results did not reach statistical difference. The slowness in RT found in the Control group may represent the progression of cognitive deficits over the 12-week period. Importantly, these results may suggest

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that exercise could have prevented worsening in cognitive function of participants with cognitive impairment in both Aerobic and Goal-based exercise groups. Although a decrease in the total number of errors was found for participants with cognitive impairment from the Aerobic group in the complex choice RT task, these results should be interpreted with caution since these participants also showed slower RT at post-test in this task. Hence, improvements in accuracy observed in individuals with cognitive impairment from the Aerobic group may have represented a change in strategy (traded speed for accuracy) at post-test rather than true improvements in accuracy.

In relation to the cognitive domains that have been linked to increased risk of dementia in PD, main effects of time of assessment for memory, language and visuospatial processing did not reveal any specific effects of exercise. Changes in cognitive domains other than executive functions have been found in older adults with normal cognition (Erickson et al., 2011) and individuals with mild cognitive impairment (Baker et al., 2010; Suzuki et al., 2013), but these studies were significantly longer than the present study (12 and 6 months, respectively). Nonetheless, it was found that participants with cognitive impairment in the Control and Goal-based groups had worse performance in a task assessing visuospatial function (Intersecting Pentagons) at post-test, while performance in this task did not change for those in the Aerobic group. This result may suggest that, even though Aerobic exercise did not improve visuospatial functions, it might have attenuated their deterioration. This is a very important result given that performance in the copy of the intersected pentagons was identified as a strong predictor of PD dementia in a large longitudinal study (Williams-Gray et al., 2009; Williams-Gray et al., 2013). Although it remains unclear whether exercise has a protective effect for neurodegenerative processes, studies have demonstrated that exercise may decrease brain atrophy (Colcombe et al.,

2006; Erickson et al., 2011; Suzuki et al., 2013) and decrease future risk of mild cognitive impairment (Geda et al., 2010) and dementia (Hamer & Chida, 2009) in older adults. Therefore, studies need to further evaluate the effects of exercise on cognitive function and brain health (e.g. brain volume and neurotransmitters activity) in individuals with PD. This should be addressed through the use of longitudinal randomized controlled trials, in order to clarify whether exercise can prevent or even delay the progression of cognitive decline in PD.

Limitations of the current study were the lack of a follow up period and sample size. Although a follow up would bring important information regarding the long lasting effects of exercise, the choice of neuropsychological tests with alternate versions would be essential to avoid practice effects due to repetition of tests. In relation to sample size, a larger sample would be especially important considering the variability in performance of participants with cognitive impairment. However, to date, this study has a sample size larger than the majority of studies available in the literature for PD.

In conclusion, the present study showed that the aerobic component of exercise is critical to improvements in executive functions in PD. In line with previous investigations, aerobic exercise improved specifically inhibitory control. This selective effect of aerobic exercise could not be attributed to changes in energization, task-setting, or monitoring, since no changes were found in these processes from pre to post-test. Importantly, positive effects of exercise on executive functions were found in PD patients with and without cognitive impairment, showing that aerobic exercise may be used as adjunct therapy in PD across different cognitive status. Finally, participants with cognitive decline who did not receive specific exercise intervention (Control group) showed deterioration in performance over the course of the study while

comparable PD patients in the exercise groups did not. These findings suggest that exercise may postpone cognitive decline in PD.

Supplementary Material – Chapter 4

Table 10 Groups' performance at baseline on RT tasks

	Aerobic (n=22)	Goal-based (n=21)	Control (n=15)	p value
Reaction Time (ms)				
SRT	320.06 (62.53)	322.80 (47.91)	315.19 (56.50)	0.92
ECRT	619.25 (122.62)	601.68 (100.34)	590.35 (127.81)	0.74
CCRT	696.22 (117.29)	715.39 (139.77)	696.10 (166.08)	0.88
Reaction Time Variability (CV)				
SRT CV	19.72 (5.6)	18.46 (4.28)	18.03 (5.29)	0.56
ECRT CV	21.12 (3.17)	22.48 (4.23)	20.01 (3.89)	0.15
CCRT CV	23.63 (4.40)	26.90 (5.15)[b]	22.53 (3.92)	**0.013**
Reaction Time by ISI (ms)				
SRT short ISI	329.80 (58.86)	337.46 (49.23)	331.17 (62.79)	0.89
SRT long ISI	309.60 (68.68)	307.71 (48.40)	298.76 (52.77)	0.84
ECRT short ISI	624.07 (121.83)	619.23 (123.15)	598.19 (144.98)	0.82
ECRT long ISI	613.50 (123.55)	586.78 (92.94)	583.52 (112.96)	0.64

Reaction time by Stimulus type(ms)				
ECRT target	647.09 (131.54)	618.78 (97.43)	601.38 (97.37)	0.46
ECRT non-target	607.90 (123.64)	597.06 (105.81)	581.03 (129.83)	0.79
CCRT target	750.38 (150.57)	786.10 (172.07)	753.52 (257.41)	0.80
CCRT non-target 0 common feature	605.57 (115.35)	630.91 (148.35)	630.36 (175.46)	0.82
CCRT non-target 1 common feature	658.70 (144.38)	659.06 (151.54)	647.45 (167.96)	0.96
CCRT non-target 2 common feature	722.21 (97.23)	757.52 (140.22)	741.39 (152.41)	0.67
Accuracy (absolute value)				
ECRT total error	4.18 (7.72)	7.09 (13.99)	6.73 (14.15)	0.69
ECRT false positive error	1.72 (4.18)	4.61 (13.04)	3.13 (8.07)	0.59
ECRT false negative error	2.45 (3.72)	2.47 (2.80)	3.60 (6.35)	0.67
CCRT total error	8.81 (14.57)	4.47 (6.85)	4.73 (7.69)	0.34
CCRT false positive error	5.36 (12.68)	2.14 (3.32)	1.46 (2.87)	0.28
CCRT false negative error	3.45 (6.56)	2.33 (4.10)	3.26 (5.04)	0.77

Legend: SRT – Simple Reaction Time ; ECRT – Easy Choice Reaction Time; CCRT – Complex Choice Reaction Time; CV – Coefficient of Variation; ISI – inter-stimulus interval; b = Goal-based different than Control (p<0.05)

Table 11 Groups' performance at baseline on neuropsychological tests

	Aerobic (n=22)	Goal-based (n=21)	Control (n=15)	p value
Working Memory/Attention				
Digit Span forward (points)	10.04 (2.47)	10.28 (1.95)	10.73 (2.31)	0.66
Digit Span backwards (points)	6.22 (2.34)	5.66 (1.85)	6.86 (2.23)	0.26
Digit Span Total (points)	16.27 (4.48)	15.95 (3.00)	17.6 (3.83)	0.42
Corsi Block Test (level)	4.40 (1.33)	4.38 (0.86)	4.26 (1.22)	0.93
Executive Function				
Trail Making Test part A (s)	40.42 (14.64)	46.72 (24.62)	43.71 (34.11)	0.74
Trail Making Test part B (s)	93.52 (48.89)	135.33 (72.81)	88.78 (70.51)	**0.07**
Trail Making Test B-A (s)	53.10 (40.28)	88.61 (63.87)[b]	45.07 (41.03)	**0.03**
Stroop Test Word condition (number of words)	80.13 (21.69)	80.95 (18.40)	82.06 (19.82)	0.95
Stroop Test Colour condition (number of words)	55.68 (17.50)	57.00 (12.04)	55.06 (16.31)	0.92
Stroop Test Colour-Word condition (number of words)	29.13 (13.55)	29.52 (8.73)	33.40 (11.51)	0.49
Memory				
CVLT short recall (number of words)	6.09 (2.22)	6.19 (1.47)	6.60 (1.95)	0.71
CVLT long recall (number of words)	5.22 (2.79)	5.76 (1.97)	6.46 (2.19)	0.30

CVLT cued recall (number of words)	5.72 (2.37)	6.14 (1.74)	6.86 (1.99)	0.26
CVLT recognition (number of words)	8.40 (1.14)	8.19 (1.03)	8.46 (0.83)	0.68
CVLT forced recall (number of words)	9.00 (0.00)	8.95 (0.21)	8.93 (0.25)	0.52
Rey-O short recall (points)	17.68 (8.53)	14.71 (6.20)	20.33 (6.52)	0.11
Rey-O long recall (points)	18.02 (8.56)	14.35 (5.72)	19.53 (5.86)	**0.07**
Language				
Phonemic fluency (number of correct words)	11.00 (3.05)[a]	11.19 (4.81)[b]	14.46 (4.45)	**0.02**
Semantic fluency (number of correct words)	18.04 (4.89)	19.25 (6.85)	19.78 (6.80)	0.68
Boston Naming Test (number of items correctly named)	13.63 (1.70)	13.28 (1.95)	14.53 (0.91)	**0.08**
Visuospatial processing				
Copy of the Intersected Pentagons (points)	9.13 (1.78)	9.09 (1.70)	9.26 (1.09)	0.94
Benton Line Orientation (number of correct judgments)	52.71 (8.29)	48.15 (11.41)	53.2 (4.57)	0.16

Legend: CVLT - California Verbal Learning Test (short form); a = Aerobic different than Control; b = Goal-based different than Control ($p<0.05$)

Chapter 5

Do exercise-induced changes in cognition influence gait in Parkinson's disease?

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Abstract

Associations between deficits in cognition and gait have been demonstrated in Parkinson's disease (PD), suggesting that individuals with PD may rely on cognition to consciously control gait. Physical exercise has been shown to improve both cognition and gait in PD. However, it remains unknown how different modes of exercise may influence cognition and gait as well as whether improvements in cognition can lead to improvements in gait in PD. This study aimed to compare the effects of aerobic and goal-based exercise on cognition and gait in PD patients with and without cognitive impairment. In addition, this study investigated whether exercise-induced changes in cognition could predict changes in gait in PD. Thirty-five PD participants were randomized into an Aerobic (n=18) or a Goal-based (n=17) exercise group and attended 1-hour sessions 3x/week for 12 weeks. Cognitive assessment included three reaction time (RT) and three executive functions tests (Digit Span, Stroop test, and Trail Making Test). Gait was assessed in single and dual-task conditions. Results showed that aerobic and goal-based exercise improved cognition of individuals with PD, irrespective of cognitive status. Specifically, aerobic exercise improved accuracy in choice RT (p=0.06) and performance in the Stroop test (p=0.032), while goal-based exercise improved performance in the Digit Span (p=0.06). Positive effects of exercise on gait were found only for PD patients with cognitive impairment and exclusively in the dual-task condition. Specifically, aerobic exercise decreased step time variability (p=0.002), whereas goal-based exercise decreased step time (p=0.05) during dual-task at post-test. Changes in cognition predicted changes in gait only for the Aerobic group. In conclusion, aerobic and goal-based affected different aspects of cognition and gait in PD. Interestingly, improvements in cognition predicted improvements in gait only after aerobic exercise.

Keywords: Parkinson's disease, exercise, cognition, executive functions, gait

5.1 Introduction

Deficits in cognition exist in Parkinson's disease (PD) and have been associated with impaired gait during single and dual-task walking (Lord et al., 2014; Rochester et al., 2004; Yogev et al., 2005). This relationship has been suggested to reflect an increased reliance on cognition to control gait in PD as a result of decreased gait automaticity (Baker, Rochester, & Nieuwboer, 2007; Iansek, Danoudis, & Bradfield, 2013; Rochester et al., 2007). Although correlational evidence does not imply causality, research has shown that activity in brain areas important for cognitive processing (e.g. dorsolateral pre-frontal cortex) is greater in individuals with PD compared to age-matched controls when performing automatic movements (Wu & Hallett, 2005). These findings suggest that individuals with PD rely on activity of brain areas involved in cognition to compensate for basal ganglia dysfunction when performing automatic movements. Hence, it has been proposed that cognitive decline may limit the ability of individuals with PD to compensate for gait disturbances.

Deficits in attention and executive functions have been consistently linked to reduced gait speed and increased step-to-step variability in individuals with PD, especially during dual-task walking (Lord, Rochester, Hetherington, Allcock, & Burn, 2010; Smulders et al., 2013; Yogev et al., 2005). Since the frontal lobes play an important role in the processing of attention and executive functions, these associations stem from the involvement of frontal lobe functioning in gait control in PD. In order to understand specific contributions of frontal areas to gait control in PD, one alternative could be to evaluate the relationship between gait and behavioural outcomes of cognitive processes in which distinct frontal lobe areas are critical (Stuss, 2011; Stuss & Alexander, 2007; Stuss et al., 2005; Stuss, Binns, Murphy, & Alexander, 2002). Previous research in individuals with focal frontal lobe lesions has repeatedly demonstrated that at least

three cognitive processes seem to be regionally organized within the frontal lobes (Alexander, Stuss, Picton, Shallice, & Gillingham, 2007; Stuss & Alexander, 2007; Stuss et al., 2005; Stuss et al., 2002). These cognitive processes were defined as the abilities [1] to initiate or sustain a response (energization), [2] to set a stimulus-response relationship (task-setting), and [3] to monitor performance over time for quality control and adjustment of behaviour (monitoring). Most importantly, the frontal areas found to be critical to each cognitive process (superior medial, left lateral, and right lateral, respectively) are known to be anatomically and functionally linked to the basal ganglia (Alexander, DeLong, & Strick, 1986; Middleton & Strick, 2000a, 2000b), and selective deficits in these processes have been previously found in individuals with PD (see Chapter 2). Thus, investigating whether a relationship exists between cognitive processes regionally organized within the frontal lobes and gait behaviour could help define the contributions of specific frontal areas to gait in PD. Moreover, if individuals with PD rely on frontal lobe functioning to compensate for gait impairments, one might expect that therapies targeting the improvement of frontal lobe functioning could benefit gait control of those with PD.

The treatment of cognitive decline in PD is a challenge due to its multifactorial underlying mechanisms (Kehagia, Barker, & Robbins, 2010). Currently, there is no standard pharmacological treatment for cognitive deficits in PD, and dopaminergic medication may only partially improves cognitive function (Cools, Barker, Sahakian, & Robbins, 2001; Gotham, Brown, & Marsden, 1988). As a complementary strategy, physical exercise has been shown to provide benefits to executive functions in PD (Cruise et al., 2011; Duchesne et al., 2015; Tanaka et al., 2009; Uc et al., 2014). Interestingly, a recent review suggested that both aerobic and goal-based exercise may improve cognitive and motor function in PD (Petzinger et al., 2013).

However, the effects of aerobic and goal based exercise on cognition and gait have never been concurrently assessed in individuals with PD. Furthermore, it remains unknown whether cognitive changes as a result of exercise may be associated with better gait control in PD.

The present study aimed to compare the effects of aerobic and goal-based exercise on three cognitive processes mediated by the frontal lobes (energization, task-setting, and monitoring), executive functions, and gait in individuals with PD. In addition, this study aimed to evaluate whether exercise-induced changes in cognition are associated with changes in gait in PD. The effects of exercise on cognition and gait were examined in PD patients with and without cognitive impairment. This was important because PD patients with cognitive impairment also have poor gait control (Amboni et al., 2012). Thus, investigating the effects of exercise on PD patients with different cognitive status could reveal the potential of exercise to treat cognitive and gait deficits in mild as well as advanced stages of impairment. Based on findings from the current thesis (see Chapter 4), it was hypothesized that aerobic exercise would be more beneficial than goal-based exercise to enhance cognition in PD. Although evidence exists that both aerobic and goal-based exercise may improve gait in PD (Sage & Almeida, 2009), it was expected that goal-based exercise would improve gait during single-task walking due to its specificity to enhance gait control (e.g. walking with longer steps, challenging dynamic balance, training inter-limb coordination). Yet, considering the link between cognition and gait in PD, it was hypothesized that aerobic exercise would improve gait during dual-task (i.e. more cognitively demanding than single-task) and that changes in cognition would be associated with changes in gait as a result of aerobic exercise.

5.2 Methods

The present study was approved by the University of Waterloo and the Wilfrid Laurier University research ethics boards. Informed consent was obtained from all individuals prior to participation.

5.2.1 Participants

Thirty-five participants with confirmed diagnosis of idiopathic PD were recruited from the Movement Disorders Research and Rehabilitation Centre database at Wilfrid Laurier University (Waterloo, Canada) over a 10 month period. Participants were randomly allocated into an Aerobic or a Goal-based exercise group (Figure 15). Exclusion criteria were defined as [1] history of neurological diseases other than PD, [2] unstable medical condition, [3] uncontrolled diabetes mellitus, [4] uncontrolled hypertension (BP>140/90), [5] history of heart disease, [6] resting heart rate >100, [7] history of stroke, [8] history chronic obstructive pulmonary disease, or [9] uncorrected visual impairments (including colour blindness). In addition, participants were excluded from the analysis if they had any changes in medication during the study period, if exercise adherence was less than 80% (29/36 classes), or if 3 classes were missed in a row. Participants were classified as cognitively normal and cognitively impaired based on the Level 1 guidelines from the Movement Disorders Task Force for PD mild cognitive impairment (Litvan et al., 2012) and PD dementia (Dubois et al., 2007). All participants (but two drug naïve), were assessed while in their ON medication state. Prior to participation, all individuals were required to obtain approval for participation in exercise from a physician (PARmed-X form). Participants in the current study were the same as those in Chapter 4 and data collection for both studies occurred simultaneously.
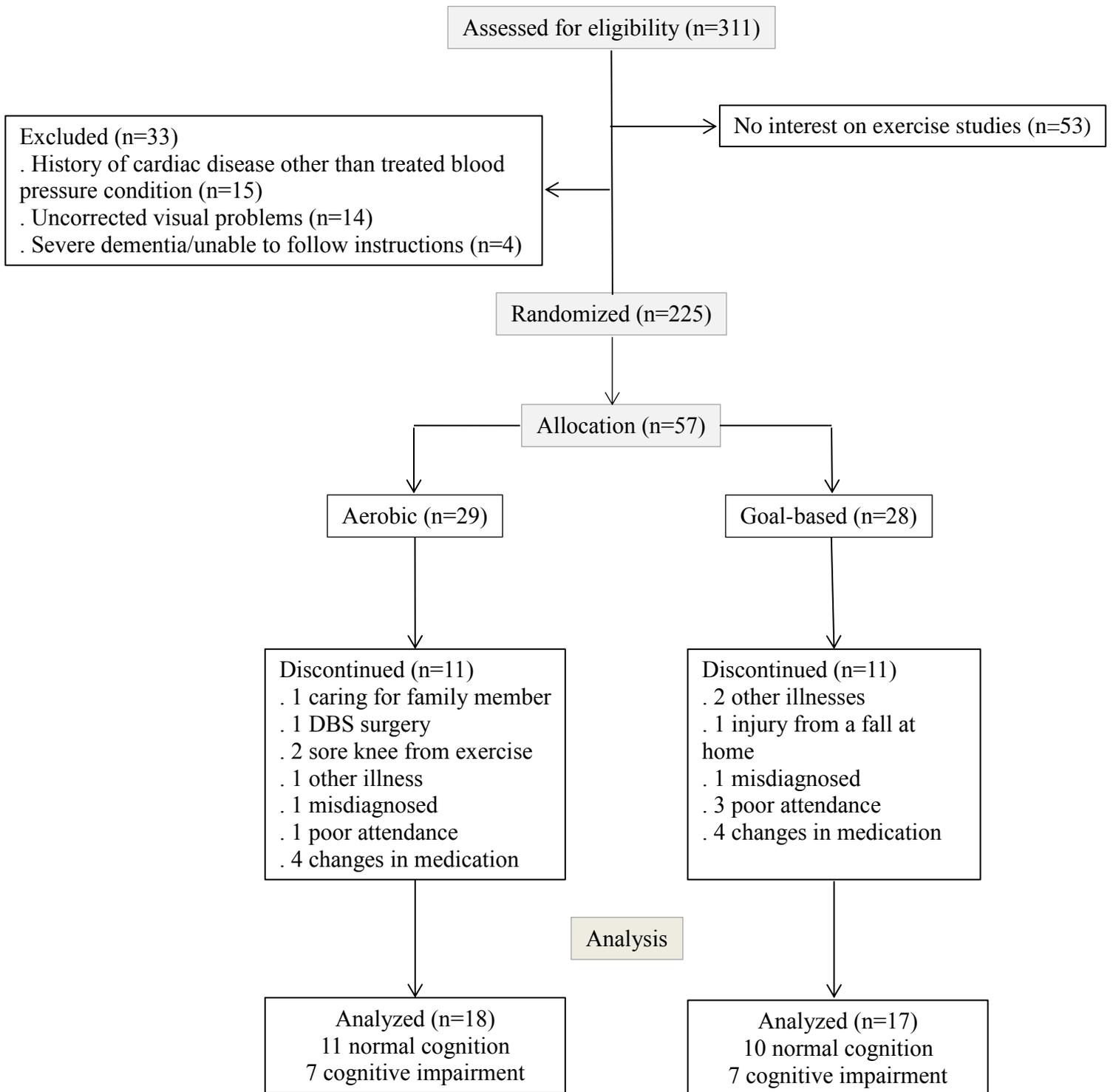
Figure 15 Flow of participants throughout the study (Study 4)

5.2.2 Apparatus and Experimental Procedures

Except for two computerized tasks (reaction time and aerobic capacity), participants were assessed at baseline and at the end of the study by trained evaluators blinded to the treatment arm. The use of research personnel blinded to study's purposes and treatment arm contributed to decrease bias in the assessment of executive functions and gait.

Demographics and clinical information

Participants had the severity of their motor symptoms assessed by a movement disorders specialist using the motor subsection of the UPDRS (UPDRS III) (Fahn & Elton, 1987), and had their general cognitive status assessed by a trained evaluator using the Montreal Cognitive Assessment (MoCA). Participants' demographic and clinical information is displayed in Table 12.

Table 12 Participants demographic and clinical information (Study 4)

	Aerobic (n=18)	*Goal-based (n=17)*
Demographic information		
Age (years)	72.11 (8.79)	68.05 (7.93)
Sex (M/F)	14/4	9/8
Handedness (R/L)	17/1	13/4
Education (years)	13.94 (2.89)	13.70 (2.86)
Clinical information		
GDS	6.72 (6.08)	9.76 (7.70)
MoCA	24.72 (4.86)	24.88 (3.93)
UPDRS III	25.36 (8.79)	29.44 (9.72)
Disease duration (years)	6.33 (5.41)	5.88 (3.99)
LED	695.22 (463.07)	442.52 (331.08)*

Legend: GDS – Geriatric Depression Scale; MoCA – Montreal Cognitive Assessment; UPDRS III – Unified Parkinson's disease Rating Scale; LED – Levodopa Equivalent Dose; * p=0.034

Exercise interventions

Participants in both groups attended three 1-hour sessions per week for 12 weeks. In the aerobic exercise sessions, recumbent cycle ergometers (700 Excite + Recline, Technogym USA©, Seattle, Washington) were used in order to provide safety and stability during training. The exercise class started with 5 minutes warm up (no load) followed by 30-40 minutes of aerobic training and 2 min cool down (no load). Participants initially cycled for 30 minutes and increased duration weekly, with all participants cycling for 40 minutes by week 4. Exercise intensity levels started at 40-50% heart rate reserve (HHR) and increased to 60-70% HHR by week 4. Intensity prescription was defined based on the Karvonen method which is expressed in the equation Target HR = ([(HRmax - HRrest)* (% exercise intensity)]+HRrest) (ACSM, 2000). Heart rate, workload, and rate of perceived exertion recordings from a baseline graded exercise test were used in order to lead participants to the desired exercise intensity. For the goal-based training, participants performed a standardized exercise protocol (PD SAFEX™ - without eyes closed condition) that involved walking exercises coordinating upper and lower limbs on a simultaneous or alternating manner, non-progressive muscle-toning exercises using resistance bands and the persons' own body weight, and whole body stretching exercises. A new sequence of exercises was introduced every week in order to increase the level of difficulty progressively.

5.2.3 Outcome measures

Reaction time

In order to assess the three cognitive processes argued to be regionally organized within the frontal lobes, participants performed reaction time (RT) tasks from the *Feature Integration Test (FIT)* (Stuss et al., 2002). These tasks were composed of a Simple RT, an Easy Choice RT, and a Complex Choice RT tasks. The stimulus in these tasks was one of the four shapes: square, circle, triangle, or cross. The shapes were dark grey or coloured on a black background. For all tasks, stimuli were randomly presented at inter-stimulus intervals varying between 3 s and 7 s. Each stimulus stayed on the screen for 2 seconds or until a response was made. Each task was programed using MEL2 (Psychology Software Tools, Inc.), and responses were made on a Serial Response Box (Psychology Software Tools, Inc.) with five buttons (numbered 1-5 from left to right) aligned horizontally. In the SRT, the stimulus was a grey square presented 50 times after 5 practice trials. Participants were instructed to press button number 1 in the serial response box as fast as possible whenever they saw the square. For both Easy and Complex Choice RT tasks, stimuli were presented 102 times in random order following 10 practice trials. In these tasks, one stimulus was pre-established as the target stimulus while all other stimuli were non-targets. Participants were asked to respond to the target stimulus by pressing button number 1 with their right index finger, while they were asked to respond to non-target stimuli by pressing button 2 with their right middle finger on the serial response box. In the easy choice RT task, all stimuli were grey and shape was the only characteristic distinguishing the target from non-target stimuli. In the Complex Choice RT tasks, each shape was coloured (red, blue, green, or yellow) and contained a pattern of internal lines (vertical, horizontal, or diagonals). Thus, each stimulus varied in a combination of shape, colour, and internal line orientation, with the target being defined by a specific combination of these three features while the other combinations were non-targets.

Outcome measures included overall RT, RT coefficient of variation (RT CV), RT for target and non-target stimuli, RT for short and long inter-stimulus interval, total error, and error type (false positive, false negative, and omissions). Based on previous research involving individuals with focal frontal lobe lesions, deficits in the ability to initiate and sustain a response were characterized by slow RT that was present in simple RT task and more pronounced in both choice RT tasks. Deficits in the ability to set a stimulus-response relationship were characterized by an increase in number of false positive errors when participants had to selectively respond to target and non-target stimuli and slowness in RT when responding to target stimuli. Finally, deficits in the ability to monitor performance over time for quality control were characterized by the lack of differences in RT for short and long inter-stimulus intervals (particularly a decrease in RT for long inter-stimulus intervals), and an increase in errors of all kinds. Therefore, if Aerobic and/or Goal-based exercise have beneficial effects on these cognitive processes, then improvements in outcomes measures reflecting each cognitive process were expected.

Executive functions

Executive functions were evaluated using three neuropsychological tests aiming to assess inhibitory control (Stroop test), working memory (Digit Span), and set-shifting (Trail Making Test) (Lezak, Howieson, & Loring, 2004). In the Stroop Test, three conditions were completed. In the first condition ("word"), participants were asked to read aloud the words RED, GREEN, and BLUE printed in black ink. In the second condition ("colour"), participants were asked to name the colour of the ink in which four Xs were printed. In the third condition ("colour-word"), participants were asked to name the colour of the ink in which the words "RED", "GREEN", and "BLUE" were printed, ignoring the word itself. For each of these three conditions, participants had 45 seconds to read/name appropriately as many items as possible (100 items total). The total

number of items correctly read/named in each condition was recorded. In the Digit Span Test, participants were verbally administered a sequence of numbers and asked to repeat the same numbers in two conditions: forward and backward orders. As participants progressed in the test (i.e. correctly recalled a sequence of numbers), the length of the number strings increased. Each condition had multiple levels, each containing two trials where the length of the sequence was the same. To move onto the next level, the subject was required to accurately recall at least one of the two strings of numbers. The test was concluded once the subject was unable to complete both trials within a level. The number of points for each forward and backward conditions were used to assess participants' working memory. The Trail Making Test (TMT) was composed of two parts. In Part A, participants were instructed to connect numbered circles in ascending order from 1 to 25. Part A was used to assess an individual's cognitive processing speed. In Part B, the circles contained both numbers and letters. This time, participants were asked to connect them in numerical and alphabetical order, alternating between numbers and letters. Part B was used to assess participants' set-shifting ability. In both conditions, participants were instructed to keep their pencil on the page at all times, and to do this task as quickly as possible. Participants were scored based on the time to complete each part. Moreover, the subtraction of time spent to complete part B from part A (B-A) generated a score that accounted for movement speed, therefore allowing a more direct assessment of set-shifting.

Gait

Participants were asked to perform 6 walking trials in the conditions as follows: single task (self-paced walking) and dual task (walking while performing a secondary task). The secondary task consisted of counting the number of times a participant heard two pre-established digits (e.g. 3 and 4) spoken in an audio track (Pieruccini-Faria, Jones, & Almeida, 2014). The

numbers on the audio track ranged from 1 to 9 and the auditory inter-stimulus intervals varied

from 100ms to 1000ms. During the walking task participants were instructed to continue

counting even if they had completed the walking. In addition, they were asked to equally

prioritize gait and digit counting tasks. In order to assess one's ability to perform the secondary

task, participants were asked to count how many times they heard the assigned digits while

sitting (3 randomized trials). Performance in the secondary task was assessed using the sum of

absolute errors (absolute error = correct response − actual response) from both pre-assigned

digits within a trial. Following this procedure, participants performed 3 single and 3 dual-task

trials in randomized order. Walking trials were collected on a Zeno Walkway System

(ProtoKinetics, Havertown, PA, USA). Step length, step time, step width and their respective

coefficient of variation (CV), as well as percentage of time spent in double support and gait

speed were calculated using the ProtoKinetics Movement Analysis Software (PKMAS) version

507c7c.

5.2.4 Statistical analysis

Independent t-tests were used to compare demographic and clinical features across

groups. Two-way Repeated Measures analyses of variance (ANOVA) were run to examine the

effects of exercise on all outcome measures. In these analyses, between factors were always

Group (aerobic vs goal-based) and Cognitive Status (normal vs impaired), while within factors

varied depending on the outcome measure. In the analyses of RT outcomes, two-way Repeated

Measures ANOVAs were used to examine the effects of exercise on overall RT and RT

variability [Group (aerobic vs goal-based) X Cognitive Status (normal vs impaired) X Time (pre

vs post)]. For Easy RT and Complex Choice RT, two-way Repeated Measures ANOVAs were

used to compare the effects of exercise on RT by stimulus type [Group (aerobic vs goal-based) X

Cognitive Status (normal vs impaired) X Time (pre vs post) X Stimulus (target vs non-target)].

While in Easy Choice RT there were two stimulus types (target or non-target), in Complex

Choice RT there were four stimulus types (0, 1, 2, or 3; where 3 is the actual target). In addition,

two-way Repeated Measures ANOVAs were used to assess the effects of exercise on RT for

short and long inter-stimulus intervals (ISI) [Group (aerobic vs goal-based) X Cognitive Status

(normal vs impaired) X Time (pre vs post) X ISI (short vs long)] in the Simple RT and Easy

Choice RT tasks. For the analyses of accuracy measures, two-way Repeated Measures ANOVAs

were used to examine the effects of exercise on total number of errors [Group (aerobic vs goal-

based) X Cognitive Status (normal vs impaired) X Time (pre vs post)] and error types [Group

(aerobic vs goal-based) X Cognitive Status (normal vs impaired) X Time (pre vs post) X Type

(FP vs FN)] in both choice RT tasks. Two-way Repeated Measures ANOVAs were used to test

the effects of aerobic and goal-based exercise on executive functions [Group (Aerobic vs Goal-

based) X Cognitive Status (normal vs impaired) X Time (pre vs post)]. Two-way Repeated

Measures ANOVAs were used to compare the effects of exercise on gait during single and dual

task and across trials [Group (aerobic vs goal-based) X Cognitive Status (normal vs impaired) X

Task (single vs dual) X Trials (T1 vs T2 vs T3) X Time (pre vs post)]. Two-way Repeated

Measures ANOVA were also used to compare performance on the secondary task between

groups and cognitive status in each condition at pre and post exercise [Group (aerobic vs goal-

based) X Cognitive Status (normal vs impaired) X Condition (sitting vs walking) X Time (pre vs

post)]. Tukey's HSD post-hoc was used to examine significant differences and alpha level was

kept at p<0.05.

In order to determine whether exercise-induced changes in cognition could predict

changes in gait, Stepwise Multiple Linear Regression analyses were implemented exclusively for

outcome measures that changed from pre to post-test. Cognitive and gait change scores (Δ) which were calculated by subtracting post scores from pre scores.

Statistical analyses were performed on SPSS® version 22 software and significant differences were kept at an alpha level of 0.05.

5.3 Results

5.3.1 Groups' demographic and clinical information at baseline

Groups were matched for age, years of education, general cognitive status (MoCA), depression signs (GDS), motor disease severity (UPDRS-III), and disease duration (years since diagnosis). However, participants in the Aerobic group were taking significantly more medication (i.e. greater LED) than those in the Goal-based group ($F(1,31)=4.91$; p=0.034; η_p^2 =0.13).

The following results focused on main effects and interactions involving assessment time that revealed the effects of exercise on cognition and gait.

5.3.2 The effects of exercise on cognition

Cognitive processes: Reaction time and accuracy

There were no differences in overall RT and RT variability from pre to post-test for Simple RT, Easy Choice RT, or Complex Choice RT tasks. In addition, no effects were found from pre to post-test on RT for short and long inter-stimulus intervals.

When RT was analyzed by stimulus type, an interaction between assessment time, stimulus type, and group was found for the Easy Choice RT task (F(1,31)=4.40; p=0.044; η_p^2 =0.12). This interaction showed that participants in the Goal-based group were slower to respond to the target stimulus at post compared to pre-test (p=0.029). Although participants in the Aerobic group responded faster to the target stimulus at post-test, this was not statistically significant (Figure 16 - left). There were no interactions between group, stimulus type, and assessment time for the complex choice RT task.

TARGET

NON-TARGET
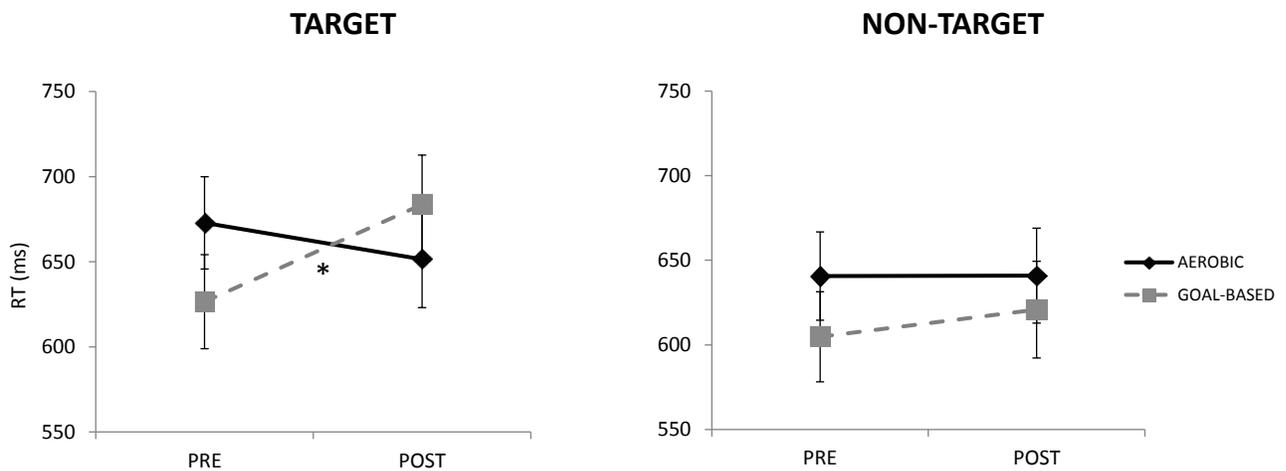
Figure 16 Participants in the Goal-based group showed slower response to the target stimulus at post compared to pre-test in Easy Choice RT task (p=0.029).

Accuracy results showed a trend for a main effect of assessment time in the Easy Choice RT task (F(1,31)=3.44; p=0.07; η_p^2 =0.10), suggesting that both groups decreased the overall number of errors in the this task at post-test. For the Complex Choice RT task, an interaction between assessment time and group neared significance (F(1,31)=3.79; p=0.06; η_p^2 =0.10),

suggesting that the total number of errors was smaller for the Aerobic group at post-test compared to pre-test (Figure 17). No changes were observed for the Goal-based group from pre to post-test. No differences were found for error type.
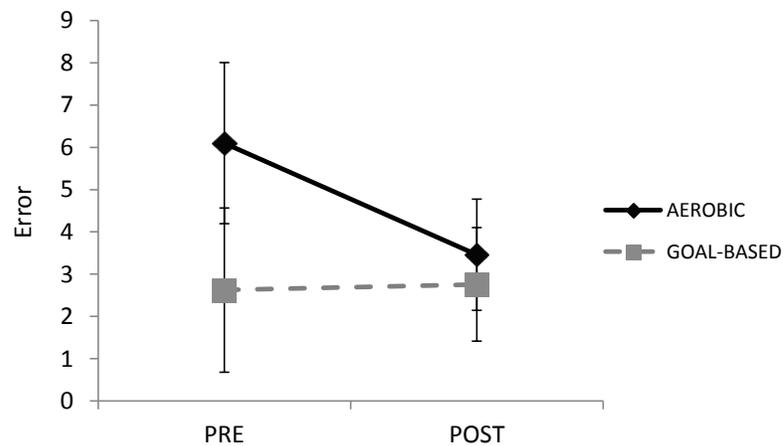
Figure 17 An interaction between assessment time and group neared significance (p=0.06) and suggested that participants in the Aerobic group were more accurate in Complex Choice RT task at post compared to pre-test.

5.3.3 Executive functions

An interaction between assessment time and group approached significance for the backwards condition of the Digit Span (F(1,31)=3.78; p=0.06; η_p^2=0.10) (Figure 18). This interaction suggested that participants in the Goal-based group increased the number of correct sequences recalled at post-test, while those in the Aerobic group maintained the number of correct sequences recalled in backwards order from pre to post-test.

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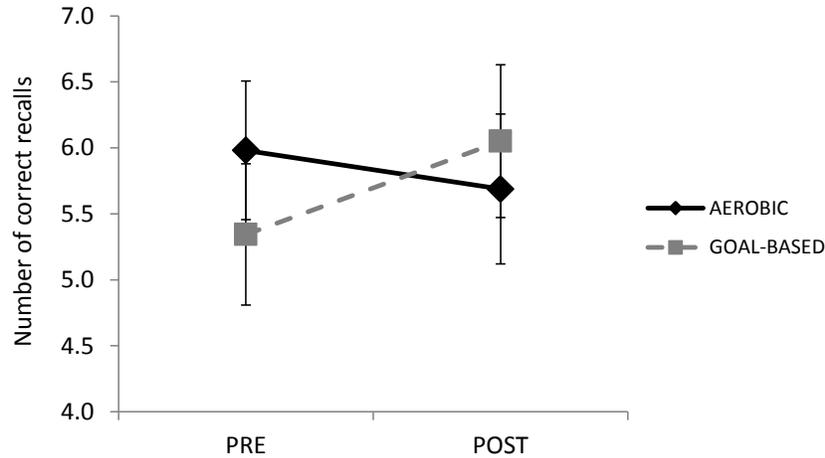
Figure 18 An interaction between group and assessment time neared significance (p=0.06) for the Digit Span backwards condition, suggesting that participants in the Goal-based group correctly recalled more number sequences in backwards order at post compared to pre-test.

In the Stroop test, no changes were found for the Word or Colour conditions from pre to post-test. Conversely, an interaction between assessment time and group was found for the Colour-Word condition ($F(1,31)=4.99$; $p=0.032$; $\eta_p^2=0.13$). Although post-hoc analysis did not reveal any significant differences, this interaction suggested that participants in the Aerobic group increased the number of correctly named items at post-test, while those in the Goal-based group decreased the number of correctly named items (Figure 19).
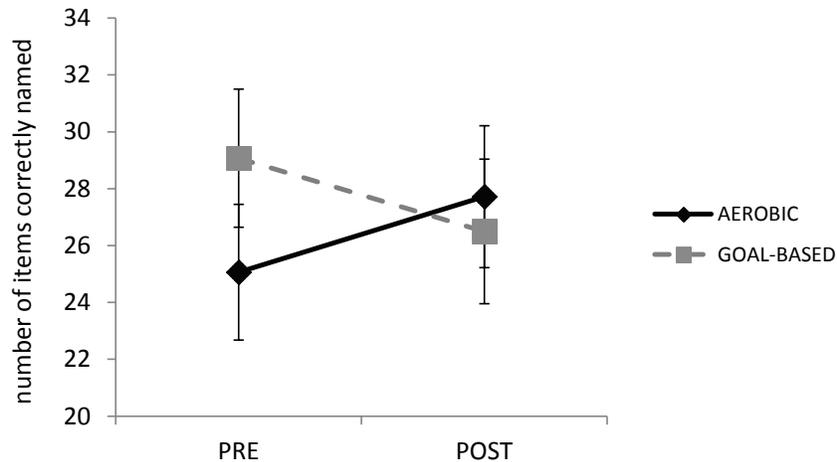
Figure 19 Group by assessment time interaction (p=0.032) suggested that participants in the Aerobic group correctly named more items in the Stroop Colour-Word condition at post compared to pre-test.

For the TMT task, a main effect of assessment time (F(1,25)=6.18; p=0.019; η_p^2=0.19) showed that, irrespective of exercise modality, participants were faster to complete the TMT A at post compared to pre-test. No differences were identified from pre to post-test for the TMT B. There was also no difference from pre to post-test for the B-A score.

5.3.4 The effects of exercise on gait

Main effects of Task showed that participants walked with shorter (step length: F(1,31)=125.29; p<0.0001; η_p^2=0.80) and more variable steps (step length variability: F(1,31)=21.74; p<0.0001; η_p^2=0.41; step time variability (F(1,31)=12.98; p=0.001; η_p^2=0.29), wider step width (F(1,31)=22.93; p<0.0001; η_p^2=0.42), longer step time and time spent in double support (step time F(1,31)=22.52; p<0.0001; η_p^2=0.42; double support F(1,31)=89.96; p<0.0001; η_p^2=0.74), and slower velocity (velocity: F(1,31)=118.77 p<0.0001; η_p^2=0.79) during

dual-task compared to single-task walking. These findings confirmed that the dual-task manipulation used in the current study appropriately interfered with gait control in individuals with PD. Interactions between task and trial for step length (F(2,62)=5.33; p=0.007; η_p^2=0.14), step time (F(2,62)=5.69; p=0.005; η_p^2=0.15), step time variability (F(2,62)=3.36; p=0.04; η_p^2=0.09), double support (F(2,62)=3.94; p=0.02; η_p^2=0.11), and gait velocity (F(2,62)=6.22; p=0.003; η_p^2=0.16) demonstrated that the changes in gait were greater in the first trial during dual-task compared to single-task walking (p<0.05).

A main effect of time was found for step width (F(1,31)=4.90; p=0.034; η_p^2=0.13), showing that participants took wider steps at post compared to pre-test. An interaction between assessment time and walking task (F(1,31)=10.91; p=0.002; η_p^2=0.26) demonstrated that all participants took wider steps at post-test specifically during dual-task walking (p<0.001), while step width did not change from pre to post during single-task. In addition, an interaction between assessment time, walking task, and cognitive status for step width (F(1,31)=4.63; p=0.039; η_p^2=0.13) revealed that primarily participants with cognitive impairment significantly increased step width during dual-task at post-test (p<0.001).

An interaction between assessment time and walking task was found for step time (F(1,31)=7.91; p=0.008; η_p^2=0.20), where participants from both groups decreased step time at post-test exclusively during dual-task walking (p=0.001). More specifically, an interaction between assessment time, task, and group (F(1, 31)=4.12; p=0.05; η_p^2=0.11), showed that mainly the Goal-based group decreased step time during dual-task at post-test (p<0.001), while no changes were observed for the Aerobic group (Figure 20).

SINGLE TASK
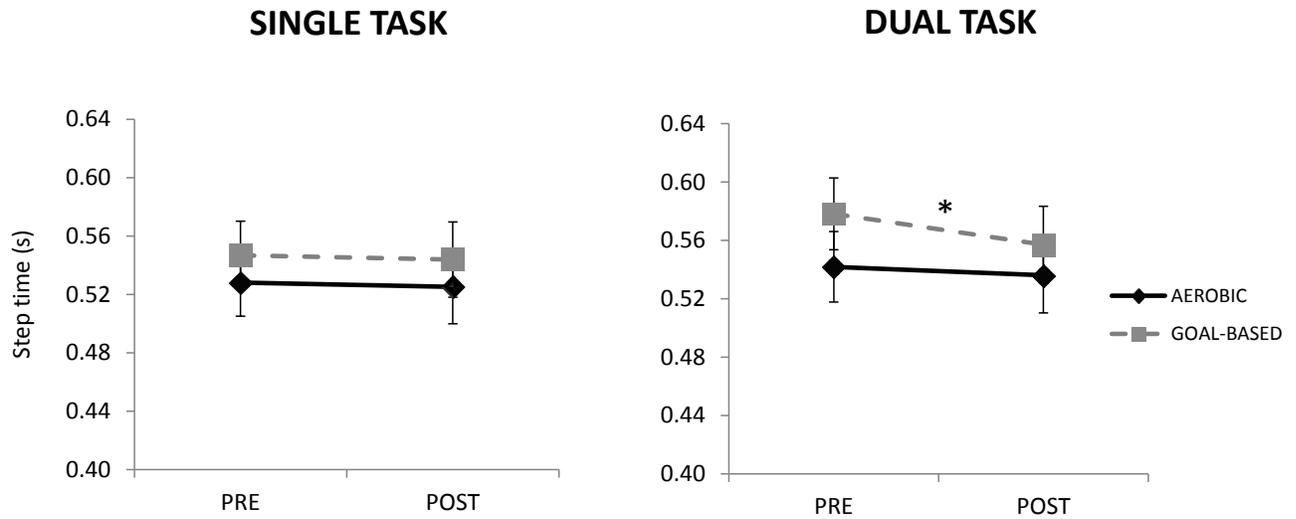
DUAL TASK

Figure 20 Step time was shorter for the Goal-based group at post compared to pre-test only during dual-task walking.

A five-way interaction between assessment time, task, trial, group and cognitive status was found for step time variability (F(2,62)=6.66; p=0.002; η_p^2=0.17). This interaction showed that individuals with cognitive impairment from the Aerobic group had reduced step time variability at post compared to pre-test in the first trial of the dual-task condition (p=0.008) (Figure 21).

SINGLE TASK
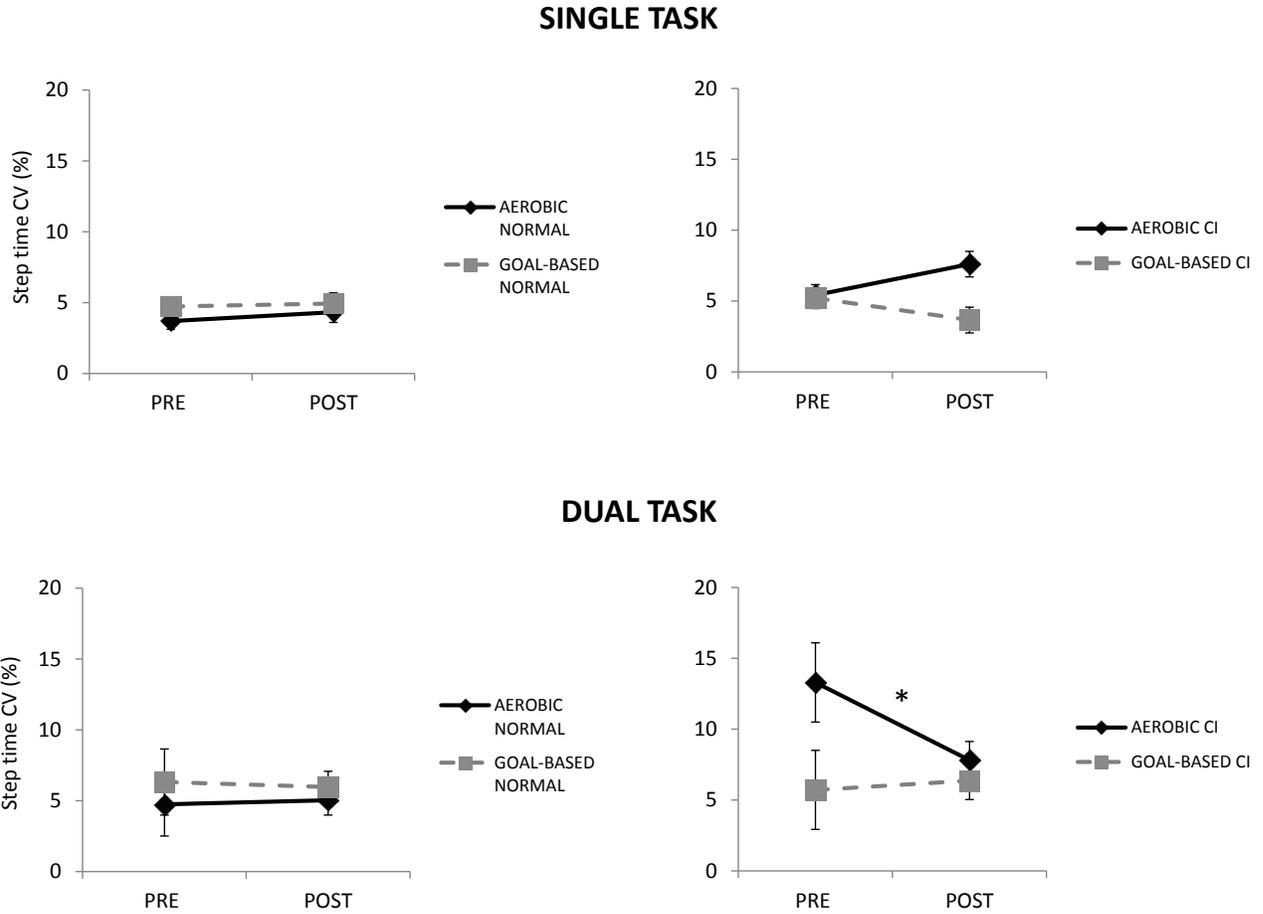
DUAL TASK

Figure 21 First trial effect for step time variability showed that individuals with cognitive impairment from the Aerobic group walked with smaller variability during dual-task at post compared to pre-test

An interaction between assessment time, walking task, trial, and cognitive status was found for the percentage of time spent in double support ($F_{(2,62)}=5.48$; p=0.006; $\eta^2_p=0.15$). Post-hoc analysis showed that individuals with cognitive impairment from both groups decreased the time spent in double support from pre to post-test in the first trial of the dual-task condition (p=0.053).

In relation to performance of the secondary (digit monitoring) task at baseline, an interaction between group and condition (i.e. sitting vs walking) (F(1,31)=5.79 p=0.022; η_p^2 =0.15) was found. However, post-hoc analysis did not reveal any significant differences. The visual inspection of mean values suggested that the Goal-based group had fewer errors than the Aerobic group when performing the task while seated at pre-test (Aerobic=3.25 and Goal-based=2.04). On the other hand, groups performed the secondary task similarly while walking at pre-test (Aerobic=2.89 and Goal-based=2.89). When assessing the effects of exercise on the secondary task, a main effect of assessment time showed that participants from both groups were less accurate when performing the secondary task at post compared to pre-test (F(1,31)=6.55 p=0.015; η_p^2 =0.17), irrespective of being seated or walking. No significant interaction between assessment time and condition was found. Moreover, there were no significant interactions between assessment time, condition, and group.

5.3.5 Relationship between changes in cognition and gait

Regression analysis showed that changes in step width during single (R^2=0.28) and dual-task (R^2=0.24) walking were predicted by changes in choice RT (easy choice RT - target stimulus) for the Aerobic group. These associations demonstrated that wider step width during single and dual-task walking was associated with faster choice RT. No changes in gait were associated with changes in cognition for the Goal-based group.

5.4 Discussion

The present study aimed to compare the effects of aerobic and goal-based exercise on cognition and gait in PD patients with or without cognitive impairment. In addition, it aimed to examine whether exercise-induced changes in cognition could predict changes in gait. Results showed that PD patients with and without cognitive impairments had similar improvements in cognitive outcomes after exercise. Specifically, aerobic exercise improved participants' monitoring (i.e. greater accuracy in RT tasks) and response inhibition (i.e. better performance in the Stroop test), whereas goal-based exercise improved participants' working memory (i.e. better performance in the Digit Span backwards). Improvements in gait after exercise were found primarily in individuals with cognitive impairment and exclusively for dual-task walking. Selective effects of exercise modality on gait were shown for step time (goal-based) and step time variability (aerobic) during dual-task. Finally, exercise-induced changes in cognition (i.e. faster choice RT) predicted changes in gait (wider step width) but only for the Aerobic group.

5.4.1 Effects of Aerobic and Goal-based exercise on cognition

One of the most relevant findings of the current study was to that cognitively normal and impaired individuals with PD benefit similarly from exercise. Given that people with PD rely heavily on cognition to control movement, improvements in cognition found in the current study may contribute to improvements in individuals' functionality, independence, and quality of life. A common finding across exercise modalities was the improvement in processing speed (Trail's A) at post-test. Improvement in processing speed may indicate a general effect of exercise on lower order cognitive functioning, given that the Trail's A is a fairly simple test. However, since

improvements were found for both exercise groups, it is important to consider that practice effects may have played a role in this finding.

Most importantly, results showed that the effects of exercise on cognition were selective. Aerobic exercise improved participants' monitoring and response inhibition. These results are in line with previous investigations showing that improvements in cardiorespiratory fitness led to improvements in monitoring (Themanson & Hillman, 2006) and response inhibition (Colcombe et al., 2004) in healthy individuals. In addition, these findings corroborate improvements in response inhibition after aerobic exercise in individuals with PD (Duchesne et al., 2015; Uc et al., 2014). According to Stuss and colleagues (Stuss & Alexander, 2007; Stuss et al., 2002), monitoring is critically mediated by right lateral areas of the pre-frontal cortex (PFC) such as dorsolateral and ventrolateral pre frontal cortices. Interestingly, in the current thesis it was found that individuals with PD in the OFF dopaminergic state (i.e. overnight medication withdraw) showed impairments in monitoring, suggesting that the basal ganglia may also be involved in mediating this cognitive process (see Chapter 2). With respect to inhibitory control, studies have suggested that this component of executive functions is mediated by inferior lateral frontal areas as well as the subthalamic nucleus in the basal ganglia (Aron, 2007; Obeso et al., 2014). Thus, findings from the current study suggest that exercise may improve functioning of circuitries between the basal ganglia and frontal lobe areas. It is important to note that neither monitoring (see Chapter 2) nor inhibition deficits (Obeso, Wilkinson, & Jahanshahi, 2011) are alleviated by dopaminergic medication. Therefore, this study shows that exercise may help treating cognitive processes/functions that cannot be treated with dopaminergic medication.

On the other hand, goal-based exercise had a selective effect on working memory. Working memory is argued to be strongly mediated by the dorsolateral pre frontal cortex and the

caudate nucleus of the basal ganglia (Lewis, Dove, Robbins, Barker, & Owen, 2003), and it is highly sensitive to dopaminergic activity (Lewis, Slabosz, Robbins, Barker, & Owen, 2005). Therefore, in contrast to cognitive functions that changed with aerobic exercise, changes in cognition after goal-based exercise could be linked to changes within the dopaminergic system. This suggestion is in line with previous research showing that goal-based exercise can significantly reduce disease severity in individuals with PD (McKee & Hackney, 2013; Sage & Almeida, 2009), since the scale that assesses disease severity in PD (UPDRS) is highly sensitive to dopaminergic medication. However, it is important to consider that during goal-based training participants had to remember instructions for executing complex and multi-part movement sequences, which could have demanded constant use of working memory. Thus, improvements in working memory found after goal-based exercise could have resulted from training specificity. In contrast, the repetitive nature of aerobic training may not have posed similar demands on specific cognitive functions.

5.4.2 Effects of Aerobic and Goal-based exercise on gait

After establishing the effects of exercise on cognition, the next step was to verify the effect of each exercise modality on gait. It was expected that goal-based exercise would improve gait during single-task because walking exercises were a component of its training sessions (specificity). However, given the link between gait and cognition, it was hypothesized that aerobic exercise would influence gait indirectly as a result of improvements in cognition, especially during dual-task performance. Results showed that both goal-based and aerobic exercise improved gait at post-test. Interestingly, changes in gait behaviour were found exclusively for the dual-task condition and the effects of exercise were observed primarily in individuals with cognitive impairment. These results support the notion of a strong link between

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cognition and gait in PD, given that the dual-task walking is argued to be more cognitively demanding than single-task walking (Holtzer et al., 2015). Interestingly, participants with cognitive impairment showed improvements in gait parameters that are very sensitive to dual-task interference (step width, double support, and step time variability) (Amboni, Barone, & Hausdorff, 2013; Amboni et al., 2012; Pieruccini-Faria et al., 2014; Rochester, Galna, Lord, & Burn, 2014; Rochester et al., 2004; Springer et al., 2006; Yogev et al., 2005). However, this study showed general (step width and double support) as well as selective (step time and step time variability) effects of exercise on gait.

Time spent in double support and step width are argued to be important parameters to gait stability. Previous research has shown that the ratio between single and double support times is shorter in PD patients with mild cognitive impairment, meaning that these individuals have a longer double support time relative to single support (Amboni et al., 2012). Thus, the reduction in double support found for individuals with cognitive impairment at post-test in the dual-task condition suggested an improvement in gait stability, irrespective of exercise modality. However, given the intricate relationship between gait parameters, it is important to reflect why two parameters linked to gait stability would change in opposition (i.e. decrease in double support and increase in step width). One possible explanation could be that at post-test individuals implemented a different strategy than at pre-test by trading time spent in double support for a wider base of support in order to control stability. However, using this logic in reverse order, thinking that a longer double support with a narrow base of support would not give individuals better stability (e.g. tandem position), this trading strategy may not seem like a reasonable argument. An alternative explanation could be that instead of changes in stability, the decrease in

double support found in this study may represent a different role of double support time on gait control during dual-task such as an improvement in planning of steps.

Increased step width has been argued to be an important gait adaptation in situations when stability is challenged, such as during dual-task walking (Rochester et al., 2014). Rochester et al. (2014) showed that while healthy older adults walked with wider step width during dual-task, individuals with PD did not change step width from single to dual-task walking. Therefore, changes in step width after exercise interventions (aerobic and goal-based) in the current study may suggest that exercise improved the ability of individuals with PD to adapt gait stability when threatened by dual-task situations. Remarkably, better performance in choice RT predicted increases in step width exclusively in the Aerobic group, suggesting that changes in cognition as a result of aerobic exercise may have contributed to improved ability of individuals with PD to adapt gait under situations that threaten gait stability.

Furthermore, it was found that aerobic and goal-based exercises had selective effects on gait at post-test in the dual-task condition. While goal-based exercise decreased step time, aerobic exercise decreased step time variability. Explaining the effects of goal-based exercise on step time is a challenge, given that step time is not commonly found to be sensitive to dual-task interference and given its interdependence with other gait parameters. For example, one would expect that changes in step time might have resulted from smaller and/or faster steps. However, no changes were found in step length or gait velocity at post-test during dual-task. When considering gait characteristics in domains rather than individually, Lord et al. (2013) showed that step time belonged to the so called "rhythmic" domain of gait. Hence, one possible explanation for this finding is that goal-based exercise decreased the effects of dual-task interference on gait rhythmicity, especially for individuals with cognitive impairment.

Differently, step time variability has been repeatedly demonstrated as a gait parameter sensitive to dual-task interference and it has been argued to reflect conscious/voluntary control of gait. Moreover, increased step time variability has been linked to increased risk of falls in older adults and individuals with PD (Springer et al., 2006; Yogev et al., 2005). Thus, the decrease in step time variability during dual-task performance as a result of aerobic exercise may suggest that aerobic exercise improved the ability of individuals PD to manage both gait and the cognitive secondary task.

Studies have shown that step time variability is not influenced by dopaminergic medication in individuals with PD (Blin, Ferrandez, Pailhous, & Serratrice, 1991; Lord, Baker, Nieuwboer, Burn, & Rochester, 2011). In fact, research involving individuals with early stages of Alzheimer's disease has demonstrated that the administration of cholinergic medication decreased step time variability in this population (Montero-Odasso et al., 2015; Montero-Odasso, Wells, & Borrie, 2009). Taken together, these results suggest that possibly a common non-dopaminergic mechanism underlies changes in cognition and gait following aerobic exercise. However, this hypothesis has yet to be tested with objective measures of neurotransmitter activity.

Finally, an important point to consider is why changes in gait were predominantly seen in individuals with cognitive impairment. One possible explanation is that at baseline individuals with cognitive impairment not only had worse gait but they also had depleted cognitive resources to voluntarily control gait. It has been suggested that treatment strategies aimed at enhancing cognitive function may lead to a decrease in the cognitive cost of dual-task walking (Montero-Odasso et al., 2015; Verghese, Mahoney, Ambrose, Wang, & Holtzer, 2010). Thus, it could be proposed that by enhancing cognition, cognitively impaired individuals with PD had more

cognitive resources available to voluntarily control gait during dual-task performance while for those with normal cognition these resources were always available.

In conclusion, this study showed that aerobic and goal-based exercises have selective effects on cognition and gait in individuals with PD. Most importantly, exercise-induced changes in cognition predicted changes in gait only after aerobic exercise. To the best of our knowledge, this is the first study to demonstrate that PD patients with and without cognitive impairment can improve cognitive outcomes after exercise, but primarily those with cognitive decline showed improvements in dual-task walking. These results support the notion that cognitive remediation through exercise can lead to improvements in gait in PD.

Chapter 6

General Discussion

The overall aim of the current thesis was to understand the effects of physical exercise on cognition in individuals with Parkinson's disease (PD). In order to achieve this aim, Study 1 introduced and tested a theoretical framework for methodological procedures and outcome measures that would be carried across the remaining studies in this thesis. This framework was based on the model proposed by Stuss (2011) which postulates that distinct cognitive processes (i.e. energization, task-setting, and monitoring) are regionally organized within specific frontal lobe areas. The frontal lobe areas argued to be critical to each of these processes (superior medial, left lateral, and right lateral) are known to be anatomically and functionally connected to the basal ganglia (Alexander, DeLong, & Strick, 1986; Middleton & Strick, 2000a, 2000b). However, it was unclear whether the basal ganglia participate in the network controlling these processes. Thus, Study 1 investigated whether energization, task-setting, and monitoring were affected by PD and whether these processes were modulated by the dopaminergic system. It was hypothesized that, if the basal ganglia were involved in the networks controlling energization, task-setting and monitoring , then individuals with PD would show impairments in all processes. Moreover, if the networks controlling these processes were modulated by the dopaminergic system, then it was expected that dopaminergic medication would alleviate deficits in these cognitive processes by re-establishing activity in fronto-striatal circuitries.

The subsequent studies then examined the potential of physical exercise to improve the processing of energization, task-setting, and monitoring in individuals with PD.   More specifically, the acute (Study 2) and chronic (Study 3) effects of aerobic exercise on these processes were examined. Based on previous research in healthy individuals, showing that aerobic exercise can increase activity in frontal brain areas (Hyodo et al., 2012) and enhance performance on tasks mediated by the frontal lobes (Yanagisawa et al., 2010), it was hypothesized that individuals with PD would show positive acute and chronic effects of exercise on behavioural outcomes (reaction time (RT) and accuracy) representing energization, task-setting, and monitoring. This hypothesis was based on the assumption that enhanced frontal lobe activity as a result of exercise could positively influence cognitive processing through fronto-striatal loops in PD.

Furthermore, Study 3 aimed to address three major gaps regarding the chronic effects of exercise on cognition in individuals with PD: [1] to directly compare the effects of two exercise modalities on cognition (Aerobic vs Goal-based), [2] to assess the effects of exercise on five different cognitive domains, and [3] to investigate the effects of exercise on cognitively normal and impaired individuals with PD. Firstly, it was predicted that, if the aerobic basis of previous multimodal exercise studies was a critical component to improvements in cognition found in these studies, then aerobic exercise would be more beneficial to cognition of individuals with PD than goal-based exercise. Secondly, since aerobic exercise has been shown to increase activity in frontal brain areas and improve performance in tasks sensitive to frontal lobe functioning, it was hypothesized that chronic aerobic exercise would improve executive functions to a greater extent than other cognitive domains. Thirdly, given that aerobic exercise has been found to improve cognition of older adults with and without cognitive decline (Baker et al., 2010; Heyn, Abreu, &

Ottenbacher, 2004), it was expected that PD patients with cognitive impairment would benefit

from exercise similarly to those with normal cognition. Finally, Study 4 examined whether

exercise-induced changes in cognition would influence gait control in individuals with PD. Since

it has been proposed that individuals with PD rely on cognition to control gait due to decreased

automaticity, it was hypothesized that cognitive remediation through exercise would lead to

improvements in gait in PD. Within this final chapter, results from all of the studies will be

reviewed to address each of these goals and will be discussed with reference to the theoretical

framework proposed for the thesis.

6.1 Contributions of the thesis

6.1.1 Defining the thesis theoretical and methodological framework

It was known from the conceptual stages that deficits in executive functions were a major

aspect of this thesis. Firstly, because deficits in executive functions are highly prevalent among

individuals with PD from early to late stages of disease progression (Aarsland et al., 2010;

Dirnberger & Jahanshahi, 2013; Kudlicka, Clare, & Hindle, 2011; Owen et al., 1992; Taylor,

Saint-Cyr, & Lang, 1986). Secondly, because previous research in healthy older adults

(Colcombe & Kramer, 2003; Colcombe et al., 2006; Colcombe et al., 2004) and individuals with

PD (Cruise et al., 2011; David et al., 2015; Tanaka et al., 2009; Uc et al., 2014) has demonstrated

that exercise primarily influences executive functions. Yet, studies have demonstrated that

selective components of executive functions improve after exercise rather than an overall

improvement in executive functions. For example, Duchesne et al. (2015) assessed the effects of

exercise in two different components of executive functions (i.e. inhibition and flexibility) and

found that only one of them (i.e. inhibition) improved post-exercise. Although it remains

unknown why selective effects of exercise on executive functions occur, research has suggested that differences in these outcomes may result from distinct underlying cognitive processes employed by each component of executive functions (Testa, Bennett, & Ponsford, 2012). Thus, it could be hypothesized that the assessment of specific cognitive processes could contribute to further understanding the effects of exercise on executive functions in PD.

In order to better understand selective effects of exercise on executive functions in individuals with PD, in the current thesis three distinct cognitive processes (i.e. energization, task-setting, and monitoring) argued to be regionally organized within the frontal lobes and participate in the processing of executive functions were examined based on the model proposed by Stuss (2011). Among the strengths of this model there were the empirical evidence from studies involving individuals with localized frontal lobe lesions, the knowledge that the basal ganglia are anatomically and functionally linked to the frontal lobe areas found to be critically involved in each cognitive process, and the use of a structured assessment battery that was proved to be sensitive to selective deficits. Furthermore, as proposed by the author, an important advantage of a model built upon lesion studies is that it allows demonstrating the critical role of a brain area to a cognitive process, in a way that if the area is "shut down" by a lesion then distinct deficits will emerge (Stuss, 2006). This is in contrast to functional imaging studies that are limited in their ability to define how critical a brain area is to a cognitive process solely based on the activation of this area during a task. Therefore, the model proposed by Stuss (2011a) would also facilitate the interpretation of brain-behaviour relationships in the current thesis. For example, if exercise selectively influenced energization outcomes, then it could be inferred that it affected superior medial areas of the frontal lobes including the anterior cingulate cortex. In contrast, if exercise selectively influenced task-setting or monitoring, then it could be inferred

that it affected left or right (respectively) lateral areas of the frontal lobes including the dorsolateral pre-frontal cortex in each hemisphere. Importantly, since the basal ganglia are known to be linked to the frontal lobe areas critical to each cognitive process and that the basal ganglia is the primary area affected in PD, one could argue that improvements in these processes in PD would represent the impact of exercise on a network involving frontal and basal ganglia areas.

6.1.2 PD selectively affects cognitive processes mediated by the frontal lobes

Study 1 investigated whether energization, task-setting, and monitoring were affected by PD and whether these processes were modulated by the dopaminergic system. In order to assess whether the basal ganglia contribute to the networks mediating energization, task-setting and monitoring, individuals with PD were assessed while in the OFF state of dopaminergic medication using the same tasks and procedures used by Stuss and colleagues (Stuss & Alexander, 2007; Stuss, Binns, Murphy, & Alexander, 2002). Findings from Study 1 revealed that individuals with PD had selective deficits in monitoring, demonstrating the contribution of fronto-striatal circuitries to the operation of this process. Deficits in monitoring were characterized by an abnormal foreperiod effect and greater number of errors of all kinds in individuals with PD compared to healthy age-matched controls. These findings demonstrated that individuals with PD were unable to monitor timing in order to predict/anticipate when stimuli would occur as well as to adjust behaviour following errors in order to maintain good accuracy levels.

Since the frontal lobe areas involved in energization, task-setting, and monitoring are known to be connected to the basal ganglia, the hypothesis of Study 1 was that individuals with

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PD would show deficits in behavioural outcomes representing all three processes. Contrary to this hypothesis, deficits in energization and task-setting were not confirmed in this study. Deficits in energization are characterized by an overall slowness in response that becomes exacerbated as task complexity increases. Although individuals with PD had slower RT in the Simple RT task, this behaviour was not exacerbated during the more complex RT tasks. One possible explanation for the selective findings of Study 1 might be that, the degeneration of basal ganglia striatal areas in PD is argued to progress from dorsal portions linked to sensorimotor processing (putamen) and later moves on to the ventral portions linked to cognitive (caudate) and limbic processing (nucleus accumbens) (Kish, Shannak, & Hornykiewicz, 1988). According to the organization of basal ganglia loops proposed by Alexander et al. (1986), ventral areas of the basal ganglia (i.e. nucleus accumbens) are connected to the anterior cingulate cortex, which is a critical area for the processing of energization. Thus, it could be that energization was not affected in individuals with PD in Study 1 since ventral areas of the striatum are only affected in advanced stages of disease progression. Similarly, ventral areas of the striatum (i.e. caudate nucleus) are connected to the dorsolateral pre-frontal cortex, which is a critical area for the processing of task-setting. Although the areas involved in task-setting and monitoring are the same (i.e. dorsolateral and ventrolateral prefrontal cortices), these processes were shown to be lateralized to the left and right hemispheres (respectively) according to Stuss and colleagues (Stuss, 2006, 2011a; Stuss & Alexander, 2007; Stuss et al., 2002). Since the majority of participants in Study 1 had more severe symptoms in the left side of the body, it was inferred that basal ganglia degeneration was greater in the right hemisphere which is in line with findings of deficits in monitoring but not in task-setting. An attempt to test the hypothesis of whether disease progression would be associated with deficits in energization, task-setting and monitoring was

made by running correlation analyses between the outcomes of cognitive tests (RT and accuracy) and the severity of motor symptoms (UPDRS-III total score and scores for each side of the body) in the OFF medication state. However, these correlations only revealed associations with sensorimotor domain (Simple RT and UPDRS OFF). Although the lack of correlation between cognitive outcomes and the severity of motor symptoms was not expected, this finding is in line with previous research (Dujardin et al., 2013). One way of interpreting these results is recognizing that the progression of motor and cognitive deficits in PD may be independent.

The second aim of Study 1 was to determine whether energization, task-setting, and monitoring were modulated by the dopaminergic system. Thus, individuals with PD were compared while in the OFF and ON state of dopaminergic medication. Results showed no improvements in behavioural outcomes (RT or accuracy) when individuals with PD were in ON compared to OFF medication state. Conversely, participants showed greater RT variability in the ON compared to OFF state. Research suggests that increased intra-individual variability may reflect deficits in attention regulation (Stuss, Murphy, Binns, & Alexander, 2003). Hence, the increased RT variability found in PD ON compared to PD OFF indicates that dopaminergic medication had detrimental effects on the cognitive control of individuals with PD. Detrimental effects of dopamine on cognition have been previously reported in individuals with PD (Cools, Barker, Sahakian, & Robbins, 2001; Gotham, Brown, & Marsden, 1988). According to these studies, it is possible that dopamine levels necessary to normalize motor function in PD may overload some pre-frontal areas (particularly the ventrolateral PFC) that operate with sufficient dopamine levels. Therefore, dopaminergic medication did not enhance the operation of monitoring. Instead, dopamine had detrimental effects on cognition (attentional control) in

individuals with PD. These findings support the notion that adjunct therapeutic strategies are necessary to treat cognitive deficits in PD.

6.1.3 Aerobic exercise does not enhance energization, task-setting, and monitoring in individuals with PD

Research in healthy young and older adults has consistently demonstrated that physical exercise (with most studies focused on aerobic exercise) can increase activity in frontal brain areas and enhance performance on tasks sensitive to frontal lobe functioning such as those involving executive functions. Interestingly, these effects have been found immediately after a single bout of aerobic exercise (immediate effect of exercise stimulation) as well as a result of chronic aerobic exercise programs (cumulative effect of exercise stimulation). Therefore, one could suggest that if acute and chronic aerobic exercise can "boost" frontal lobe functioning, these effects could have a positive impact on cognitive processes mediated by the frontal lobes. In the current thesis the acute (Study 2) and chronic (Study 3) effects of moderate intensity aerobic exercise were assessed on energization, task-setting, and monitoring. Based on the evidence that even healthy young adults with normal cognitive functioning may show positive exercise-induced changes in cognition, improvements in all cognitive processes (regardless of impairment) were expected.

Contrary to the hypotheses of Study 2, there were no positive effects of an acute bout of exercise on energization, task-setting, or monitoring in individuals with PD. Results from this study can be interpreted in one of two ways: [1] there could have been cognitive and neurophysiological changes that our tasks were unable to capture, or [2] that individuals with PD do not respond to an acute bout of aerobic exercise.

In regards to the first explanation, previous investigations in healthy older adults have found that neurophysiological changes (e.g. latency of P300 event-related potential) may occur irrespective of changes in behavioural outcomes (Kamijo et al., 2009), suggesting that neurophysiological measures may be more sensitive to acute effects of exercise than behavioural measures. Although neurophysiological changes could have occurred in Study 2, this hypothesis cannot be confirmed with the methodology implemented in this thesis. Given that several studies in the literature (Hillman, Snook, & Jerome, 2003; Hyodo et al., 2012; Kamijo et al., 2004; Yanagisawa et al., 2010) were able to capture changes in behaviour following an acute bout of exercise, one could suggest that methodological procedures might have influenced the outcomes of Study 2 .

In Study 2, participants exercised at intensity levels comparable to previous investigations (Hyodo et al., 2012; Kamijo et al., 2009) and were assessed within a time window suggested to be optimal to evaluate behavioural effects of an acute bout of exercise according to a recent meta-analysis (Chang, Labban, Gapin, & Etnier, 2012). Moreover, the cross-over design of this study allowed the comparison of the same individuals under each experimental condition, which may have decreased the inter-individual variability therefore facilitating the occurrence of statistical differences between experimental conditions. Finally, the order of experimental conditions was counterbalanced between participants in order to control for practice effects. Taken together, the design of Study 2 decreased the likelihood of null results being associated with exercise intensity, inter-individual variability, and practice effects.

The only remaining point that could have influenced the results was the sensitivity of the tasks to the acute effects of exercise on cognition. One common characteristic among studies that found differences in behavioural outcomes was the use of tasks that strongly rely on inhibitory

control such as the Flanker and Stroop test. During the pilot stages of Study 1, performance in a task similar to Stroop (Suppress from the ROBBIA battery data not reported) was compared between individuals with PD and age-matched controls; however, no significant differences were found between groups or PD medication states. Thus, in order to optimize assessment time and focus on tasks in which deficits were identified, the Supress task was not carried forward in the thesis. Importantly, the Complex Choice RT task used in Study 2 imposes high demands on inhibitory control (similarly to Stroop). Therefore, the lack of changes in behavioural outcomes in PD patients after a single bout of exercise may not be simply explained by task selection. Conversely, it might be that individuals with PD did not respond to a single bout of exercise.

Previous studies have suggested that not all individuals respond similarly to exercise. Individual characteristics such as fitness level (Tsai et al., 2014) and gender (Baker et al., 2010) can influence ones' response to exercise. Yet, there were no differences in performance between male and female participants or associations between participants' cognitive outcomes and fitness level in Study 2. Therefore, an alternative explanation to the null findings of Study 2 was outlined based on how the pathophysiology of PD could influence the proposed mechanisms underlying the acute effects of exercise on cognition. More specifically, how impaired neurotransmitter activity as result of PD could influence the ability of individuals with PD to acutely respond to single bout of exercise.

Current theories about the acute effects of exercise on cognition argue that responses to exercise may be modulated by changes in catecholamine concentration and/or changes in arousal levels. While there is limited evidence confirming the catecholamine hypothesis in humans, studies have consistently showed that acute responses to exercise stimulation follows an inverted-U shape pattern in which moderate intensity exercise leads to optimal levels of arousal

which consequently facilitate cognitive processing (Chang, Etnier, & Barella, 2009; Kamijo et al., 2009; Kamijo et al., 2004). Arousal levels are suggested to be mediated by serotonergic and noradrenergic activity in the brain stem and modulated by cholinergic activity in cortical regions (Gratwicke, Jahanshahi, & Foltynie, 2015). Importantly, in addition to low dopamine levels, individuals with PD also show deficits in cholinergic (Bohnen et al., 2006; Bohnen et al., 2003), serotonergic (Politis & Niccolini, 2015), and noradrenergic (Riekkinen, Kejonen, Jakala, Soininen, & Riekkinen, 1998) activity. Therefore, it is possible that low levels of neurotransmitter activity may limit the acute response to exercise in individuals with PD.

Nonetheless, given that changes in cognition in individuals with PD have been found after chronic exercise studies, it might be that chronic exercise stimulation could promote neurotransmitter activity through neuroplastic mechanisms. This hypothesis has been supported by research with animal models of PD as presented in a recent literature review showing that chronic exercise enhances neurotransmitter activity (Petzinger et al., 2015). In this context, Study 3 aimed to test whether chronic exercise stimulation would influence energization, task-setting, and monitoring.

In Study 3, the effects of aerobic and goal-based exercises on energization, task-setting, and monitoring were compared. This comparison was deemed necessary because previous studies investigating the effects of exercise on cognition in PD used multimodal exercise protocols combining goal-based and aerobic exercise. However, the isolated contributions of each exercise modality to cognition in PD remained unclear, since these exercise modalities had never been directly compared. Goal-based exercise is composed of activities that focus on learning and mastering motor skills, which have been suggested to improve motor and cognitive function in individuals with PD through experience dependent plasticity (Petzinger et al., 2013;

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Petzinger et al., 2015). Although the mechanisms underlying cognitive changes following each exercise modality are unclear in humans, studies using animal models of PD suggest the involvement of differential mechanisms. For example, it has been demonstrated that rats engaged in goal-based exercise showed increase in synaptic parameters (i.e. dendritic spine density) without an increase in density of capillaries in motor regions of the brain. This result was counter to that found for rats which practiced unskilled/repetitive aerobic exercise, which increased the density of capillaries without an increase in synaptic parameters (Black, Isaacs, Anderson, Alcantara, & Greenough, 1990; Petzinger et al., 2015). These findings suggest that while both aerobic and goal-based exercise might improve cognition in PD, the mechanisms underlying exercise-induced changes in cognition for exercise modality likely differ.

Results from Study 3 demonstrated that neither aerobic nor goal-based exercise significantly improved energization, task-setting, or monitoring (i.e. no improvements on RT or accuracy) from pre to post-exercise. However, it was found that cognitively impaired individuals in the Control group had slower choice RT at post-test. The slower RT of cognitively impaired participants in the Control group but not those in the exercise groups suggests that exercise may have protected and/or delayed the decline in speed. While it remains unclear whether exercise has protective effects against neurodegenerative processes in humans, studies have showed that it may decrease brain atrophy (S. J. Colcombe et al., 2006; Erickson et al., 2011; Suzuki et al., 2013) and prospectively decrease the risk of mild cognitive impairment (Geda et al., 2010) and dementia (Hamer & Chida, 2009). Therefore, in comparison to the slowing observed in the Control group, the finding that cognitively impaired participants in both exercise groups did not change from pre to post-test could be interpreted as a positive effect of exercise on cognition. Accuracy results revealed that only cognitively impaired participants in the Aerobic group were

more accurate in the complex choice RT task at post-test. The improvement in response accuracy in cognitively impaired participants in the Aerobic group is challenging to interpret for two reasons: first, because their baseline error was greater than the other two groups; and second, because these participants were approximately 100ms slower while performing this task at post-test. Thus, it might be that participants in the Aerobic group traded speed for accuracy in the complex choice RT task at post-test. Previous research has suggested that speed-accuracy trade-off often observed in older adults and individuals with PD may represent a *"very reasonable and sensible course to adopt"* in order to maximize their overall achievement in a task (Evarts, Teravainen, & Calne, 1981). However, it is difficult to conclude whether these results represent positive or negative effects of aerobic exercise on cognition, given that they seem to be based on a change in strategy.

Taken together, results from this thesis with regard to exercise show that neither acute nor chronic exercise enhanced energization, task-setting, or monitoring in individuals with PD. However, evidence that slowing in choice RT over a 12-week period was observed primarily in cognitively impaired individuals from the Control group suggests that exercise may have the potential to protect or delay the decline in cognitive functions. Nonetheless, it is important to acknowledge three factors that could have influenced findings of Study 2 and Study 3 and which should be considered in future research.

The first factor is that in both studies participants with PD were assessed while in the ON medication state. Study 1 showed that deficits in monitoring were only observed in the OFF medication state. Yet, the choice of assessing the effects of exercise in the ON medication state was made in order to increase ecological validity in the studies' results, since PD patients perform daily living activities in the ON state the majority of the time. Another reason why

participants were assessed in the ON medication state was that it would be extremely challenging to complete Study 2 while in the OFF medication state, since participants had to pedal relatively fast in order to keep intensity levels. Further, it would be difficult for participants to perform the long assessment sessions of Study 3 while in the OFF medication state. Nonetheless, if one wants to know the isolated effects of exercise on cognition without the confounding of pharmacological therapy, then the assessment of individuals with PD in the OFF state would be valuable.

The second factor is that the duration of Study 3 may have played a role on the lack of changes in RT. Although the duration of Study 3 was based on previous studies in PD showing positive results of exercise on cognition, the majority of trials investigating the effects of exercise on cognition in healthy older adults are 6 to 12 months long. Thus, it is possible that if participants had exercised longer some of the expected changes would likely have been observed.

The third factor was the large variability in response to exercise observed in both Study 2 and Study 3. Although these studies had considerably more participants than previous investigations, the sample was not large enough to further explore individual characteristics such as gender, symptom subtype, and symptom laterality.

6.1.4 The effects of aerobic and goal-based exercise on different cognitive domains in individuals with PD

Although it is important to address the executive functions deficits in therapeutic research, recent studies provide evidence that cognitive domains such as memory, language and

visuospatial function are better predictors of dementia in individuals with PD (Williams-Gray et al., 2009; Williams-Gray et al., 2013) than executive functions. Importantly, while deficits in executive functions may partially respond to dopaminergic treatment, deficits in memory, language and visuospatial processing do not respond to dopaminergic treatment. Thus, it is critical that research investigating the effects of adjunct therapies (such as exercise) on multiple cognitive domains continues to develop, in order to determine the potential of these therapies to prevent or post-pone the progression of cognitive decline in PD.

To the best of my knowledge, only two studies have attempted to assess the chronic effects of exercise on multiple cognitive domains in PD. The first assessed the effects of a 12-week program combining aerobic and strength training in comparison to a control non-exercise group (Cruise et al., 2011), while the second consisted of a 24-week long aerobic exercise program (no control comparison). In both cases, it was found that exercise improved executive functions exclusively. This is in contrast to previous research in healthy older adults that showed improvements in memory after a 24-week aerobic exercise program (Erickson et al., 2011). Thus, considering the limited number of studies that investigate this question and the inconsistency of results in the literature, more research in this field was necessary.

In Study 3, participants in both aerobic and goal-based exercise showed improvement in processing speed (TMT A). In addition, cognitively impaired individuals from the Control group were slower at post compared to pre-test. With respect to set-shifting (TMT B), there were no changes from pre to post-test for both exercise groups. However, cognitively impaired individuals from the Control group showed slower performance at post-test (similarly to the slowing in RT found in this group). Furthermore, it was found that only PD patients in the Aerobic group improved inhibitory control (Stroop test) from pre to post-test. These results

collectively suggest that aerobic exercise was more effective than goal-based exercise at improving cognition in PD, specifically in executive functions. On the other hand, neither aerobic nor goal-based exercises were able to enhance performance on memory, language, or visuospatial function.

Findings that aerobic exercise can improve inhibitory control in individuals with PD are in line with results from previous investigations (Duchesne et al., 2015; Uc et al., 2014). Yet, the present study is the first to show that aerobic exercise was more effective at improving cognition than goal-based exercise, suggesting that the aerobic basis of previous multimodal studies may have been the critical component to the observed improvements in cognition. Inhibition is considered a component of executive functions and its neural network is hosted in inferior lateral areas of the frontal lobes, pre-supplementary motor area, and the subthalamic nucleus of the basal ganglia (Aron, 2007). Thus, the fact that inhibition may be mediated by frontal areas that are different than the ones underlying energization, task-setting and monitoring (superior medial, left lateral and right lateral frontal areas, respectively) may help to explain why no significant differences were found in Study 2 and Study 3 for the outcomes linked to each cognitive process. Importantly, these findings support the notion of a non-unitary structure of executive functions, where specific components of executive functions are differently influenced by brain disorders such as PD as well as by therapy strategies such as exercise. Moreover, it is still puzzling to think why exercise would selectively affect certain brain areas or specific brain functions. Considering some of the proposed underlying mechanisms by which exercise may influence cognition such as increases in blood flow, catecholamine concentration, levels of neurotrophic factors, and neurotransmitter activity, it remains unclear why exercise has selective rather than general effects on brain function and cognition.

Deficits in inhibitory control are commonly observed in individuals with PD (Jahanshahi, Obeso, Baunez, Alegre, & Krack, 2015). Moreover, deficits in inhibition are not responsive to dopaminergic treatment (Obeso, Wilkinson, & Jahanshahi, 2011) , but they are responsive to deep brain stimulation in the subthalamic nucleus (Obeso et al., 2014). Thus, findings from the current thesis suggest that improvements in cognition as a result of aerobic exercise may be mediated by changes in non-dopaminergic circuitries, potentially involving the subthalamic nucleus. However, evaluating the effects of exercise on the neural circuitry involved in inhibitory control will be necessary in order to confirm this hypothesis.

One of the most unique findings of Study 3 was that cognitively normal and impaired individuals with PD benefited similarly from aerobic exercise. Combined with the observed worsening in the Control group, findings from this research suggest that exercise may post-pone the incidence of cognitive decline and potentially slow down its progression.

Finally, neither aerobic nor goal-based exercises alone were able to improve cognitive domains that are linked to increased risk of dementia in PD. These findings are in contrast with previous research in healthy older adults showing that exercise can enhance memory function (Erickson et al., 2011; Nagamatsu et al., 2013). However, it is important to note that the majority of exercise trials involving healthy older adults are significantly longer (e.g. 24 weeks) than the 12-week period chosen for Study 3. Moreover, research in healthy older adults often have a proportional number of male and female participants or greater number of female individuals, whereas Study 3 had predominantly male participants. This could have influenced the results from Study 3, since previous research has demonstrated that female participants had greater exercise-induced improvements in cognition compared to male participants (Baker et al., 2010). Nonetheless, it was found that cognitively impaired individuals from the Aerobic group

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maintained performance levels in the Pentagons task from pre to post-test, while those in the

goal-based group were worse at post-test. This finding could suggest that aerobic exercise may

prevent or post-pone the decline in visuospatial functions which is one the best predictors of

dementia in PD. Therefore, future studies should investigate the effects of exercise on memory,

language, and visuospatial function in trials with longer durations and in samples with similar

numbers of male and female participants.

6.1.5 Exercise-induced improvement in cognition leads to better gait control in PD

The relationship between deficits in cognition (especially attention and executive

functions) and gait has been consistently demonstrated in individuals with PD. According to

previous investigations (Lord, Rochester, Hetherington, Allcock, & Burn, 2010; Yogev et al.,

2005), these associations suggest that a decrease in gait automaticity as a result of basal ganglia

degeneration lead individuals with PD to rely on cognition to control gait. Thus, it has been

proposed that cognitive decline could limit the capacity of individuals with PD to compensate for

decreased gait automaticity. Hence, one could propose that therapeutic strategies aiming to

improve cognitive function might improve gait control in individuals with PD, especially under

circumstances with high cognitive demands such as dual-task walking. Therefore, Study 4

aimed to investigate the impact of aerobic and goal-based exercise on cognition and gait in

cognitively normal and impaired individuals with PD.

Results of Study 4 showed that exercise similarly improved cognition in cognitively

normal and impaired individuals with PD. However, only individuals with impaired cognition

showed improvements in gait after exercise. Importantly, changes in gait parameters in

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cognitively impaired individuals were found exclusively in the dual task condition at post-test. Overall, effects of exercise were observed for cognitive processing speed as well as gait parameters linked to gait stability (step width and double support). Specific effects of aerobic exercise on cognition were characterized by an improvement in response inhibition and better accuracy in RT tasks, while goal-based exercise improved working memory. In relation to gait, aerobic exercise selectively decreased step time variability, while goal-based exercise decreased step time at post-test. Most importantly, associations between changes in cognition and in gait were found only for the aerobic group.

The most important finding of Study 4 was that only cognitively impaired individuals showed improvements in dual-task walking, despite improvement in cognition being similar for those with normal and impaired cognition. These findings support the existence of a strong relationship between cognition and gait in PD and that cognitive remediation through exercise can improve mobility of individuals with PD, especially under circumstances with high cognitive demands (i.e. dual-task walking). Interestingly, associations between changes in cognition and gait were found exclusively for the aerobic group.

Results from the current thesis and previous investigations have suggested that aerobic training maybe a powerful therapy strategy to treat cognitive deficits in older adults (Colcombe et al., 2006; Colcombe et al., 2004; Erickson et al., 2011). In order to investigate the influence of aerobic exercise on cognition and gait, participants in this thesis were trained on a cycle ergometer in order to avoid training specificity (e.g. walking training) to influence the results and interpretations. Thus, results from Study 4 suggest that potentially a common mechanism resulting from an increase in aerobic function promoted changes in cognition and gait in individuals with PD.

Studies have showed that cognitive inhibition and step time variability are not responsive to dopaminergic treatment (Blin, Ferrandez, Pailhous, & Serratrice, 1991; Lord, Baker, Nieuwboer, Burn, & Rochester, 2011; Obeso et al., 2011). Therefore, it might be that the effects of aerobic exercise on cognition and gait were mediated by non-dopaminergic circuitries. Previous research with individuals at early stages of Alzheimer's disease showed that cholinergic medication decreased step time variability during single task walking (Montero-Odasso et al., 2015; Montero-Odasso, Wells, Borrie, & Speechley, 2009) and gait velocity during dual-task walking. Moreover, cholinergic deficits have been associated with impaired cognitive function, gait slowness, and falls in individuals with PD (Bohnen et al., 2006; Bohnen et al., 2009; Dubois, Pilon, Lhermitte, & Agid, 1990). Thus, one could hypothesize that changes in cholinergic activity could have played a role in the observed changes in cognition and gait after aerobic exercise. Yet, to my knowledge, the effects of exercise on cholinergic activity in humans have never been investigated. Therefore, future studies should investigate whether aerobic exercise can influence cholinergic activity in PD and whether improvements in cholinergic activity can be translated into cognitive and gait improvements in PD.

6.2 Limitations

Limitations of the current thesis include the lack of objective measures of brain activity pre and post-exercise interventions. Although in the current thesis theoretical and methodological framework were based on well designed and controlled lesion studies, the objective evaluation of brain activity could have been more sensitive to the effects of exercise on cognition than some of the behavioural measures used in this thesis. A second important limitation is the lack of a washout period in which the long lasting effects of exercise on cognition could have been assessed. Time constrains and potential practice effects of repeating the assessment battery for

the third time were the main reasons why the washout period did not occur in the present thesis.

Another limitation involves the blinding procedures of the chronic exercise trial. The ideal

blinding procedure would have all assessments performed by blinded personnel, the exercise

sessions being led by blinded instructors, and participants being blinded to the therapeutic effects

of each exercise modality. Even though the number of participants in the current thesis is one of

the largest available, it is reasonable to suggest that a larger sample size would help to decrease

variability and potentially bring some of the trending results to statistically significant findings.

A larger sample size would also allow to explore important aspects such as if cognitive processes

that are hemisphere-specific were differently affected in individuals with PD with predominant

right and left side affected. In addition, knowing that individuals with posture and gait

impairments usually show greater cognitive impairments than tremor dominant patients, it would

be interesting to investigate whether exercise influences cognition and gait differently in these

two subgroups of patients. Lastly, the current study was 3 months in duration in contrast to most

trials that investigate the effects of exercise on cognition which are 6 months long, meaning that

results could have been more pronounced if the trial was longer.

6.3 Concluding remarks and clinical implication

Taken together findings from the current thesis demonstrated that individuals with PD

show selective deficits in cognitive processes mediated by the frontal lobes, specifically in

monitoring. These deficits were evident when individuals with PD were in the OFF state of

dopaminergic medication, thus supporting the notion that the basal ganglia integrate the

networks that mediate these cognitive processes (Stuss, 2011). Dopaminergic medication did not

alleviate deficits in these cognitive processes. There were also no improvements in these

cognitive processes after an acute bout of aerobic exercise or chronic aerobic and goal-based

training programs. With respect to cognitive domains, results showed that aerobic exercise was more beneficial to cognition than goal-based exercise, by improving not only processing speed but also participants' response inhibition. Therefore, these findings help to clarify that improvement in cognition after multimodal exercise programs were likely influenced by their aerobic basis. Furthermore, aerobic training was found to improve cognition of individuals with normal and impaired cognition, which leads to the conclusion that exercise may be an effective adjunct strategy to help individuals with PD to maintain good cognitive function. These effects were observed primarily within the executive functions domain, while no changes in cognitive domains linked to the incidence of dementia in PD (memory, language, and visuospatial function) were found in this thesis. Importantly, participants in a control group who did not receive any special exercise treatment but only carried on with their regular activities showed significant worsening over 12 weeks. Thus, even if exercise did not improve all cognitive domains, it may have helped to prevent cognitive decline. Aerobic exercise was found to improve cognition and dual-task gait of cognitively impaired individuals with PD, and exercise-induced changes in cognition and gait were associated. Thus, findings confirm the hypothesis that cognitive remediation may result in improved gait control of individuals with PD.

Findings from this thesis have important clinical implications, since cognitive deficits cannot be fully alleviated by current pharmacological treatments for PD symptoms. Specifically, this thesis shows that moderate intensity aerobic exercise should be recommended to PD patients regardless of their cognitive status (normal or impaired). Since the majority of individuals with PD had deficits in gait and balance, the use of recumbent cycle ergometers was shown to be a safe and effective way of aerobic training in this population. Most importantly, the use of cycle

ergometers did not prevent participants in this thesis to show improvements in mobility due to

reduced training specificity.

References

Aarsland, D., Bronnick, K., Williams-Gray, C., Weintraub, D., Marder, K., Kulisevsky, J., . . . Emre, M. (2010). Mild cognitive impairment in Parkinson disease: a multicenter pooled analysis. *Neurology*, 75(12), 1062-1069. doi: 10.1212/WNL.0b013e3181f39d0e

ACSM. (2000). *American College of Sports Medicine: guidelines for exercise testing and prescription* (6th ed.). Baltimore, Maryland: Lippincott Williams & Wilkins.

Alexander, G. E., DeLong, M. R., & Strick, P. L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annual Review of Neuroscience, 9*, 357-381. doi: 10.1146/annurev.ne.09.030186.002041

Alexander, M. P., Stuss, D. T., Picton, T., Shallice, T., & Gillingham, S. (2007). Regional frontal injuries cause distinct impairments in cognitive control. *Neurology, 68*(18), 1515-1523. doi: 10.1212/01.wnl.0000261482.99569.fb

Amboni, M., Barone, P., & Hausdorff, J. M. (2013). Cognitive contributions to gait and falls: evidence and implications. *Movement Disorders, 28*(11), 1520-1533. doi: 10.1002/mds.25674

Amboni, M., Barone, P., Iuppariello, L., Lista, I., Tranfaglia, R., Fasano, A., . . . Sorrentino, G. (2012). Gait patterns in Parkinsonian patients with or without mild cognitive impairment. *Movement Disorders, 27*(12), 1536-1543. doi: 10.1002/mds.25165

Aron, A. R. (2007). The neural basis of inhibition in cognitive control. *Neuroscientist, 13*(3), 214-228. doi: 10.1177/1073858407299288

Baker, K., Rochester, L., & Nieuwboer, A. (2007). The immediate effect of attentional, auditory, and a combined cue strategy on gait during single and dual tasks in Parkinson's disease. *Archives of Physical Medicine and Rehabilitation, 88*(12), 1593-1600. doi: 10.1016/j.apmr.2007.07.026

Baker, L. D., Frank, L. L., Foster-Schubert, K., Green, P. S., Wilkinson, C. W., McTiernan, A., . . . Craft, S. (2010). Effects of aerobic exercise on mild cognitive impairment: a controlled trial. *Archives of Neurology, 67*(1), 71-79. doi: 10.1001/archneurol.2009.307

Barella, L. A., Etnier, J. L., & Chang, Y. K. (2010). The immediate and delayed effects of an acute bout of exercise on cognitive performance of healthy older adults. *Journal of Aging and Physical Activity, 18*(1), 87-98. doi: http://journals.humankinetics.com/AcuCustom/Sitename/Documents/DocumentItem/17737.pdf

Barone, P., Antonini, A., Colosimo, C., Marconi, R., Morgante, L., Avarello, T. P., . . . group, P. s. (2009). The PRIAMO study: A multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. *Movement Disorders, 24*(11), 1641-1649. doi: 10.1002/mds.22643

Black, J. E., Isaacs, K. R., Anderson, B. J., Alcantara, A. A., & Greenough, W. T. (1990). Learning causes synaptogenesis, whereas motor activity causes angiogenesis, in cerebellar cortex of adult rats. *Proceedings of the National Academy of Sciences U S A, 87*(14), 5568-5572. doi: 10.1073/pnas.87.14.5568

Blin, O., Ferrandez, A. M., Pailhous, J., & Serratrice, G. (1991). Dopa-sensitive and dopa-resistant gait parameters in Parkinson's disease. *Journal of Neurological Sciences, 103*(1), 51-54. doi:10.1016/0022-510X(91)90283-D

Bohnen, N. I., Kaufer, D. I., Hendrickson, R., Ivanco, L. S., Lopresti, B. J., Constantine, G. M., . . . Dekosky, S. T. (2006). Cognitive correlates of cortical cholinergic denervation in Parkinson's disease and parkinsonian dementia. *Journal of Neurology, 253*(2), 242-247. doi: 10.1007/s00415-005-0971-0

Bohnen, N. I., Kaufer, D. I., Ivanco, L. S., Lopresti, B., Koeppe, R. A., Davis, J. G., . . . DeKosky, S. T. (2003). Cortical cholinergic function is more severely affected in parkinsonian dementia than in Alzheimer disease: an in vivo positron emission tomographic study. *Archives of Neurology, 60*(12), 1745-1748. doi: 10.1001/archneur.60.12.1745

Bohnen, N. I., Muller, M. L., Koeppe, R. A., Studenski, S. A., Kilbourn, M. A., Frey, K. A., & Albin, R. L. (2009). History of falls in Parkinson disease is associated with reduced cholinergic activity. *Neurology, 73*(20), 1670-1676. doi: 10.1212/WNL.0b013e3181c1ded6

Bouquet, C. A., Bonnaud, V., & Gil, R. (2003). Investigation of supervisory attentional system functions in patients with Parkinson's disease using the Hayling task. *Journal of Clinical Experimental Neuropsychology, 25*(6), 751-760. doi: 10.1076/jcen.25.6.751.16478

Brawner, C. A., Ehrman, J. K., Schairer, J. R., Cao, J. J., & Keteyian, S. J. (2004). Predicting maximum heart rate among patients with coronary heart disease receiving beta-adrenergic blockade therapy. *American Heart Journal, 148*(5), 910-914. doi: 10.1016/j.ahj.2004.04.035

Brown, V. J., & Robbins, T. W. (1991). Simple and choice reaction time performance following unilateral striatal dopamine depletion in the rat. Impaired motor readiness but preserved response preparation. *Brain, 114 (Pt 1B)*, 513-525. http://dx.doi.org/10.1093/brain/114.1.513

Chang, Y. K., Etnier, J. L., & Barella, L. A. (2009). Exploring the relationship between exercise-induced arousal and cognition using fractionated response time. *Research Quaterly for Exercise and Sport, 80*(1), 78-86. doi: 10.1080/02701367.2009.10599532

Chang, Y. K., Labban, J. D., Gapin, J. I., & Etnier, J. L. (2012). The effects of acute exercise on cognitive performance: a meta-analysis. *Brain Research, 1453*, 87-101. doi: 10.1016/j.brainres.2012.02.068

Colcombe, S., & Kramer, A. F. (2003). Fitness effects on the cognitive function of older adults: a meta-analytic study. *Psychological Science, 14*(2), 125-130. doi: 10.1111/1467-9280.t01-1-01430

Colcombe, S. J., Erickson, K. I., Scalf, P. E., Kim, J. S., Prakash, R., McAuley, E., . . . Kramer, A. F. (2006). Aerobic exercise training increases brain volume in aging humans. *Journal of Gerontology Series A Biological Sciences and Medical Sciences, 61*(11), 1166-1170. doi: http://biomedgerontology.oxfordjournals.org/content/61/11/1166.full.pdf+html

Colcombe, S. J., Kramer, A. F., Erickson, K. I., Scalf, P., McAuley, E., Cohen, N. J., . . . Elavsky, S. (2004). Cardiovascular fitness, cortical plasticity, and aging. *Proceedings of the National Academy of Sciences U S A, 101*(9), 3316-3321. doi: 10.1073/pnas.0400266101

Cools, R., Barker, R. A., Sahakian, B. J., & Robbins, T. W. (2001a). Enhanced or impaired cognitive function in Parkinson's disease as a function of dopaminergic medication and task demands. *Cerebral Cortex, 11*(12), 1136-1143. doi: 10.1093/cercor/11.12.1136

Cools, R., Barker, R. A., Sahakian, B. J., & Robbins, T. W. (2001b). Mechanisms of cognitive set flexibility in Parkinson's disease. *Brain, 124*(Pt 12), 2503-2512. doi: http://dx.doi.org/10.1093/brain/124.12.2503

Crizzle, A. M., Classen, S., & Uc, E. Y. (2012). Parkinson disease and driving: an evidence-based review. *Neurology, 79*(20), 2067-2074. doi: 10.1212/WNL.0b013e3182749e95

Cruise, K. E., Bucks, R. S., Loftus, A. M., Newton, R. U., Pegoraro, R., & Thomas, M. G. (2011). Exercise and Parkinson's: benefits for cognition and quality of life. *Acta Neurologica Scandinavica, 123*(1), 13-19. doi: 10.1111/j.1600-0404.2010.01338.x

David, F. J., Robichaud, J. A., Leurgans, S. E., Poon, C., Kohrt, W. M., Goldman, J. G., . . . Corcos, D. M. (2015). Exercise improves cognition in Parkinson's disease: The PRET-PD randomized, clinical trial. *Movement Disorders, 30*(12), 1657-1663. doi: 10.1002/mds.26291

Dirnberger, G., & Jahanshahi, M. (2013). Executive dysfunction in Parkinson's disease: a review. *Journal of Neuropsychology, 7*(2), 193-224. doi: 10.1111/jnp.12028

Domellof, M. E., Ekman, U., Forsgren, L., & Elgh, E. (2015). Cognitive function in the early phase of Parkinson's disease, a five-year follow-up. *Acta Neurologica Scandinavica*. doi: 10.1111/ane.12375

Dubois, B., Pilon, B., Lhermitte, F., & Agid, Y. (1990). Cholinergic deficiency and frontal dysfunction in Parkinson's disease. *Annals of Neurology, 28*(2), 117-121. doi: 10.1002/ana.410280202

Dubois, B., Burn, D., Goetz, C., Aarsland, D., Brown, R. G., Broe, G. A., . . . Emre, M. (2007). Diagnostic procedures for Parkinson's disease dementia: recommendations from the movement disorder society task force. *Movement Disorders, 22*(16), 2314-2324. doi: 10.1002/mds.21844

Duchesne, C., Lungu, O., Nadeau, A., Robillard, M. E., Bore, A., Bobeuf, F., . . . Doyon, J. (2015). Enhancing both motor and cognitive functioning in Parkinson's disease: Aerobic exercise as a rehabilitative intervention. *Brain and Cognition, 99*, 68-77. doi: 10.1016/j.bandc.2015.07.005

Dujardin, K., Degreef, J. F., Rogelet, P., Defebvre, L., & Destee, A. (1999). Impairment of the supervisory attentional system in early untreated patients with Parkinson's disease. *Journal of Neurology, 246*(9), 783-788. doi: 10.1007/s004150050455

Dujardin, K., Tard, C., Duhamel, A., Delval, A., Moreau, C., Devos, D., & Defebvre, L. (2013). The pattern of attentional deficits in Parkinson's disease. *Parkinsonism and Related Disorders, 19*(3), 300-305. doi: 10.1016/j.parkreldis.2012.11.001

Emre, M., Ford, P. J., Bilgic, B., & Uc, E. Y. (2014). Cognitive impairment and dementia in Parkinson's disease: practical issues and management. *Movement Disorders, 29*(5), 663-672. doi: 10.1002/mds.25870

Erickson, K. I., Voss, M. W., Prakash, R. S., Basak, C., Szabo, A., Chaddock, L., . . . Kramer, A. F. (2011). Exercise training increases size of hippocampus and improves memory. *Proceedings of the Nationall Academy of Sciences U S A, 108*(7), 3017-3022. doi: 10.1073/pnas.1015950108

Evarts, E. V., Teravainen, H., & Calne, D. B. (1981). Reaction time in Parkinson's disease. *Brain, 104*(Pt 1), 167-186. doi: 10.1093/brain/104.1.167

Fahn, S., & Elton, R. (1987). members of the UPDRS Development Committee 1987. *Recent Developments in Parkinson's Disease. In: Fahn, S*, 153-163.

Fisher, B. E., Li, Q., Nacca, A., Salem, G. J., Song, J., Yip, J., . . . Petzinger, G. M. (2013). Treadmill exercise elevates striatal dopamine D2 receptor binding potential in patients with early Parkinson's disease. *Neuroreport, 24*(10), 509-514. doi: 10.1097/WNR.0b013e328361dc13

Fisher, B. E., Wu, A. D., Salem, G. J., Song, J., Lin, C. H., Yip, J., . . . Petzinger, G. (2008). The effect of exercise training in improving motor performance and corticomotor excitability in people with early Parkinson's disease. *Archives of Physical Medicine and Rehabilitation, 89*(7), 1221-1229. doi: 10.1016/j.apmr.2008.01.013

Frazzitta, G., Maestri, R., Ghilardi, M. F., Riboldazzi, G., Perini, M., Bertotti, G., . . . Comi, C. (2014). Intensive rehabilitation increases BDNF serum levels in parkinsonian patients: a randomized study. *Neurorehabilitation and Neural Repair, 28*(2), 163-168. doi: 10.1177/1545968313508474

Geda, Y. E., Roberts, R. O., Knopman, D. S., Christianson, T. J., Pankratz, V. S., Ivnik, R. J., . . . Rocca, W. A. (2010). Physical exercise, aging, and mild cognitive impairment: a population-based study. *Archives of Neurology, 67*(1), 80-86. doi: 10.1001/archneurol.2009.297

Gotham, A. M., Brown, R. G., & Marsden, C. D. (1988). 'Frontal' cognitive function in patients with Parkinson's disease 'on' and 'off' levodopa. *Brain, 111 (Pt 2)*, 299-321. doi: http://brain.oxfordjournals.org/content/brain/111/2/299.full.pdf

Gratwicke, J., Jahanshahi, M., & Foltynie, T. (2015). Parkinson's disease dementia: a neural networks perspective. *Brain, 138*(Pt 6), 1454-1476. doi: 10.1093/brain/awv104

Hamer, M., & Chida, Y. (2009). Physical activity and risk of neurodegenerative disease: a systematic review of prospective evidence. *Psychological Medicine, 39*(1), 3-11. doi: 10.1017/S0033291708003681

Heaton, R. K., Chelune, G. J., Talley, J. L., Kay, G. G., & Curtiss, G. (1993). *Wisconsin Card Sorting Test Manual: revised and expanded*. Odessa, Florida: Psychological Assessment Resources, Inc. .

Heyn, P., Abreu, B. C., & Ottenbacher, K. J. (2004). The effects of exercise training on elderly persons with cognitive impairment and dementia: a meta-analysis. *Archives of Physical Medicine and Rehabilitation, 85*(10), 1694-1704. doi:10.1016/j.apmr.2004.03.019

Hillman, C. H., Snook, E. M., & Jerome, G. J. (2003). Acute cardiovascular exercise and executive control function. *Internaltional Journal of Psychophysiology, 48*(3), 307-314. doi:10.1016/S0167-8760(03)00080-1

Holtzer, R., Mahoney, J. R., Izzetoglu, M., Wang, C., England, S., & Verghese, J. (2015). Online fronto-cortical control of simple and attention-demanding locomotion in humans. *Neuroimage, 112*, 152-159. doi: 10.1016/j.neuroimage.2015.03.002

Hyodo, K., Dan, I., Suwabe, K., Kyutoku, Y., Yamada, Y., Akahori, M., . . . Soya, H. (2012). Acute moderate exercise enhances compensatory brain activation in older adults. *Neurobiology of Aging, 33*(11), 2621-2632. doi: 10.1016/j.neurobiolaging.2011.12.022

Iansek, R., Danoudis, M., & Bradfield, N. (2013). Gait and cognition in Parkinson's disease: implications for rehabilitation. *Reviews in the Neurosciences, 24*(3), 293-300. doi: 10.1515/revneuro-2013-0006

Jahanshahi, M., Brown, R. G., & Marsden, C. D. (1992). Simple and choice reaction time and the use of advance information for motor preparation in Parkinson's disease. *Brain*, 115 (Pt 2), 539-564. http://dx.doi.org/10.1093/brain/115.2.539

Jahanshahi, M., Obeso, I., Baunez, C., Alegre, M., & Krack, P. (2015). Parkinson's disease, the subthalamic nucleus, inhibition, and impulsivity. *Movement Disorders, 30*(2), 128-140. doi: 10.1002/mds.26049

Jurado, M. B., & Rosselli, M. (2007). The elusive nature of executive functions: a review of our current understanding. *Neuropsychology Review, 17*(3), 213-233. doi: 10.1007/s11065-007-9040-z

Jurkowski, A. J., Stepp, E., & Hackley, S. A. (2005). Variable foreperiod deficits in Parkinson's disease: dissociation across reflexive and voluntary behaviors. *Brain and Cognition, 58*(1), 49-61. doi: 10.1016/j.bandc.2004.09.008

Kamijo, K., Hayashi, Y., Sakai, T., Yahiro, T., Tanaka, K., & Nishihira, Y. (2009). Acute effects of aerobic exercise on cognitive function in older adults. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences, 64*(3), 356-363. doi: 10.1093/geronb/gbp030

Kamijo, K., Nishihira, Y., Hatta, A., Kaneda, T., Wasaka, T., Kida, T., & Kuroiwa, K. (2004). Differential influences of exercise intensity on information processing in the central nervous system. *European Journal of Applied Physiology, 92*(3), 305-311. doi: 10.1007/s00421-004-1097-2

Kehagia, A. A., Barker, R. A., & Robbins, T. W. (2010). Neuropsychological and clinical heterogeneity of cognitive impairment and dementia in patients with Parkinson's disease. *Lancet Neurology, 9*(12), 1200-1213. doi: 10.1016/S1474-4422(10)70212-X

Kish, S. J., Shannak, K., & Hornykiewicz, O. (1988). Uneven pattern of dopamine loss in the striatum of patients with idiopathic Parkinson's disease. Pathophysiologic and clinical implications. *New England Journal of Medicine, 318*(14), 876-880. doi: 10.1056/NEJM198804073181402

Kudlicka, A., Clare, L., & Hindle, J. V. (2011). Executive functions in Parkinson's disease: systematic review and meta-analysis. *Movement Disorders, 26*(13), 2305-2315. doi: 10.1002/mds.23868

Lewis, S. J., Dove, A., Robbins, T. W., Barker, R. A., & Owen, A. M. (2003). Cognitive impairments in early Parkinson's disease are accompanied by reductions in activity in frontostriatal neural circuitry. *The Journal of Neurosciences, 23*(15), 6351-6356. doi: http://www.jneurosci.org/content/23/15/6351.short

Lewis, S. J., Slabosz, A., Robbins, T. W., Barker, R. A., & Owen, A. M. (2005). Dopaminergic basis for deficits in working memory but not attentional set-shifting in Parkinson's disease. *Neuropsychologia, 43*(6), 823-832. doi: 10.1016/j.neuropsychologia.2004.10.001

Lezak, M. D., Howieson, D. B., & Loring, D. W. (2004). *Neuropsychological Assessment* (Fourth ed.). New York: Oxford.

Litvan, I., Goldman, J. G., Troster, A. I., Schmand, B. A., Weintraub, D., Petersen, R. C., . . . Emre, M. (2012). Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. *Movement Disorders, 27*(3), 349-356. doi: 10.1002/mds.24893

Lord, S., Baker, K., Nieuwboer, A., Burn, D., & Rochester, L. (2011). Gait variability in Parkinson's disease: an indicator of non-dopaminergic contributors to gait dysfunction? *Journal of Neurology, 258*(4), 566-572. doi: 10.1007/s00415-010-5789-8

Lord, S., Galna, B., Coleman, S., Yarnall, A., Burn, D., & Rochester, L. (2014). Cognition and gait show a selective pattern of association dominated by phenotype in incident Parkinson's disease. *Frontiers in Aging Neurosciences, 6*, 249. doi: 10.3389/fnagi.2014.00249

Lord, S., Galna, B., Verghese, J., Coleman, S., Burn, D., & Rochester, L. (2013). Independent domains of gait in older adults and associated motor and nonmotor attributes: validation of a factor analysis approach. The *Journal of Gerontology Series A Biological Sciences and Medical Sciences, 68*(7), 820-827. doi: 10.1093/gerona/gls255

Lord, S., Rochester, L., Hetherington, V., Allcock, L. M., & Burn, D. (2010). Executive dysfunction and attention contribute to gait interference in 'off' state Parkinson's Disease. *Gait Posture, 31*(2), 169-174. doi: 10.1016/j.gaitpost.2009.09.019

Marusiak, J., Zeligowska, E., Mencel, J., Kisiel-Sajewicz, K., Majerczak, J., Zoladz, J. A., . . . Jaskolska, A. (2015). Interval training-induced alleviation of rigidity and hypertonia in patients with Parkinson's disease is accompanied by increased basal serum brain-derived neurotrophic factor. *Journal of Rehabilitation Medicine, 47*(4), 372-375. doi: 10.2340/16501977-1931

McKee, K. E., & Hackney, M. E. (2013). The effects of adapted tango on spatial cognition and disease severity in Parkinson's disease. *Journal of Motor Behavior, 45*(6), 519-529. doi: 10.1080/00222895.2013.834288

McMorris, T., & Hale, B. J. (2012). Differential effects of differing intensities of acute exercise on speed and accuracy of cognition: a meta-analytical investigation. *Brain and Cognition, 80*(3), 338-351. doi: 10.1016/j.bandc.2012.09.001

Middleton, F. A., & Strick, P. L. (2000a). Basal ganglia and cerebellar loops: motor and cognitive circuits. *Brain Research Reviwes, 31*(2-3), 236-250. doi:10.1016/S0165-0173(99)00040-5

Middleton, F. A., & Strick, P. L. (2000b). Basal ganglia output and cognition: evidence from anatomical, behavioral, and clinical studies. *Brain and Cognition, 42*(2), 183-200. doi: 10.1006/brcg.1999.1099

Milner, B. (1963). Effects of different brain lesions on card sorting: The role of the frontal lobes. *Archives of Neurology, 9*(1), 90-00. doi:10.1001/archneur.1963.00460070100010

Montero-Odasso, M., Muir-Hunter, S. W., Oteng-Amoako, A., Gopaul, K., Islam, A., Borrie, M., . . . Speechley, M. (2015). Donepezil improves gait performance in older adults with mild Alzheimer's disease: a phase II clinical trial. *Journal of Alzheimers Disease, 43*(1), 193-199. doi: 10.3233/JAD-140759

Montero-Odasso, M., Wells, J. L., Borrie, M. J., & Speechley, M. (2009). Can cognitive enhancers reduce the risk of falls in older people with mild cognitive impairment? A protocol for a randomised controlled double blind trial. *BMC Neurology, 9*, 42. doi: 10.1186/1471-2377-9-42

Muller, M. L., & Bohnen, N. I. (2013). Cholinergic dysfunction in Parkinson's disease. *Current Neurology and Neuroscience Reports, 13*(9), 377. doi: 10.1007/s11910-013-0377-9

Murray, D. K., Sacheli, M. A., Eng, J. J., & Stoessl, A. J. (2014). The effects of exercise on cognition in Parkinson's disease: a systematic review. *Translational Neurodegeneration, 3*(1), 5. doi: 10.1186/2047-9158-3-5

Nagamatsu, L. S., Chan, A., Davis, J. C., Beattie, B. L., Graf, P., Voss, M. W., . . . Liu-Ambrose, T. (2013). Physical activity improves verbal and spatial memory in older adults with probable mild cognitive impairment: a 6-month randomized controlled trial. *Journal of Aging Research, 2013*, 861893. doi: 10.1155/2013/861893

Nocera, J. R., Altmann, L. J., Sapienza, C., Okun, M. S., & Hass, C. J. (2010). Can exercise improve language and cognition in Parkinson's disease? A case report. *Neurocase, 16*(4), 301-306. doi: 10.1080/13554790903559663

Obeso, I., Wilkinson, L., Casabona, E., Speekenbrink, M., Luisa Bringas, M., Alvarez, M., . . . Jahanshahi, M. (2014). The subthalamic nucleus and inhibitory control: impact of subthalamotomy in Parkinson's disease. *Brain, 137*(Pt 5), 1470-1480. doi: 10.1093/brain/awu058

Obeso, I., Wilkinson, L., & Jahanshahi, M. (2011). Levodopa medication does not influence motor inhibition or conflict resolution in a conditional stop-signal task in Parkinson's disease. *Experimental Brain Research, 213*(4), 435-445. doi: 10.1007/s00221-011-2793-x

Owen, A. M. (2004). Cognitive dysfunction in Parkinson's disease: the role of frontostriatal circuitry. *Neuroscientist, 10*(6), 525-537. doi: 10.1177/1073858404266776

Owen, A. M., Doyon, J., Dagher, A., Sadikot, A., & Evans, A. C. (1998). Abnormal basal ganglia outflow in Parkinson's disease identified with PET. Implications for higher cortical functions. *Brain, 121 (Pt 5)*, 949-965. doi: http://dx.doi.org/10.1093/brain/121.5.949

Owen, A. M., James, M., Leigh, P. N., Summers, B. A., Marsden, C. D., Quinn, N. P., . . . Robbins, T. W. (1992). Fronto-striatal cognitive deficits at different stages of Parkinson's disease. *Brain, 115 (Pt 6)*, 1727-1751. doi: http://dx.doi.org/10.1093/brain/115.6.1727

Petzinger, G. M., Fisher, B. E., McEwen, S., Beeler, J. A., Walsh, J. P., & Jakowec, M. W. (2013). Exercise-enhanced neuroplasticity targeting motor and cognitive circuitry in Parkinson's disease. *Lancet Neurology, 12*(7), 716-726. doi: 10.1016/S1474-4422(13)70123-6

Petzinger, G. M., Holschneider, D. P., Fisher, B. E., McEwen, S., Kintz, N., Halliday, M., . . . Jakowec, M. W. (2015). The Effects of Exercise on Dopamine Neurotransmission in Parkinson's Disease: Targeting Neuroplasticity to Modulate Basal Ganglia Circuitry. *Brain Plasticity, 1*(1), 29-39. doi: 10.3233/BPL-150021

Picton, T. W., Stuss, D. T., Shallice, T., Alexander, M. P., & Gillingham, S. (2006). Keeping time: effects of focal frontal lesions. *Neuropsychologia, 44*(7), 1195-1209. doi: 10.1016/j.neuropsychologia.2005.10.002

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. doi: 10.1016/j.bandc.2014.03.005

Politis, M., & Niccolini, F. (2015). Serotonin in Parkinson's disease. *Behavioural Brain Research, 277*, 136-145. doi: 10.1016/j.bbr.2014.07.037

Ridgel, A. L., Kim, C. H., Fickes, E. J., Muller, M. D., & Alberts, J. L. (2011). Changes in executive function after acute bouts of passive cycling in Parkinson's disease. *Journal of Aging and Physical Activity, 19*(2), 87-98. doi: http://www.acutech.co.nz/Portals/Main/Acutech/MOTOmed/parkinson_gb_vt_ridgel_motomed_2.pdf

Riekkinen, M., Kejonen, K., Jakala, P., Soininen, H., & Riekkinen, P., Jr. (1998). Reduction of noradrenaline impairs attention and dopamine depletion slows responses in Parkinson's disease. *European Journal of Neuroscience, 10*(4), 1429-1435. doi: 10.1046/j.1460-9568.1998.00145.x

Rochester, L., Galna, B., Lord, S., & Burn, D. (2014). The nature of dual-task interference during gait in incident Parkinson's disease. *Neuroscience, 265*, 83-94. doi: 10.1016/j.neuroscience.2014.01.041

Rochester, L., Hetherington, V., Jones, D., Nieuwboer, A., Willems, A. M., Kwakkel, G., & Van Wegen, E. (2004). Attending to the task: interference effects of functional tasks on walking in Parkinson's disease and the roles of cognition, depression, fatigue, and balance. *Archives of Physical Medicine and Rehabilitation, 85*(10), 1578-1585. doi:10.1016/j.apmr.2004.01.025

Rochester, L., Nieuwboer, A., Baker, K., Hetherington, V., Willems, A. M., Chavret, F., . . . Jones, D. (2007). The attentional cost of external rhythmical cues and their impact on gait in Parkinson's disease: effect of cue modality and task complexity. *Journal of Neural Transmission, 114*(10), 1243-1248. doi: 10.1007/s00702-007-0756-y

Rochester, L., Yarnall, A. J., Baker, M. R., David, R. V., Lord, S., Galna, B., & Burn, D. J. (2012). Cholinergic dysfunction contributes to gait disturbance in early Parkinson's disease. *Brain, 135*(Pt 9), 2779-2788. doi: 10.1093/brain/aws207

Sage, M. D., & Almeida, Q. J. (2009). Symptom and gait changes after sensory attention focused exercise vs aerobic training in Parkinson's disease. *Movement Disorders, 24*(8), 1132-1138. doi: 10.1002/mds.22469

Smulders, K., van Nimwegen, M., Munneke, M., Bloem, B. R., Kessels, R. P., & Esselink, R. A. (2013). Involvement of specific executive functions in mobility in Parkinson's disease. *Parkinsonism and Related Disorders, 19*(1), 126-128. doi: 10.1016/j.parkreldis.2012.06.010

Springer, S., Giladi, N., Peretz, C., Yogev, G., Simon, E. S., & Hausdorff, J. M. (2006). Dual-tasking effects on gait variability: the role of aging, falls, and executive function. *Movement Disorders, 21*(7), 950-957. doi: 10.1002/mds.20848

Stuss, D. T. (2006). Frontal lobes and attention: processes and networks, fractionation and integration. *Journal of the International Neuropsychology Society, 12*(2), 261-271. doi: 10.1017/S1355617706060358

Stuss, D. T. (2011). Functions of the frontal lobes: relation to executive functions. *Journal of the International Neuropsychological Society, 17*(5), 759-765. doi: 10.1017/S1355617711000695

Stuss, D. T., & Alexander, M. P. (2007). Is there a dysexecutive syndrome? *Philosophical Transactions of the Royal Society of London B: Biological Sciences, 362*(1481), 901-915. doi: 10.1098/rstb.2007.2096

Stuss, D. T., Alexander, M. P., Shallice, T., Picton, T. W., Binns, M. A., Macdonald, R., . . . Katz, D. I. (2005). Multiple frontal systems controlling response speed. *Neuropsychologia, 43*(3), 396-417. doi: 10.1016/j.neuropsychologia.2004.06.010

Stuss, D. T., Binns, M. A., Murphy, K. J., & Alexander, M. P. (2002). Dissociations within the anterior attentional system: effects of task complexity and irrelevant information on reaction time speed and accuracy. *Neuropsychology, 16*(4), 500-513. doi: http://dx.doi.org/10.1037/0894-4105.16.4.500

Stuss, D. T., Levine, B., Alexander, M. P., Hong, J., Palumbo, C., Hamer, L., . . . Izukawa, D. (2000). Wisconsin Card Sorting Test performance in patients with focal frontal and posterior brain damage: effects of lesion location and test structure on separable cognitive processes. *Neuropsychologia, 38*(4), 388-402. doi:10.1016/S0028-3932(99)00093-7

Stuss, D. T., Murphy, K. J., Binns, M. A., & Alexander, M. P. (2003). Staying on the job: the frontal lobes control individual performance variability. *Brain, 126*(Pt 11), 2363-2380. doi: 10.1093/brain/awg237

Suzuki, T., Shimada, H., Makizako, H., Doi, T., Yoshida, D., Ito, K., . . . Kato, T. (2013). A randomized controlled trial of multicomponent exercise in older adults with mild cognitive impairment. *PLoS One, 8*(4), e61483. doi: 10.1371/journal.pone.0061483

Tabak, R., Aquije, G., & Fisher, B. E. (2013). Aerobic exercise to improve executive function in Parkinson disease: a case series. *Journal of Neurologic Physical Therapy, 37*(2), 58-64. doi: 10.1097/NPT.0b013e31829219bc

Tanaka, H., Monahan, K. D., & Seals, D. R. (2001). Age-predicted maximal heart rate revisited. *Journal of the American College of Cardiology, 37*(1), 153-156. doi: 10.1016/S0735-1097(00)01054-8

Tanaka, K., Quadros, A. C., Jr., Santos, R. F., Stella, F., Gobbi, L. T., & Gobbi, S. (2009). Benefits of physical exercise on executive functions in older people with Parkinson's disease. *Brain and Cognition, 69*(2), 435-441. doi: 10.1016/j.bandc.2008.09.008

Taylor, A. E., Saint-Cyr, J. A., & Lang, A. E. (1986). Frontal lobe dysfunction in Parkinson's disease. The cortical focus of neostriatal outflow. *Brain, 109 (Pt 5)*, 845-883. doi: http://dx.doi.org/10.1093/brain/109.5.845

Testa, R., Bennett, P., & Ponsford, J. (2012). Factor analysis of nineteen executive function tests in a healthy adult population. *Archives of Clinical Neuropsychology, 27*(2), 213-224. doi: 10.1093/arclin/acr112

Themanson, J. R., & Hillman, C. H. (2006). Cardiorespiratory fitness and acute aerobic exercise effects on neuroelectric and behavioral measures of action monitoring. *Neuroscience, 141*(2), 757-767. doi: 10.1016/j.neuroscience.2006.04.004

Tsai, C. L., Chen, F. C., Pan, C. Y., Wang, C. H., Huang, T. H., & Chen, T. C. (2014). Impact of acute aerobic exercise and cardiorespiratory fitness on visuospatial attention performance and serum BDNF levels. *Psychoneuroendocrinology, 41*, 121-131. doi: 10.1016/j.psyneuen.2013.12.014

Uc, E. Y., Doerschug, K. C., Magnotta, V., Dawson, J. D., Thomsen, T. R., Kline, J. N., . . . Darling, W. G. (2014). Phase I/II randomized trial of aerobic exercise in Parkinson disease in a community setting. *Neurology, 83*(5), 413-425. doi: 10.1212/WNL.0000000000000644

Verghese, J., Mahoney, J., Ambrose, A. F., Wang, C., & Holtzer, R. (2010). Effect of cognitive remediation on gait in sedentary seniors. *Journal of Gerontology Series A Biological Sciences and Medical Sciences, 65*(12), 1338-1343. doi: 10.1093/gerona/glq127

Williams-Gray, C. H., Evans, J. R., Goris, A., Foltynie, T., Ban, M., Robbins, T. W., . . . Barker, R. A. (2009). The distinct cognitive syndromes of Parkinson's disease: 5 year follow-up of the CamPaIGN cohort. *Brain, 132*(Pt 11), 2958-2969. doi: 10.1093/brain/awp245

Williams-Gray, C. H., Mason, S. L., Evans, J. R., Foltynie, T., Brayne, C., Robbins, T. W., & Barker, R. A. (2013). The CamPaIGN study of Parkinson's disease: 10-year outlook in an incident population-based cohort. *Journal of Neurology Neurosurgery and Psychiatry, 84*(11), 1258-1264. doi: 10.1136/jnnp-2013-305277

Wu, T., & Hallett, M. (2005). A functional MRI study of automatic movements in patients with Parkinson's disease. *Brain, 128*(Pt 10), 2250-2259. doi: 10.1093/brain/awh569

Yanagisawa, H., Dan, I., Tsuzuki, D., Kato, M., Okamoto, M., Kyutoku, Y., & Soya, H. (2010). Acute moderate exercise elicits increased dorsolateral prefrontal activation and improves cognitive performance with Stroop test. *Neuroimage, 50*(4), 1702-1710. doi: 10.1016/j.neuroimage.2009.12.023

Yogev, G., Giladi, N., Peretz, C., Springer, S., Simon, E. S., & Hausdorff, J. M. (2005). Dual tasking, gait rhythmicity, and Parkinson's disease: which aspects of gait are attention demanding? *European Journal of Neuroscience, 22*(5), 1248-1256. doi: 10.1111/j.1460-9568.2005.04298.x