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The effects of external focus of attention exercise rehabilitation on dual task walking in Parkinson's disease

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THE EFFECTS OF EXTERNAL FOCUS OF ATTENTION EXERCISE REHABILITATION ON DUAL TASK WALKING IN PARKINSON'S DISEASE

by

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ABSTRACT

Parkinson's disease impairs control of well-learned movements, and therefore, individuals with Parkinson's disease are forced to walk with greater conscious control. This causes difficulties while walking and completing a secondary task simultaneously (dual tasking), in that distractions from conscious control of walking increase the risk of falls and injury. Although, attention-based exercise may be a potential avenue to decrease the demands associated with walking in Parkinson's disease. For example, an external focus of attention (on manipulated objects) has been found to recruit the networks that are important for walking with little conscious control (automatic control networks). In contrast, an internal focus (on limb movements) has been found to recruit conscious control networks. Unexpectedly, an external focus of attention (compared to an internal) has been found to improve postural stability in Parkinson's disease (compared to internal) despite that this attentional focus recruits damaged automatic control circuits. Therefore, promoting an external focus during goal-based exercise may improve upon automatic control functioning, and therefore, improve the ability to dual task and reduce the severity of symptoms.

A parallel group, single blind, randomized controlled trial was conducted. Thirty-nine participants with Parkinson's disease were randomized to one of two exercise groups: 1) External focus of attention (focus on movement of coloured labels attached to limbs, n=19) or 2) Internal focus of attention (focus on movement of limbs, n=20). Both exercise groups completed 33 one-hour goal-based exercise sessions over 11 weeks. Eleven participants were assigned to a non-exercise control group. Walking ability (single and dual tasking) and symptom severity

(Unified Parkinson's disease Rating Scale motor subsection [UPDRS-III] ON and OFF dopamine medications) were assessed before and after (pre/post) the completion of the program, and 8 weeks after exercise cessation (washout). As a result of the intervention, walking ability while completing a secondary task became significantly worse in the Internal focus of attention exercise group, while dual tasking ability did not change in the external group. Symptom severity significantly improved in only the External group from pre to post. From pre to washout, dual task walking ability and motor symptom severity improved in both exercise groups. However, the Internal group had increased errors on the dual task, whereas the External group did not, indicating that improvements were only demonstrated in the External group.

Thus, External focus of attention exercise may provide benefits that establish a foundation for improvements to dual task walking ability in Parkinson's disease, whereas adopting an Internal focus of attention during goal-based exercise appeared to increase reliance on conscious control of movement, hindering dual tasking ability. Additionally, after the exercise program, greater improvements to symptom severity were found after externally focused exercise compared to internally focused. Together, these findings indicate that focusing externally on the manipulation of coloured labels while exercising provides greater rehabilitation effectiveness in Parkinson's disease compared to focusing internally on limb movements.

PROBLEM STATEMENT

Despite a great body of research, one of the most devastating aspects of Parkinson's disease, walking detriments unresponsive to Parkinsonian medication, remains to be ameliorated by adjunct therapies. More specifically, individuals with Parkinson's disease are forced to constantly attend focus towards walking in order to successfully ambulate. In the event that they are distracted while walking, the result can be tripping, falling, serious injury, and even hospitalization. To date, understanding the mechanisms underlying this dysfunction is limited, and few randomized controlled exercise trials have been conducted.

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CHAPTER 1: INTRODUCTION

In healthy individuals, well-learned movements can be performed automatically (without conscious control and with little demand on attention) [1,2]. Walking, or gait, is an example of a well-learned movement [3], since it is learned as a child and carried with us in a very adaptable way throughout our development. When healthy individuals walk, afferent information regarding limb position in physical space from proprioceptors is transmitted to the sensorimotor cortices of the brain, which relay an efferent copy of this information to the nuclei of the basal ganglia where the information is processed and integrated with inputs from various locations of the brain [2,4–11]. The information then leaves the basal ganglia and returns to the sensorimotor cortex where it is used to guide movement. If this process of integrating sensory information through the basal ganglia is functional, and the individual can efficiently use this information, then walking can be completed without a great degree of conscious control, and therefore automatically [1–3]. Without the necessity to consciously control walking, the degrees of movement freedom are minimized [12–16], and therefore spatio-temporal walking parameters (ie. length, time, and variability of stepping behaviour) are consistent between steps and accomplished successfully with little vigilance. Since automatic walking requires very little central processing capacity, it also allows one to dual task, or walk while performing another task simultaneously, without interference to gait parameters, which would present as decreased step length and time, slower velocity and increased step-to-step variability [17–22]. The ability to dual task with minimal interference is possible in healthy individuals because frontal areas of the brain involved in conscious control of limb movements are less required to complete the automatic movement (ie. walking), and are therefore available for performance of a secondary

task [12,23–28]. It then stands to reason that if there is a segment of dysfunction in the process of completing a movement automatically, dual task performance (ie. walking and completing a secondary task) might be impaired. This is the case in Parkinson's disease.

When individuals with Parkinson's disease walk, the integrated information that projects from the basal ganglia and return to the sensorimotor cortex is "noisy" (i.e. abnormal electrical oscillatory frequencies), due to degeneration of dopamine producing cells of the basal ganglia [4]. In other words, the processing of proprioception (or the sensory information regarding limb position in physical space) is impaired in Parkinson's disease [4,11,29]. Without the functional integration of sensory information through the basal ganglia, individuals with Parkinson's disease cannot efficiently use proprioception to guide movements [11,30–40]. To compensate for this problem, individuals with Parkinson's disease attempt to consciously control their movements [24,40–45]. Increased demand on conscious control increases the problematic degrees of freedom associated with the complexity of walking [46]. This problem further results in inaccurate perception of where one's own lower limbs are in physical space [30] and thus a greater chance of tripping over obstacles when one is forced to rely on proprioception (when vision of the lower limbs is occluded) [47]. With greater demand required to consciously control walking (compared to healthy individuals), the availability of attentional resources to complete a secondary task is limited [19–21,48,49]. Walking while simultaneously attempting to complete another task (dual tasking) thus significantly deteriorates gait in individuals with Parkinson's disease, such that step length decreases, whereas time spent in double support and gait variability increase [19–22,38,43,50–52]. These impairments in gait have been found to lead to increased risk of falls [17,53–56]. Interestingly, previous work has found that walking resulted in the greatest percentage of falls compared to turning, transferring, reaching, and standing up from a

seated position [57]. A recent 8-year cohort study investigating the history of falls in individuals with Parkinson's found that among participants who were classified as non-fallers at baseline, 68% became consistent fallers by the end of the study [58], matching previous findings [59]. These falls unfortunately underlie the leading cause of hospitalization in Parkinson's disease [60] where typically in Canada, 54% of falls in individuals over the age of 75 years result in hospitalization [57].

Unfortunately, dopaminergic medications aimed to alleviate symptoms of Parkinson's disease offer only limited alleviation to gait impairments that are exacerbated when dual tasking and linked to increased risk of falls. For example, regardless of medication state (ON vs. OFF dopaminergic medication states), previous work utilizing measures of proprioception have consistently found that individuals with Parkinson's disease are more variable in their ability to perceive where their limbs and body are in physical space compared to healthy age-matched individuals [4]. Specifically, the increased threshold of limb movement perception and decreased accuracy of limb placement (which translate into greater deficits in postural stability) are not improved in Parkinson's disease with dopamine replacement medication [11,32,61–64]. With respect to gait, while individuals with Parkinson's disease walk at a comfortable pace, impaired step time and length variability (i.e. increased variability) are also not alleviated by dopamine replacement medication [65,66]. Furthermore, Lord and colleagues (2011) found that dopamine replacement does not alleviate increased variability of the percentage of time spent in double support when individuals with Parkinson's disease walked and completed a secondary task [66]. In fact, dopaminergic replacement medications have been found to exacerbate dysfunctional proprioception [64], which may explain findings of increased step time variability while individuals with Parkinson's disease walk with dopaminergic replacement compared to walking

after withdrawn from medication [67]. In general, sensory processing that allows the automatic system to function is not enhanced by dopaminergic medication in Parkinson's disease. Therefore, alternative methods to improve upon the ability to dual task in Parkinson's disease is necessary to improve quality of life in individuals with Parkinson's disease and decrease the potential of falls.

Aiming to improve dual task walking in Parkinson's disease is not a new concept. It has been proposed by research groups that to improve dual task walking, one must simply train dual tasking specifically [68,69]. Previous work has found that one session of dual task training (combination of gait training and working memory language tasks) led individuals with Parkinson's disease to significantly increase step length and velocity (ie. improve gait) while dual tasking at post-test compared to pre-test [70,71]. Longer dual task gait training interventions that have included 1 session per week for 3 weeks [72], 3 sessions per week for 4 weeks [73], and 3 sessions per week for 6 weeks [74] have each demonstrated improved dual task walking step length and velocity in individuals with Parkinson's disease. Interestingly, Yogev-Seligmann and colleagues (2012) demonstrated that dual task training significantly decreased stride time variability while walking and completing a secondary task [73], an impaired domain of walking not responsive to dopaminergic medication [65,66]. Most recently, a single-blind randomized controlled trial investigated the influence of a 10-week (3 sessions per week) dual task balance training intervention on dual task walking ability in individuals with Parkinson's disease [75]. Although dual task walking (step length and velocity) was not improved, Conradsson and colleagues (2015) found that performance on the secondary task (measured in % error compared to baseline) significantly improved at post-test compared to pre-test without causing greater interference to walking. This suggests an improvement to dual task capability since participants

were better able to prioritize the secondary task at post-assessment compared to pre without detriments to gait [75]. It should be noted that the previously mentioned studies compared all dual task training groups to a control group that was not given an intervention, and found significant differences between groups that suggest improvements to dual task ability in those with Parkinson's disease who completed the associated interventions.

Dual task training interventions have therefore successfully improved upon the ability to walk and complete a secondary task simultaneously in individuals with Parkinson's disease. However, when individuals with Parkinson's disease dual task, they naturally recruit futile areas of the brain to compensate for the inaccurate information that is output from the basal ganglia [24]. For example, in an innovative functional magnetic resonance imaging study, Wu and Hallett (2005) measured cortical activity in healthy individuals while they completed a dual task (finger-tapping task while simultaneously completing a secondary cognitive task). These measures were collected before participants were given an opportunity to practice the finger-tapping and cognitive dual task (to the point where the cognitive task no longer interfered with the finger-tapping task) and after. The researchers found that after the dual task was well learned (ie. finger-tapping became automatic), areas of the brain involved in conscious control of movements became less recruited at post-test compared to pre-test, whereas areas of the brain involved in automatic control became more recruited. In contrast, when this protocol was completed in individuals with Parkinson's disease, practicing the dual task to the point where no dual task interference was found did not result in decreased recruitment of areas in the brain involved in conscious control like that found in healthy individuals. Therefore, dual task training interventions, such as those presented above, would only be expected to improve upon conscious control abilities in Parkinson's disease, but not unconscious control associated with their

impaired automatic control networks. Thus, after completion of a dual task intervention, individuals with Parkinson's disease would still be unable to efficiently use their automatic control networks during walking so that conscious control networks could be used to accomplish secondary tasks. To improve upon one's ability to efficiently use their automatic control networks, a modality that fosters increased drive of sensory areas of the brain (since sensory areas of the brain underlie automatic control networks) could be utilized. Exercise has been found to be one such modality.

The purpose of using exercise (specifically goal-based exercise to train walking) as an intervention is to induce neuroplastic changes in the brain, or more specifically, changes to neuronal connections in response to new stimulation and/or information that bring about altered behaviour [76–78]. By using an exercise intervention that increases neuronal drive of areas in the brain associated with the automatic system (i.e. sensorimotor cortex projections into the basal ganglia), functioning neuronal connections could be strengthened or formed, allowing for improved automatic control, and therefore, ability to dual task. Many forms of exercise would be expected to increase sensorimotor drive in the brain, since the very act of increasing muscle activation would also increase the amount of afferent sensory information projecting to the brain from proprioceptors such as muscle spindles sensitive to muscle stretch and golgi tendon organs sensitive to muscle tension [79–84]. However, since automatic control over the vast degrees of freedom associated with gait requires the interaction of visual, vestibular, and somatosensory information that are specific to walking, an exercise program that trains aspects of gait (such as dynamic balance and coordination) and increases neuronal drive in sensorimotor areas of the brain (due to proprioceptor activity) would be optimal to improve dual task walking. A previous functional magnetic resonance imaging study investigated the influence of the long-term effects

on neurological function resulting from goal-based exercise that trains dynamic balance and coordination in healthy individuals. Wei and colleagues (2014) found significantly greater sensorimotor cortex synchronization in individuals who trained dynamic balance and coordination through Tai Chi (n=18, average age=52.4), compared to a group of individuals who did not (n=22, average age=54.8) [85]. Greater synchronization of the automatic system might allow for more effective and unconscious recruitment of muscle synergies involved in well-learned movements, decreasing the degrees of freedom that need to be controlled and the demand placed on attentional resources. However, as discussed previously, when individuals with Parkinson's disease complete movements such as those that would be involved in a goal-based exercise program, they naturally recruit vast cortical areas of the brain [24]. This is presumably to compensate for the inaccurate information that is being output from the basal ganglia [24], such as sensory information that they are unable to efficiently use. By recruiting areas of the brain to compensate for the impaired automatic processes, a goal-based exercise that increases sensorimotor drive into the basal ganglia would not be expected to improve ones' use of this information alone because the individuals with Parkinson's would not be trained to efficiently use the sensory information, only compensate for it. Therefore, an instruction that forces individuals with Parkinson's disease to utilize their automatic control networks in addition to goal-based exercise might improve upon the functioning and ability to efficiently use automatic processes, allowing for improved ability to walk and complete a second task. An instruction that pertains to where attention is focused while performing different movements has been found to allow individuals with Parkinson's disease to efficiently use automatic processes to control movement, and benefits to movement performance result.

While performing movements, one can focus on the control of an object that is being manipulated (such as the control of a golf ball while completing a golf putt), or they can focus on their limbs to ensure that the movement is accurate. Previous work has demonstrated that when healthy individuals perform tasks and focus attention on the control of an object that is being manipulated (i.e. an external focus of attention), movement performance is typically more successful than when the movement is completed while attention is focused towards controlling movement of ones' limbs (i.e. an internal focus of attention) [86–91]. Adopting an external focus of attention while completing a movement has been argued to naturally recruit automatic processes indicative of unconscious control of the movement [46]. Thus, an external focus of attention might improve recruitment of muscle synergies that decrease the number of degrees of freedom that need to be controlled for. In contrast, it has been argued that an internal focus of attention promotes a more conscious control of movement, increasing the number of degrees of freedom that need to be controlled and causing detriments to performance [46]. However, the pathophysiological mechanism underlying the influence of an external and internal focus of attention is not completely understood. Regardless, Zentgraf and colleagues (2009) found through functional magnetic resonance imaging, that when healthy individuals adopted an external focus of attention (i.e. focus attention on pressing keys) during a finger tapping task, greater involvement of cortical areas that are typically recruited during automatic movement control was demonstrated [23,92]. On the other hand, directing attention internally (i.e. on the movements of ones' fingers) promoted recruitment of frontal areas of the brain involved in conscious control of movement [92]. Therefore, one might expect that if an external focus of attention promotes the involvement of impaired automatic processes in Parkinson's disease, movement performance should be worse if an external focus of attention is adopted throughout

the control of a movement task. In contrast to this assumption, Wulf and colleagues (2009) found that when individuals with Parkinson's disease were asked to control their postural stability on an inflated disk, participants demonstrated significantly less postural sway (improved control of postural stability) when focus of attention was directed to minimizing movements of the platform they stood on (external focus of attention) compared to minimizing movements of their feet (internal focus of attention) [93,94]. Importantly, postural stability testing in the previously mentioned study took place while individuals with Parkinson's were ON dopamine replacement medications (continuing their normal Parkinsonian medication regimen). This suggests that as long as dopamine is present in the basal ganglia, individuals with Parkinson's disease are able to effectively use their automatic control networks to perform movements, and this proves beneficial for control. On the other hand, removing dopamine from the basal ganglia (OFF medication state) might be expected to negate the benefits of an external focus of attention while controlling posture. With greater understanding regarding how dopamine modulates focus of attention strategies during postural control, an effective intervention that manipulates focus of attention could be formed. For this reason, Beck and Almeida (2016) investigated the influence of dopaminergic modulation (ON dopamine medication vs. OFF dopamine medication) on postural stability while contrasting focus of attention strategies were adopted (external vs. internal vs. control) in Parkinson's disease [95].

Since an external focus of attention was found to be more beneficial for control of postural stability in Parkinson's disease compared to an internal focus of attention while participants were ON dopaminergic medications, but was detrimental to postural control while participants were OFF dopamine medications, an external focus of attention was suggested to recruit automatic processes that include the basal ganglia [95]. This also suggests that training an

external focus of attention in combination with a goal-based exercise program could improve upon automatic processes in Parkinson's disease, whereas training an internal focus of attention in combination with an identical exercise program would not be expected to improve upon these automatic control networks. Therefore, in the present study, we aimed to investigate whether combining a goal-based exercise program with an external focus of attention could improve upon dual task walking (ability to efficiently use automatic processes) in individuals with Parkinson's disease. It was expected that promoting an external focus of attention (i.e. adopt use of the automatic system) while individuals with Parkinson's disease complete a goal-based exercise program would improve dual task walking (i.e. increase step length, decrease % of time in double support, and decrease step-to-step variability) at post-test compared to pre-test. In contrast, it was expected that promoting an internal focus of attention (i.e. recruit conscious control networks) while individuals with Parkinson's disease complete a goal-based exercise program might hinder dual task walking performance since this training might increase reliance on conscious control of movement. Additionally, since automatic processes rely on basal ganglia function, it was expected that goal-based exercise combined with an external focus of attention would improve upon Parkinson's disease symptom severity associated with basal ganglia dysfunction (measured with the Unified Parkinson's Disease Rating scale motor subsection). In contrast, it was expected that goal-based exercise combined with an internal focus of attention that promotes the use of conscious control networks less influenced by the basal ganglia would not improve upon Parkinson's disease symptom severity. By extension, if changes to neuronal connections took place (neuroplasticity) to either automatic and/or conscious networks, one might expect that any changes to walking behaviour (both single and dual task) should endure for a given period of time after cessation of an exercise intervention [40,73,74,96–99]. Therefore,

the last aim of the present study was to determine whether changes to gait and symptom severity as a result of a goal-based exercise program persist throughout a washout period.

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CHAPTER 2

CAN DUAL TASK WALKING IMPROVE IN PARKINSON'S DISEASE AFTER EXTERNAL FOCUS OF ATTENTION EXERCISE? A SINGLE BLIND RANDOMIZED CONTROLLED TRIAL

ABSTRACT

Background. Individuals with Parkinson's disease demonstrate difficulty walking while completing a secondary task (dual tasking), which increases risk of falls and injury. It may be possible to use attention-based exercise to decrease the demands associated with walking ability. For example, an external focus of attention (on movement of manipulated objects) is argued to recruit automatic control networks in the basal ganglia, whereas an internal focus (on limb movements) may recruit conscious control networks. Thus, it might be expected that promoting an external focus in exercise may improve automatic control, and therefore lead to improved dual tasking and the severity of symptoms in Parkinson's disease. Therefore, we aimed to investigate how training with external focus compared to internal focus of attention during exercise influences dual task walking ability and symptom severity in Parkinson's disease.

Methods. Thirty-nine participants with Parkinson's disease randomized to one of two focus of attention exercise groups: 1) External (focus on coloured labels attached to limbs, n=19) or 2) Internal (focus on limb movements, n=20). Each group completed 33 one-hour exercise rehabilitation sessions (Parkinson's disease Sensory Attention Focused Exercise, PD-SAFEx™) over 11 weeks. Eleven participants were assigned to a non-exercise control group. Before and after (pre/post) program completion, and at 8 weeks after exercise cessation (washout),

spatiotemporal gait patterns were measured during single and dual task walking, and symptom severity (UPDRS-III) was assessed ON and OFF dopamine replacement. A Two-part analysis was conducted: Part A evaluated changes from pre to post in the External, Internal and control groups; Part B evaluated pre to post to washout changes in the External and Internal groups.

Results. Part A: From pre assessment to post, neither single task nor dual task walking ability changed in the external group. The Internal group had significantly shorter step length ($p<0.001$) and slower velocity ($p=0.007$) while dual task walking as a result of intervention. Additionally, motor symptom severity significantly improved in only the External group from pre to post ($p=0.002$). Part B: From pre to washout, while dual tasking, step time ($p=0.005$) and percentage of time in double support ($p=0.014$) significantly decreased in both exercise groups, although the Internal group increased errors on the dual task by 51%, whereas the External group increased error on the dual task by 8%. Finally, at washout, both groups had significantly lower UPDRS-III scores ($p=0.001$) compared to pre.

Conclusions. Although improvements to dual task walking were not found immediately at post, external focus of attention exercise may have provided a foundation for continued benefit that eventually (washout) amounted to improvements to dual task walking. Internal focus of attention exercise appeared to increase reliance on conscious control of movement, hindering dual tasking ability. Despite that Part A analysis demonstrated benefits to motor symptom severity in only the external group, Part B demonstrated that both externally and internally focused exercise improved UPDRS-III at post and this benefit persisted for 8 weeks. Thus, these findings suggest that externally focused exercise leads to greater rehabilitation benefits (to dual tasking and symptom severity) than internally focused exercise (symptom severity) in Parkinson's disease.

INTRODUCTION

In healthy individuals without any neurological disorders, well-learned movements can be accomplished with minimal conscious control or demand on attention, and it is argued to be under more automatic control [1,2]. Walking, or gait, is believed to be one such well-learned movement [3]. These well-learned movements are believed to be facilitated by a group of subcortical nuclei, known as the basal ganglia, especially through motor loops of the dorsal striatum [4–6] that link with the sensorimotor cortex [2,7–14]. Without the necessity to consciously control walking, spatio-temporal gait parameters (ie. length, time, and variability of stepping behaviour) are consistent (i.e. little variability) between footfalls [15]. During the more automatic control of gait, there are less overall cortical processing demands on conscious control, which also allows one to walk without interference to gait parameters (ie. decreased step length, increased step time, increased percentage of time spent in double support, and increase step-to-step variability) while performing another task simultaneously (dual task). These conscious control areas are thus available for performance of a secondary task [16–22]. In individuals with Parkinson's disease, the dopamine producing cells of the basal ganglia degenerate, initially in dorsal areas of the striatum more involved in motor loops [4–6], causing impairment to automatic control. In compensation, individuals with Parkinson's disease shift to a more conscious control of walking [18,23–29], and as a result there is greater demand on attention resources to control gait (compared to healthy individuals) [30–34]. Thus, attempting to consciously control walking and complete a secondary task has been found to overload conscious control resources, causing substantial deterioration to gait in individuals with Parkinson's disease [15,25,30–32,35–38]. Decreased gait amplitude and increased gait variability inherently increase the risk of falling [39–43], and therefore place individuals with

Parkinson's disease at greater susceptibility to injury [44,45] and hospitalization [46,47]. Unfortunately, dopaminergic replacement medications offer limited mitigation to gait impairments exacerbated when dual tasking, suggesting that adjunct rehabilitation is necessary.

Previous work investigating gait in Parkinson's disease have found that impaired step time (ie. greater step time), step time and length variability (ie. increased variability) are not alleviated by dopamine replacement medication (ON dopamine vs. OFF dopamine) [48,49]. Dopamine replacement has also been found to be ineffective at improving upon increased percentage of time in double support variability when individuals with Parkinson's disease walked and completed a secondary task [49]. Therefore, to decrease the potential of falls associated with diverting attention away from walking in individuals with Parkinson's disease, alternative methods to improve upon the ability to dual task (and thus improve upon functioning of ones' automatic control) are necessary. One such possibility may be goal-based exercise rehabilitation that strives to draw attention to impaired movements as they are being performed.

While performing a movement, individuals can direct their focus of attention towards the control of a manipulated object (for example, towards a golf ball during a putt), or towards their limbs to ensure movement accuracy. Task performance is typically more successful in healthy individuals when focus of attention is directed towards control of an object that is being manipulated (ie. external focus of attention) compared to the completion of movements while attention is focused towards controlling ones' limbs (ie. an internal focus of attention) [50–55]. It has been argued that an external focus of attention naturally promotes recruitment of automatic processes indicative of automatic (or unconscious) movement control, providing benefits to performance [56,57]. In contrast, it has been argued that an internal focus of attention promotes a more conscious control of movement that can be detrimental to motor performance [56,57].

Interestingly, when individuals with Parkinson's disease were asked to control postural stability on an inflated disk (to increase task difficulty) in a previous study, significantly less postural sway (improved control) was found when participants were instructed to focus attention on minimizing movements of the platform (external focus) compared to minimizing movements of their feet (internal focus) [58]. Moreover, Beck and Almeida (2016) found that improvements to postural control that were modulated by attention were dependent on the presence of dopamine in individuals with Parkinson's disease [59]. Specifically, an external focus of attention was only found beneficial to movement control (compared to an internal focus of attention) when dopamine replacement was present, but not in the absence of dopamine. These findings suggest that as long as dopamine replacement is present, individuals with Parkinson's disease are better able to effectively use their automatic systems to perform movements, and this proves beneficial for overall motor control [58]. However, due to years of progressive basal ganglia degeneration and conscious compensation, individuals with Parkinson's disease either refrain from, or are unable to effectively utilize their automatic processes, regardless of whether the automatic networks function properly. Therefore, by combining a goal-based exercise program that trains specific aspects of walking with an external focus of attention, ability to dual task might be improved through enhanced automatic control.

Thus, the present study aimed to investigate if combining a goal-based exercise program with an external focus of attention might improve upon dual task walking in individuals with Parkinson's disease. It was expected that if an external focus of attention does promote the use of automatic control networks while completing a goal-based exercise program, then improvements to dual task walking might be fostered (ie. increase step length, decrease step time, decrease percentage of time in double support, and decrease step-to-step variability) in individuals with

Parkinson's disease. In contrast, it was expected that promoting an internal focus of attention while individuals with Parkinson's disease complete a goal-based exercise program might hinder dual task walking performance since this training might increase reliance on conscious control of movement. The present study further aimed to explore the influence of external and internal focus of attention exercise on motor symptom severity (measured with the Unified Parkinson's disease Rating scale motor subsection). Since automatic processes rely on basal ganglia function, it was expected that goal-based exercise combined with an external focus of attention would lead to greater improvements to motor symptom severity when compared to an internal focus of attention, which it is argued promotes the use of conscious control networks less influenced by the basal ganglia. Finally, if changes to neuronal connections took place (neuroplasticity) after the present intervention to either automatic and/or conscious control networks, one might expect that changes to single and dual task walking behaviour should persist for a given period of time after cessation of the exercise intervention [26,60–65]. Therefore, we also sought to explore whether changes to gait and symptom severity as a result of a goal-based exercise program persist throughout an eight-week washout period.

METHODS

Participants

Participants diagnosed with idiopathic Parkinson's disease by a neurologist were randomly recruited from the Movement Disorders Research and Rehabilitation Centre (MDRC) *exercise* database at Wilfrid Laurier University, Waterloo, Canada. Participants of both genders were included in the present study if they possessed the ability to understand verbal instructions in English, were able to walk 10-metres unassisted, and were able to stand for 5 minutes

unassisted. Exclusion criteria included a diagnosis of a neurological disease other than Parkinson's disease, peripheral neuropathy, diabetes, or a clinical diagnosis of dementia (as stated in the participant's information chart). The prescription of dopaminergic replacement medications was not a requirement, and thus participants naive to anti-Parkinsonian medications were not excluded. Prior to any evaluation or participation in exercise, written informed consent was obtained from individuals interested in participation according to the Declaration of Helsinki. The Research Ethics Board at Wilfrid Laurier University granted full ethical approval of this research study. This study was registered with the U.S. National Institutes of Health (ClinicalTrials.gov Identifier: NCT02476240). All individuals included in the rehabilitation program were also required to complete a Physical Activity Readiness Medical Examination (ParMed X) signed by a physician prior to joining the rehabilitation program.

Study Design and Exercise Intervention

The present study was a parallel group, single center, single blind, randomized controlled trial. Although this was single blind (in that assessment evaluators were blinded to group allocation), participants in both exercise groups were receiving an intervention that was believed to be beneficial [63,66]. All individuals with Parkinson's disease interested in participating in the study, and who fit the inclusion criteria, were asked to visit the MDRC one week prior to the scheduled start-date of the exercise program for pre assessment evaluation of baseline walking ability and symptom severity (discussed further in the evaluation section). After pre assessment, participants interested in the exercise program were randomized to one of two groups:

i) External Focus of Attention Exercise (External)- Participants randomized to this group were consistently instructed to focus on the movement of coloured labels

attached to the posterior side of their hands (red label), medial epicondyle of the humerus (yellow label), superior aspect of the patella (green label), and dorsal aspect of the foot (blue label; Fig1). An example of instruction given to this group during a knee raise movement was "focus on pushing the green label up in a slow, controlled manner".

ii) Internal Focus of Attention Exercise (Internal)- Participants randomized to this group were consistently instructed to focus on the movement of their limbs in physical space. An example of instruction given to this group during a knee raise movement was "focus on lifting your knee up in a slow, controlled manner".

Individuals who were not interested in participating in the exercise program (despite their inclusion in the *exercise* database) and/or believed they could not meet the necessary time commitment for involvement in the program, but were interested in participating, were assigned to the:

iii) Non-Active Control Group- Participants in this group did not participate in an exercise program. Rather, they were asked to continue with their normal daily routine.

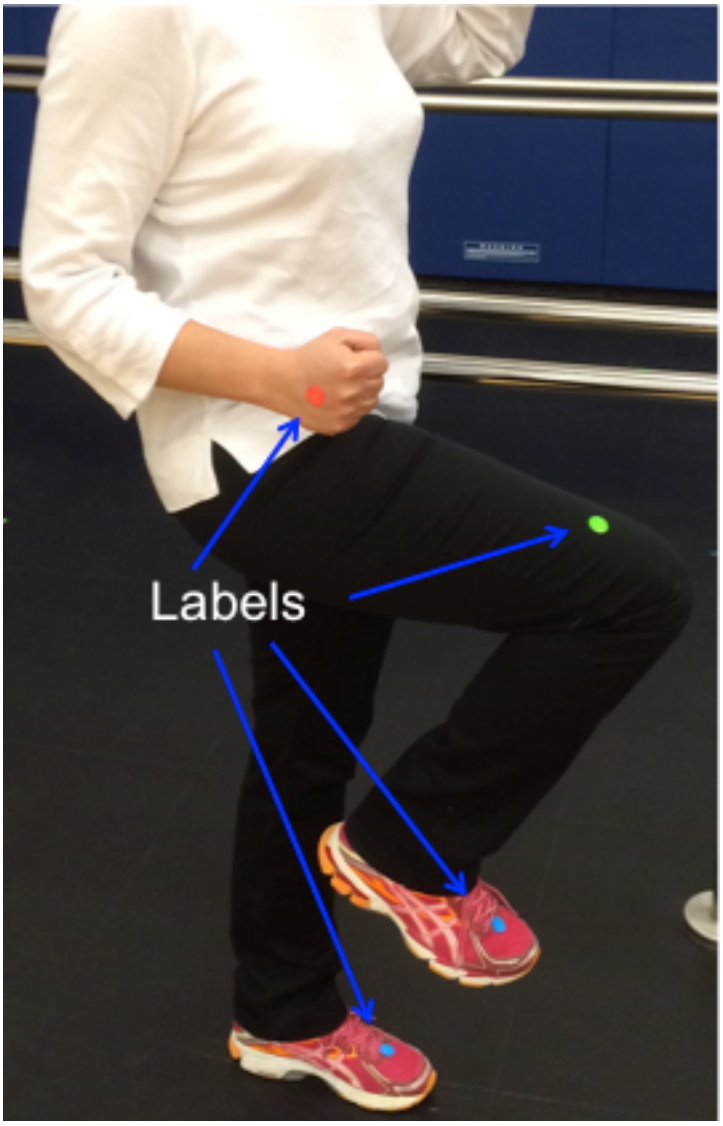

Fig 1: Participants randomized the External focus of attention exercise group wore coloured labels on the posterior side of their hands (red label), medial epicondyle of the humerus (yellow label), superior aspect of the patella (green label), and dorsal aspect of the foot (blue label). These individuals were consistently instructed to focus on the movement of the coloured labels.

The randomization of individuals who were involved in exercise began with computerized randomization to one of two ambiguous groups (not to either the External or Internal, but rather two separate groups without designation). After randomization, group demographics and outcome measures were checked for homogeneity. If groups were not similar, computer randomization took place again. Once groups were similar, one group was assigned as group A and the other assigned group B. Two pieces of paper were then used, one with the designation A (and then folded), the other with the designation B (also folded). Pieces of paper were then entered into a bin. Starting with the randomization to the External group, an impartial blinded party then selected either the group A or B designation from the bin. Participants who were randomized to the designation selected by the impartial party were therefore randomized to the External group. The participants who had been randomized to the other designation were by default randomized to the Internal group. Therefore, randomization took place twice, once to a designation (A vs. B, 50% chance), and then to a group (External vs. Internal, 50% chance). Ensuring similar demographics and outcome measures between exercise groups and the control was not an objective since the purpose of the control group was to present typical disease progression and control for bias and learning effects.

The exercise program commenced one week after pre assessment, and lasted a duration of 11-weeks, one week shorter than exercise program durations that have consistently shown improvements to gait and UPDRS-III scores [63,66]). Participants in the exercise groups completed walking, balance, stretching and coordination exercises each session, following the Parkinson's disease Sensory Attention Focused Exercise (PD-SAFEx™) program designed by Sage and Almeida (2009). Each exercise session duration was 60 minutes and was completed three times per week. PD-SAFEx™ is a group setting intervention that progressively increases in

difficulty each week to ensure that balance and coordination are constantly challenged throughout the program. The only amendment made to the program design pertained to the manipulation of vision. Since one group was asked to focus on the manipulation of an external object (coloured labels) that could only be perceived through vision (as opposed to tactile stimulation), removing vision in this group was expected to impede the effects that focusing externally was hypothesized to provide. Therefore, the program was completed with full use of vision in both exercise groups. To aid participants in completing the exercise protocol, trained undergraduate Kinesiology student volunteers were present (participant to volunteer ratio was 1:1). Participants were asked to complete exercises slowly, correctly, and under control. Both exercise groups completed the PD-SAFEx™ program identically (with regards to the type of movements completed, number of sets, repetitions and sets completed). The only difference between the exercise groups was the instruction which the exercise instructor directed participants' attention toward with respect to their movements. Post assessment of walking ability and symptom severity was assessed one-week immediately after the cessation of the exercise program. A washout assessment took place 8 weeks after the cessation of the intervention, a period of time in which participants were asked to continue activities of daily living, but not asked to attend exercise sessions at the centre, or make any further adjustments to their medications. The control group did not participate in the washout evaluation since the purpose of this group was to control for bias and learning effects, and any changes that may have occurred over the 11-week intervention period would not be expected to differ over another subsequent 8 weeks. Participants completed all exercise sessions in the ON dopaminergic medication state (approximately 1 hour after taking their normal dopaminergic medication). Individuals' naïve to dopaminergic medication (Internal group n=1) completed exercise sessions

in the OFF dopaminergic state. Participants were asked not to change any aspects of their Parkinsonian medication regime throughout the duration of the study. However, to control for any changes that may have taken place, the levodopa equivalent dose (LED) was calculated for each assessment time point. Please see the profile flow chart in Figure 2 for a full breakdown of participant recruitment, randomization, assessment time points, and withdraws from the study.

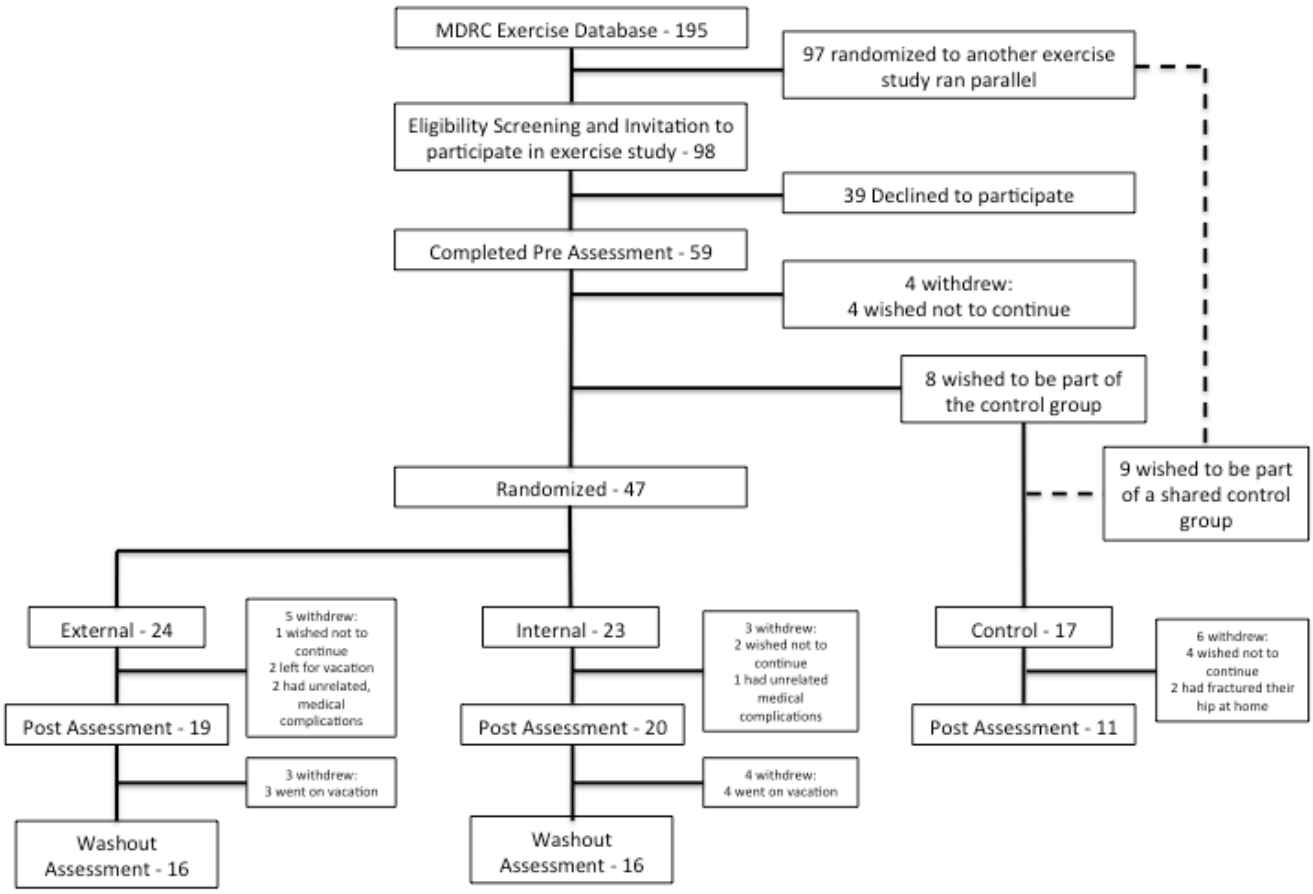

Fig 2: Profile flow chart for the present single-blind randomized controlled trial

Evaluation at Pre, Post and Washout Assessments

Since the present study aimed to not only investigate the influence of an external and internal focus of attention exercise program on dual task walking in Parkinson's disease, but also the mechanism that might underlie this influence, motor symptom severity was measured with the Unified Parkinson's Disease Rating Scale Motor Section (UPDRS Sub-section III) in participants while they were both OFF (>12 hour withdrawal from dopaminergic medication) and ON (1 hour after taking their normal dopaminergic medication) their dopaminergic medication. The UPDRS-III assessment has been found to reflect the level of dopamine present in the basal ganglia [67]. Therefore, the purpose of assessing the UPDRS-III both OFF and ON dopaminergic medications was to investigate the effects of the exercise program on endogenous basal ganglia function without and with the influence of exogenous dopamine, respectively, that has been found to mask true UPDRS-III improvements after an exercise intervention [68].

During pre assessment, post assessment, and washout evaluation time-points, participants visited the centre while in the OFF medication state, unless they opted out of the OFF medications UPDRS-III assessment portion of the research study (External n=2; Internal n=2; Control n=1). UPDRS-III assessment was completed immediately by a movement disorders specialist, whom at post-assessment and washout evaluation time-points was blinded to which group participants were randomized and to whom was allocated to the control group. Participants subsequently took their normal dopaminergic medications and completed the Community Health Activities Model Program for Seniors questionnaire (CHAMPS) while the medications were digested. The CHAMPS questionnaire is a validated self-report measure utilized to quantify how physically active one has been during the previous 4 weeks. This measure allowed determination

of all physical activity (specified by the measure) and specifically moderate intensity physical activity (≥3 METs) levels prior to commencement in the program, during the program, and after the program for the washout period [69]. The CHAMPS questionnaire further allowed for more effective comparisons to be made between the exercise and control groups. After one hour ON medications [48,70], participants were re-assessed with the UPDRS-III assessment by the same (blinded) movement disorders specialist. Individuals naïve to dopaminergic medication were only assessed once in the OFF dopaminergic state (EFA n=0; IFA n=1; Control n=0).

After the ON medication UPDRS-III assessment, the degree to which gait was affected by a dual task was evaluated. However, before walking parameters could be tested, participants completed three seated trials of the secondary task to familiarize them with the protocol and to assess baseline ability. For a full description of the secondary task, see Beck et al. (2015) and Pieruccini-Faria et al. (2014) [38,71]. In brief, participants listened to an audio track of numbers between 1 and 9. They were assigned two digits and asked to count (without manual aid) the number of times they heard the two assigned digits announced by the audio track, separately. When the trial ended, participants informed the researcher (blinded to group allocation at post-assessment and washout evaluation time-points) of the number of times they heard each digit. The difference between participants' response and the actual number of digits that were announced by the audio track was calculated. Therefore, the degree to which participants prioritized the digit-monitoring task compared to walking was quantified. During walking trials, participants were asked to walk across a 9.75m long and 0.61m wide electronic walkway carpet (Zeno Walkway – ProtoKinetics, Havertown, PA, USA) at a comfortable pace. Participants began walking 2 meters before the start of the Zeno Walkway to avoid collecting acceleration, and to continue walking past the end of the Zeno Walkway to avoid collecting deceleration. Two

walking tasks were assessed. Three single task, and three dual task (walking while simultaneously completing the digit-monitoring secondary task) walking trials were completed in random order after the seated baseline assessment of the secondary task performance. After walking trials were completed, participants' general cognitive status was evaluated with the Montreal Cognitive Assessment (MoCA), and the participants' perceived quality of life was quantified with the 39-item Parkinson's disease Questionnaire (PDQ-39).

Data and Statistical Analysis

Since a combined seven participants from the exercise groups were unable to complete the washout assessment, and the control group was not included in this assessment, statistical analysis was divided in two parts: Part A included statistical analysis of External, Internal and control participant assessments at pre and post exercise, while Part B included statistical analysis of only those participants in the External and Internal groups who completed pre, post and washout assessments.

PART A: Pre and Post Assessments

Participant demographics

To determine whether significant differences between the External, Internal and control groups existed at pre assessment that could not have been influenced by the exercise intervention but may have had an influence on benefits that could be gained (such as age, number of years diagnosed with Parkinson's disease), one-way analysis of variance (ANOVA) statistical tests were utilized. Although body mass could have changed, it was not measured at post-assessment, and therefore, a one-way ANOVA was utilized to determine whether groups were different at pre

assessment. The percentage of exercise program adherence was calculated ([# of classes attended/33] x 100) and an independent samples t-test was used to determine whether one group participated in more or fewer sessions than the other. To determine whether any significant differences were obtained, Tukey's Honest Significant Difference post hoc was utilized. Alpha level was set to $p<0.05$. Tukey's post hoc and alpha level of $p<0.05$ were also used for all statistical analyses in this study.

Single and dual tasking data and statistical analysis

ProtoKinetics Movement Analysis Software™ (ProtoKinetics, Havertown, PA, USA) was used to analyze gait parameters. Despite the fact that walking acceleration and deceleration were not collected on the Zeno Walkway, the first and last footfalls were removed offline. Left and right footfalls were collapsed. The Zeno Walkway captured the following spatiotemporal gait characteristics that were used in the statistical analyses: i) step length (cm), ii) step length variability (coefficient of variation [CV]), iii) step time (s), iv) step time variability (CV), v) double support time percentage (%), vi) double support time percentage variability (CV), and vii) velocity (cm/s). Four-factor mixed repeated measures ANOVA (3 groups x 2 evaluation times x 2 tasks [single and dual tasks] x 3 trials) assessed group differences and changes at each evaluation time-point, with respect to each gait parameter.

To determine if participants prioritized walking or the secondary task while completing the dual task walking assessment, error on the digit-monitoring task was calculated after both the baseline (completed the secondary task while seated quietly) and the dual task walking conditions at pre and post assessment. The three trials of both baseline and dual task conditions

were then averaged and input into a three-factor mixed repeated measures ANOVA (3 groups x 2 evaluation times x 2 tasks) [38,71].

Motor symptom severity data and statistical analysis

The UPDRS-III assessment provides a single discrete score on a scale that ranges from 0 to 108. Three-factor mixed repeated measures ANOVA (3 groups x 2 evaluation times x 2 medication states) assessed group differences and changes at each evaluation time-point, with respect to each motor symptom severity.

Secondary outcome measures

To investigate whether significant differences in cognitive status, levels of physical activity, and perceived quality of life (MoCA, CHAMPS, and PDQ-39, respectively) were present between groups at pre assessment and post assessment; and to determine whether significant changes within groups took place between evaluation time-points that might have been influenced by the exercise program, 2 two-factor mixed repeated measures ANOVA were utilized (3 groups x 2 evaluation times). Finally, although participants were instructed not to change any aspects of their dopaminergic medication regime while participating in the present study, 2 two-factor mixed repeated measures ANOVA (3 groups x 2 evaluation times) were used to evaluate whether significant differences between groups were present, and changes within groups took place, with respect to LED.

PART B: Pre, Post, and Washout Assessments

Participant demographics

Independent samples t-tests were used to identify differences between the External and Internal groups at pre assessment with respect to age, number of years since diagnosis, body-mass, and percent adherence to the exercise program.

Single and dual tasking data and statistical analysis

Gait data in Part B was analyzed in an identical fashion to Part A. Four-factor mixed repeated measures ANOVA (2 groups x 3 evaluation times x 2 tasks x 3 trials) assessed group differences and changes at each evaluation time-point, for each gait parameter. Performance on the secondary task that was completed while walking during the dual task condition was assessed with a three-factor mixed repeated measures ANOVA (2 groups x 3 evaluation times x 2 tasks).

Motor symptom severity data and statistical analysis

Three-factor mixed repeated measures ANOVA (2 groups x 3 evaluation times x 2 medication states) assessed group differences and changes between each evaluation time-point, with respect to UPDRS-III scores.

Secondary outcome measures

Two-factor mixed repeated measures ANOVA were utilized (2 groups x 3 evaluation times) to determine whether significant differences (between groups and evaluation times) were present with respect to LED and CHAMPS. An independent samples t-test was used to discern whether one group adhered to exercise more than the other (percentage of exercise program adherence).

RESULTS

Fifty-nine participants diagnosed with idiopathic Parkinson's disease by a neurologist completed pre assessment. Forty-seven of these individuals were randomized to either the External or Internal focus of attention exercise groups. Of the remaining twelve, four wished to discontinue their inclusion and eight believed they could not meet the necessary time commitment for involvement in the program, but participated in the Control group. A separate exercise research study was conducted at the centre simultaneously, in which nine individuals from that sample also wished to be part of the Control group. Therefore, seventeen individuals with Parkinson's disease in the Control group were shared between research studies. After randomization and commencement in the exercise program, five participants from the External group, five from the Internal group, and six from the Control group withdrew from the study. Reasons for withdraw can be found in Figure 2. Both exercise rehabilitation programs were well tolerated, and besides expected fatigue associated with physical activity, no adverse effects related to the PD SAFEx exercise programs were reported. Since the purpose of the washout assessment was to determine whether gait measures or motor symptoms revert back to pre assessment levels or persist, data from participants who withdrew after post assessment were not carried forward.

PART A: Pre and Post Assessments

Participant demographics

All participant demographic effects can be found in Table 1. No significant differences were found between groups at pre assessment.

Table 1: Part A participant demographics as group averages (standard deviation in brackets).

Demographics	External	Internal	Control	Effect
Number (M/F)	19 (15/4)	20 (16/4)	11 (10/1)	
Age (years)	68.63 (9.91)	73.05 (7.84)	71.27 (6.57)	p=0.273
Number of Years Since Diagnosis	7.0 (5.01)	6.7 (4.16)	8.36 (5.87)	p=0.652
Weight (kg)	76.53 (21.10)	87.15 (20.86)	83.33 (12.61)	p=0.241
Percent Adherence to Exercise Program (%)	95.53 (4.56)	97.42 (2.65)	-	p=0.120

Influence of the intervention on single and dual tasking

Significant main effects and interactions, with respect to gait parameters, are presented in Table 2. Significant interactions between group, evaluation time (pre and post) and task (single and dual task) were found with respect to step length ($F(2,41)=5.34$, $p=0.009$), step length variability ($F(2,41)=3.92$, $p=0.028$), percentage of time in double support ($F(2,41)=7.13$, $p=0.002$) and velocity ($F(2,41)=4.00$, $p=0.026$). Across both pre and post assessment, all groups were influenced (as expected) by the addition of a secondary counting task, with significantly shorter step length ($p<0.001$), greater percentage of time in double support ($p<0.001$), and slower velocity ($p<0.001$) compared to the single task condition. Post hoc analysis also revealed that at pre assessment, all groups walked with significantly greater step length variability during the dual task condition compared to the single task ($p<0.01$). However, at post assessment (but not pre assessment), only the External and Internal groups walked with significantly greater step length variability during the dual task condition compared to the single task condition ($p<0.001$), whereas the control group did not ($p=1.00$). Main effects of task were found with respect to step time ($F(1,41)=10.65$, $p=0.002$) and step time variability ($F(1,41)=7.09$, $p=0.011$), demonstrating

that participants walked with a significantly greater step time and step time variability while dual task walking compared to single task walking. With respect to single task walking, no changes to any gait parameters from pre assessment to post were found. Dual task walking ability did not change from pre assessment to post in the external or control groups. Importantly, post hoc analyses revealed that participants in the Internal exercise group walked with a significantly shorter step length ($p<0.001$) and slower velocity ($p=0.007$) while dual task walking at post assessment compared to pre (Fig 3). The Internal group also walked with a greater percentage of time in double support while dual tasking at post assessment compared to pre that approached significance ($p=0.081$; Fig 3).

Table 2: Part A gait parameter averages (Standard deviations in brackets), significant main effects and interactions.

	Single Task			Dual Task			Effects
	External	Internal	Control	External	Internal	Control	
Step Length (cm)							Group*Time* Task Interaction: F(2,41)=5.337, p=0.0087
Pre	57.00 (14.1)	54.67 (11.2)	59.01 (9.7)	54.21 (15.5)	51.22 (11.8)	55.30 (9.7)	
Post	56.02 (14.9)	53.50 (13.0)	58.46 (10.9)	52.94 (15.6)	48.62 (13.3)	55.88 (10.9)	
Step Length Variability (CV)							Group*Time* Task Interaction: F(2,41)=3.9204, p=0.02767
Pre	6.92 (5.9)	6.54 (5.8)	5.15 (2.6)	9.23 (9.3)	9.01 (9.7)	6.45 (4.5)	
Post	7.29 (5.5)	7.58 (8.7)	5.16 (2.0)	9.79 (8.9)	9.71 (11.2)	5.59 (2.6)	
Step Time (s)							Task: (F(1,41)= 10.65, p=0.002)
Pre	0.61 (0.2)	0.55 (0.1)	0.54 (0.05)	0.63 (0.2)	0.56 (0.1)	0.55 (0.1)	
Post	0.56 (0.1)	0.54 (0.1)	0.54 (0.05)	0.59 (0.1)	0.56 (0.1)	0.56 (0.1)	
Step Time Variability (CV)							Task: (F(1,41)= 7.09, p=0.011)
Pre	6.74 (8.3)	5.29 (3.2)	4.19 (1.5)	8.37 (8.2)	7.12 (9.2)	5.15 (3.2)	
Post	5.19 (2.5)	5.73 (5.6)	3.63 (1.1)	8.38 (14.7)	7.55 (10.3)	4.69 (1.7)	
Percentage of Time Spent in Double Support (%)							Group*Time* Task Interaction: F(2,41)=7.13, p=0.002
Pre	28.65 (9.2)	28.85 (5.8)	26.06 (4.6)	30.75 (9.7)	30.98 (7.6)	28.07 (4.7)	
Post	27.60 (6.9)	28.88 (7.5)	26.58 (4.9)	30.03 (8.1)	32.12 (8.8)	28.02 (5.6)	
Percentage of Time Spent in Double Support Variability (CV)							No Significant Effects or Interactions
Pre	7.18 (3.8)	6.02 (1.7)	6.19 (2.5)	7.64 (4.2)	6.55 (3.2)	6.45 (2.4)	
Post	6.90 (3.0)	7.15 (2.9)	5.84 (2.4)	7.97 (4.9)	7.01 (3.5)	6.09 (2.1)	
Velocity (cm/s)							Group*Time* Task Interaction: F(2,41)=4.00, p=0.026
Pre	101.55 (34.2)	100.53 (22.9)	110.40 (17.8)	94.50 (35.4)	93.71 (24.0)	101.30 (17.2)	
Post	102.71 (30.8)	99.53 (25.0)	108.57 (21.6)	94.01 (32.8)	88.39 (25.0)	101.69 (23.7)	

CV = Coefficient of Variation

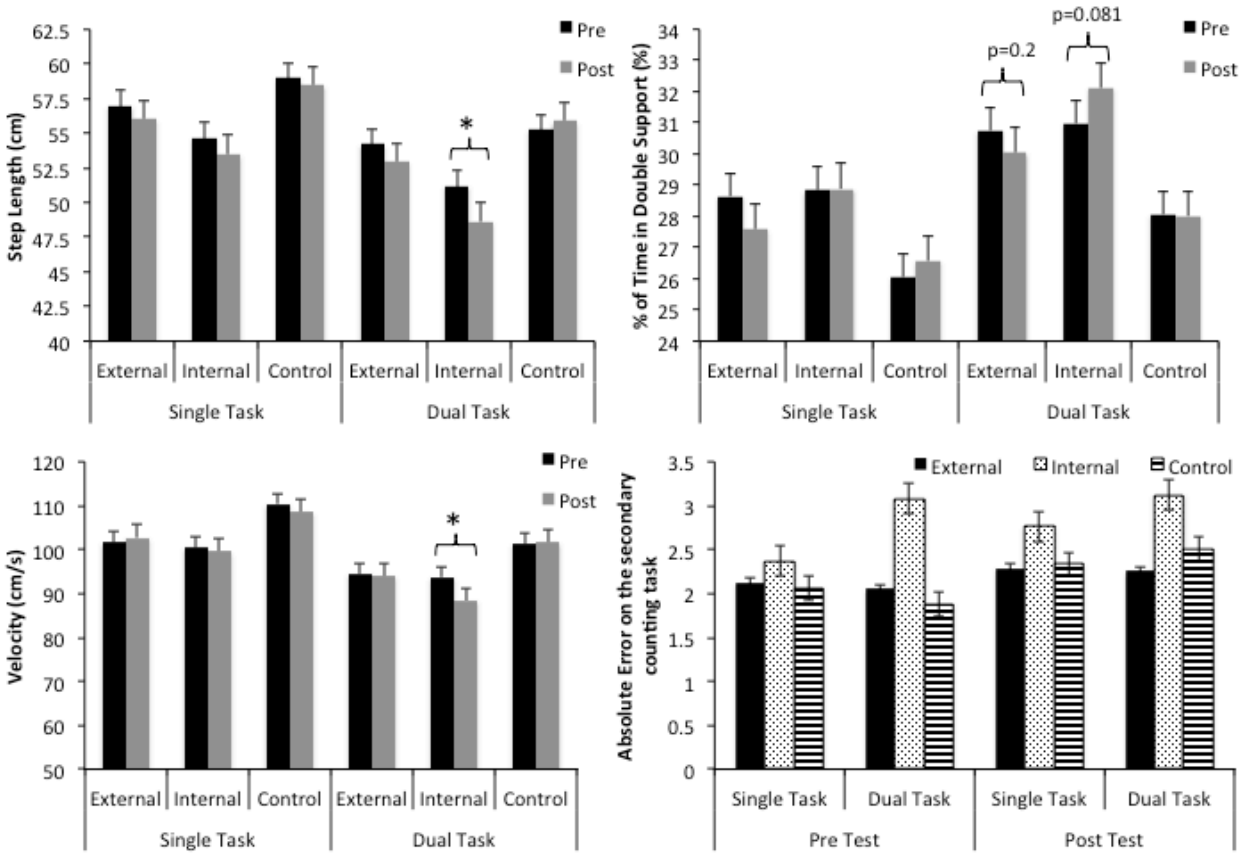

Fig 3: Graphical illustrations of part A significant gait interactions between group (External, Internal and Control), evaluation time (pre and post), and task (single task and dual task) with respect to step length (top left), percentage of time in double support (top right), and velocity (bottom left). Illustration of absolute error on the secondary digit-motoring task can also be found in the bottom right graph. * represents a significant difference at the $p<0.05$.

There were no significant main effects or interactions found for performance on the secondary digit-monitoring task employed during the dual task walking trials (Fig 3). However, it should be noted that the number of errors made on the secondary digit-monitoring task, while dual task walking, increased from pre assessment to post by 9.82% in the External group, 1.28% in the Internal group, and 33.06% in the control group.

Influence of the intervention on motor symptom severity

A significant main effect of medication state was found ($F(1,41)=90.37$, $p<0.001$), demonstrating that UPDRS-III scores were significantly greater in the OFF medication state compared to the ON state, regardless of evaluation time. A significant interaction between group and evaluation time was found in regards to UPDRS-III scores ($F(2,41)=3.89$, $p=0.028$), and Tukey's post hoc analysis revealed that motor symptom severity scores were significantly lower at post assessment compared to pre in only the External group ($p=0.002$; Fig 4) (UPDRS-III point score changes and percent improvement from pre assessment to post: External group ON = -4.58 [17.7%], OFF = -5.4 [15.7%]; Internal group ON = -3.92 [14.4%], OFF = -2.56 [8.7%]; Control group ON = +0.95 [-9.5%], OFF = +0.05 [-2.9%]).

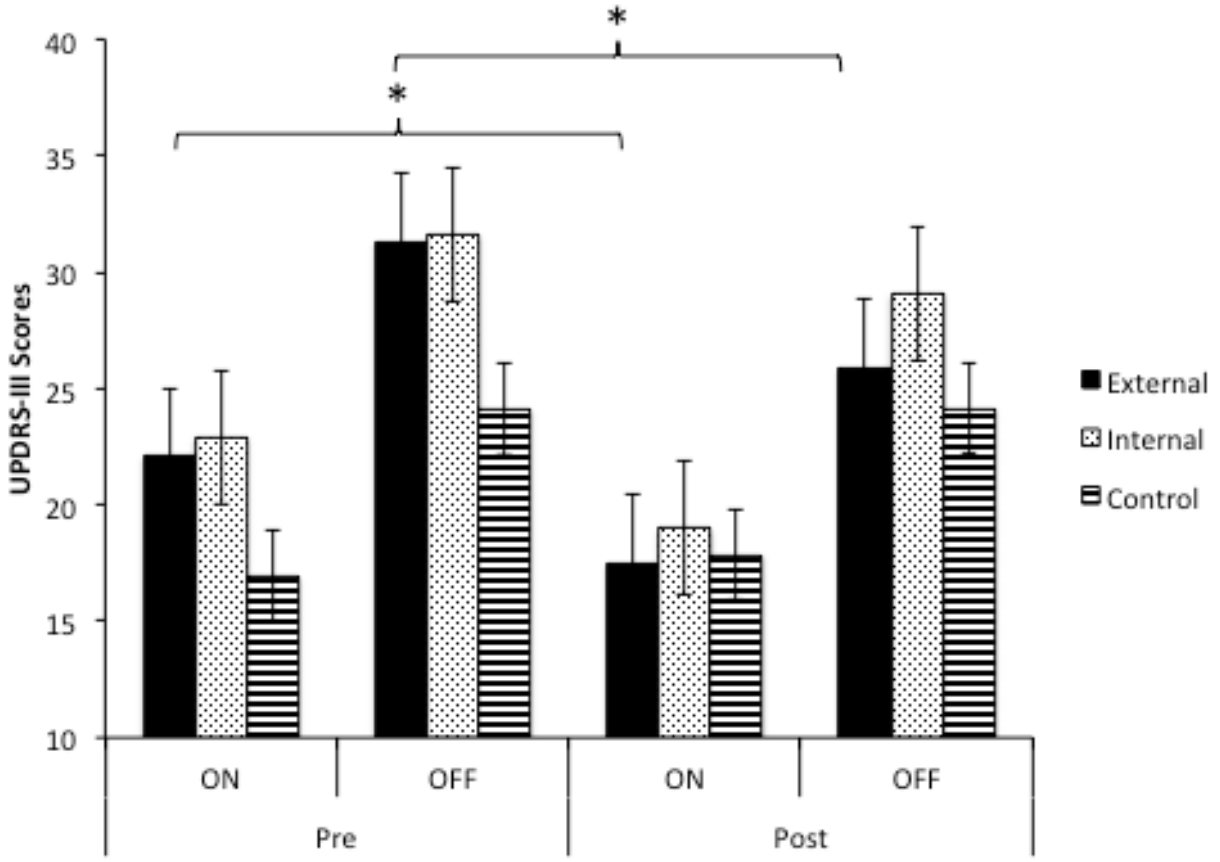

Fig 4: Graphical Illustration of the significant interaction between group (External, Internal, and Control) and evaluation time (pre and post assessment) for the Unified Parkinson's disease Rating Scale Motor subsection-III (UPDRS-III). UPDRS-III Point Changes from pre assessment to post: External OFF = -5.4, ON = -4.58; Internal OFF = -2.56, ON = -3.92; control OFF = +0.05, ON = +0.95.

Secondary Measures

Average pre and post outcomes for secondary measures (MOCA, LED, CHAMPS, and PDQ-39) can be found in Table 3. The only significant finding was a group by time interaction for PDQ-39 score ($F(2,37)=4.06$, $p=0.025$). Tukey's post hoc did not reveal any significant differences between groups or evaluation time points. However, on the PDQ-39 in which greater numbers indicate poorer reported quality of life, scores increased in both the external and control group, whereas scores decreased in the internal group.

Table 3. Part A secondary measures.

Measure		External	Internal	Control	Effect
MOCA	Pre	23.5 (4.64)	23.5 (4.22)	22.8 (6.38)	Group: p=0.844 Time: p=0.083 Group*Time: p=0.793
	Post	23.87 (5.63)	24.16 (4.69)	23.50 (6.13)	
Levodopa Equivalent Dose (mg/day)	Pre	647.97 (232.86)	594.04 (358.25)	867.73 (674.62)	Group: p=0.214 Time: p=0.186 Group*Time: p=0.316
	Post	630.45 (220.75)	596.54 (358.32)	858.64 (684.38)	
Activity Level (CHAMPS) (kcal/week)	Pre	3056.98 (3290.96)	4446.60 (2862.48)	4420.00 (2331.97)	Group: p=0.666 Time: p=0.068 Group*Time: p=0.733
	Post	4326.30 (4649.48)	5280.89 (3937.88)	4705.66 (1743.92)	
Activity Level > 3METs (CHAMPS) (kcal/week)	Pre	1479.37 (2050.33)	2956.68 (2408.31)	2968.55 (2240.72)	Group: p=0.361 Time: p=0.520 Group*Time: p=0.857
	Post	2083.19 (2659.12)	2880.80 (2963.80)	2826.29 (1819.40)	
PDQ-39	Pre	39.33 (27.08)	38.73 (20.35)	37.36 (24.27)	Group: p=0.653 Time: p=0.499 Group*Time: p=0.025
	Post	42.38 (31.35)	31.72 (19.83)	41.30 (25.4)	

Montreal Cognitive Assessment = MoCA; Community Health Activities Model Program for Seniors questionnaire = CHAMPS; kilocalorie = kcal; Metabolic Equivalent = MET; 39-item Parkinson's disease Questionnaire = PDQ-39

PART B: Pre, Post, and Washout Assessments

Participant demographics

Part B participant demographic effects can be found in Table 4. No significant differences were found between groups at pre assessment.

Table 4. Part B participant demographics as group averages (standard deviation in brackets).

Demographics	External	Internal	Effect
Number (M/F)	16 (12/4)	16 (12/4)	
Age (years)	68.81 (10.05)	73.69 (8.57)	p=0.154
Number of Years Since Diagnosis	6.38 (5.02)	6.38 (4.21)	p=1.000
Weight (kg)	75.86 (23.99)	83.26 (17.89)	p=0.327
Percent Adherence to Exercise Program (%)	95.64 (4.66)	97.54 (2.28)	p=0.174

Influence of the intervention on single and dual tasking

Table 5 presents all significant Part B gait parameter main effects and interactions. With respect to step length, a significant interaction between group and task was found ($F(1,23)=4.56$, $p=0.044$), although post hoc only revealed a main effect of task, in that both the External and Internal group walked with a significantly shorter step length while dual task walking compared to single task walking ($p<0.02$). Main effects of task were found, and demonstrated that participants walked with a significantly greater step length variability ($F(1,23)=11.07$, $p=0.003$), step time ($F(1,23)=7.60$, $p=0.011$), step time variability ($F(1,23)=5.87$, $p=0.023$), percentage of time in double support ($F(1,23)=38.40$, $p<0.001$), and slower velocity ($F(1,23)=39.15$, $p<0.0001$)

while dual tasking compared to single tasking, regardless of training group or evaluation time. Significant main effects of evaluation time, with respect to step time ($F(2,46)=5.43$, $p=0.008$) and percentage of time in double support ($F(2,46)=4.25$, $p=0.02$), were found (Fig 5). Post hoc analysis showed that participants demonstrated significantly shorter step time ($p=0.005$) and lower percentage of time in double support ($p=0.014$) at washout compared to pre assessment, but not post.

Table 5: Part B gait parameter averages (standard deviations in brackets), significant main effects and interactions.

	Single Task		Dual Task		Effect
	External	Internal	External	Internal	
Step Length (cm)					Group*Task Interaction: F(1,23)=4.56, p=0.044)
Pre	55.93 (14.5)	53.75 (12.3)	53.17 (16.2)	49.57 (12.6)	
Post	55.47 (15.6)	52.63 (13.8)	52.43 (16.2)	47.16 (14.0)	
Washout	55.77 (14.1)	55.63 (14.6)	52.70 (14.6)	51.16 (12.7)	
Step Length Variability (CV)					Group*Time*Task*Trial Interaction: F(4,92)=3.16, p=0.017
Pre	7.47 (6.2)	6.54 (6.1)	9.69 (10.0)	9.23 (10.6)	
Post	7.74 (5.8)	7.78 (9.3)	10.11 (9.5)	10.23(12.0)	
Washout	7.74 (8.5)	7.61 (14.9)	8.38 (7.4)	8.82 (17.6)	
Step Time (s)					Time: (F(2,46)=5.43, p=0.008) Task: (F(1,23)=7.60, p=0.011) Trials: (F(2,46)=18.06, p<0.001)
Pre	0.63 (0.2)	0.55 (0.1)	0.65 (0.2)	0.56 (0.1)	
Post	0.57 (0.1)	0.54 (0.1)	0.60 (0.1)	0.56 (0.1)	
Washout	0.50 (0.2)	0.50 (0.1)	0.53 (0.2)	0.51 (0.2)	
Step Time Variability (CV)					Task: (F(1,23)=5.87, p=0.023) Trials: (F(2,46)=3.83, p=0.029)
Pre	7.35 (9.0)	5.21 (3.4)	8.88 (8.8)	7.48 (10.3)	
Post	5.36 (2.7)	6.05 (6.3)	8.89 (16.0)	8.04 (11.4)	
Washout	4.98 (3.8)	4.76 (3.8)	5.66 (3.4)	6.72 (11.0)	
Percentage of Time Spent in Double Support (%)					Time: (F(2,46)=4.25, p=0.020) Tasks*Trial Interaction: F(2,46)=3.5907, p=0.03556
Pre	29.60 (9.8)	29.38 (6.2)	31.64 (10.2)	31.92 (8.1)	
Post	27.99 (7.3)	29.09 (8.0)	30.36 (8.7)	32.85 (9.5)	
Washout	24.44 (11.4)	26.07(10.3)	26.64 (12.2)	28.34(11.1)	
Percentage of Time Spent in Double Support Variability (CV)					Trials: (F(2,46)=5.82, p=0.006)
Pre	7.47 (4.0)	5.94 (1.9)	7.72 (4.4)	6.74 (3.4)	
Post	6.99 (3.1)	7.01 (2.8)	8.04 (5.1)	6.80 (2.8)	
Washout	6.10 (3.4)	6.30 (2.7)	6.00 (3.2)	5.94 (2.9)	
Velocity (cm/s)					Task: (F(1,23)=39.15, p<0.001) Trial: F(2,46)=16.58, p<0.001)
Pre	98.08 (35.7)	99.09 (24.9)	90.77 (36.6)	90.63 (25.6)	
Post	100.77 (32.5)	97.48 (26.1)	92.40 (34.4)	84.92 (25.8)	
Washout	93.62 (37.3)	98.73 (37.3)	88.47 (42.1)	89.69 (34.5)	

CV = Coefficient of Variation

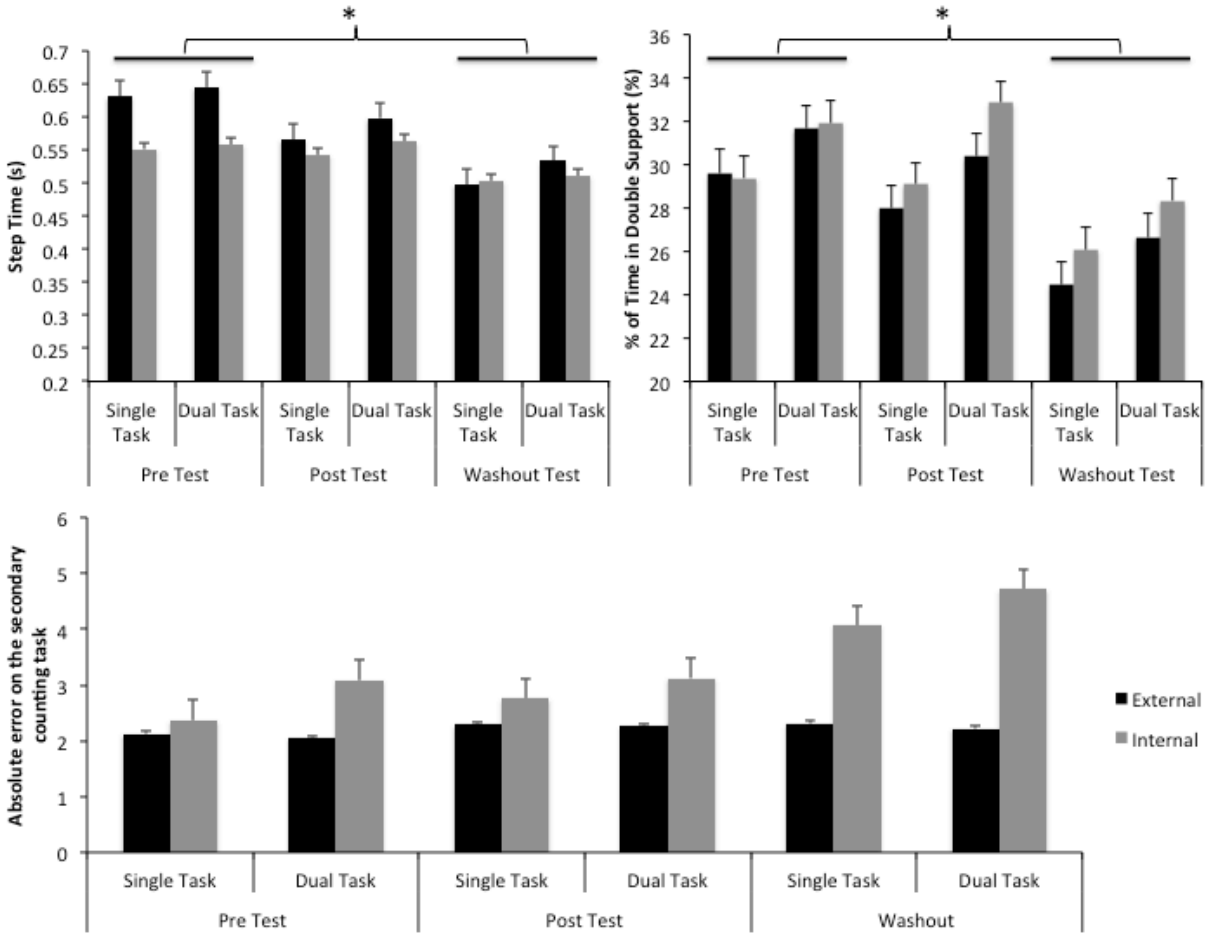

Fig 5: Graphical illustrations of part B significant gait parameter main effects of evaluation time (pre, post and washout) with respect to step time (top left) and percentage of time in double support (top right). Absolute error on the secondary digit-motoring task can also be found in the bottom graph. * represents a significant difference at the $p<0.05$.

No significant main effects or interactions were found for performance on the secondary digit-monitoring task employed during the dual task walking trials. However, it is important to note that from pre assessment to washout, participants in the External group increased the number of errors on the secondary task while dual task walking by 8.23%, and decreased by 1.58% from post assessment to washout. In contrast to these minimal changes, the Internal group increased the number of errors on the secondary task while dual task walking by 53.04% from pre assessment to washout, and 51.11% from post assessment to washout (Fig 5).

Influence of the intervention on motor symptom severity

Illustrated by a significant main effect of evaluation time ($F(2,52)=11.09$, $p<0.001$), UPDRS-III scores were significantly lower at post assessment compared to pre ($p<0.001$) in both exercise groups, and these lower scores persisted to the washout assessment where UPDRS-III scores were significantly lower at washout assessment compared to pre ($p=0.001$; Fig 6). No other main effects or significant interactions were found.

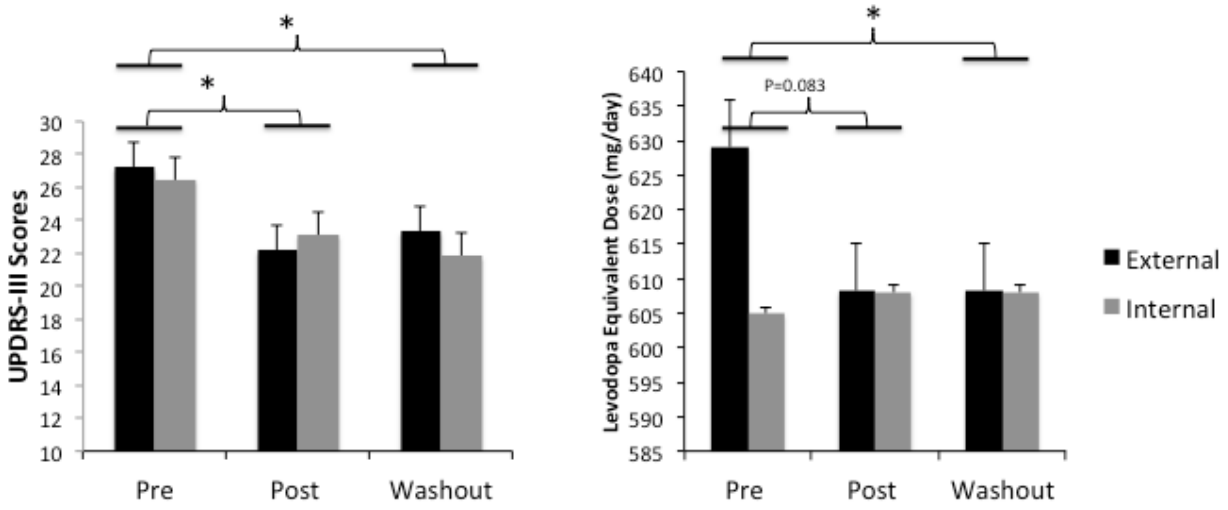

Fig 6: Graphical Illustration of the significant main effect of evaluation time (pre, post, and washout) for the Unified Parkinson's disease Rating Scale Motor subsection-III (UPDRS-III) (left graph) and levodopa equivalent dosage (right graph). * represents a significant difference at the $p<0.05$.

Secondary Measures

Average pre, post and washout outcomes for secondary measures (LED and CHAMPS) can be found in Table 6. A significant main effect of evaluation time was found for LED ($F(2,60)=4.04$, $p=0.023$). Tukey's post hoc uncovered that on average, participants in the exercise groups significantly decreased their LED per day from pre assessment to washout ($p=0.026$, Fig 6 above).

Table 6. Part B secondary measures.

Measure		External	Internal	Effect
Levodopa Equivalent Dose (mg/day)	Pre	629.00 (220.01)	604.89 (384.26)	Group: p=0.959 Time: p=0.023 Group*Time: p=0.652
	Post	608.19 (202.23)	608.02 (384.25)	
	Washout	564.53 (138.02)	572.70 (350.39)	
Activity Level (CHAMPS) (kcal/week)	Pre	3150.82 (3768.68)	4347.89 (3045.56)	Group: p=0.981 Time: p=0.067 Group*Time: p=0.755
	Post	5134.12 (5040.94)	4801.18 (2861.29)	
	Washout	3494.48 (1949.46)	4138.51 (2828.65)	
Activity Level > 3METS (CHAMPS) (kcal/week)	Pre	1616.92 (2329.71)	2944.36 (2573.73)	Group: p=0.689 Time: p=0.305 Group*Time: p=0.713
	Post	2439.10 (2949.12)	2528.42 (2077.11)	
	Washout	1509.34 (974.17)	2077.61 (2188.94)	

Montreal Cognitive Assessment = MoCA; Community Health Activities Model Program for Seniors questionnaire = CHAMPS; kilocalorie = kcal; Metabolic Equivalent = MET

DISCUSSION

This is the first single-blind randomized controlled trial investigating the effects of goal-based exercise with an external and internal focus of attention on Parkinson's disease. However, the proposition that external focus of attention exercise should be beneficial for Parkinson's disease has been in existence for nearly a decade. It was hypothesized that if an external focus of attention does promote the use of automatic control during an exercise program, then the ability to walk and complete a secondary task (dual task) might be improved in individuals with Parkinson's disease. Further, if the automatic networks are basal ganglia dependent, then it might

be possible that overall motor symptom severity might also improve with externally focused exercise. Since gait during the dual task did not significantly improve from pre to post (ie. no increases in step length, decreases in percentage of time in double support, nor step-to-step variability decrease was found) our hypothesis was not supported. It could even be suggested that the dual task performance was worse at post assessment compared to pre, since error on the secondary task increased by 9.82% (not significant), indicating that gait may have become more consciously controlled. However, since a 9.82% increase in dual task error indicates only a 0.2 digit error, it could be argued that this increase does not demonstrate a meaningful change in dual task performance. The only finding that might signify improved dual tasking ability in the External group was a non-significant decrease in percentage of time spent in double support ($p=0.20$, Fig 3) while dual tasking at post assessment compared to pre, indicating greater dynamic stability. Nevertheless, these results might suggest that either the external focus of attention exercise increased the demand of walking on conscious control, did not improve upon functioning of participants' automatic control networks, or that improvements to automatic processes were not translated to the walking. It is also possible that improvements began to emerge (non-significant decrease in percentage of time in double support while dual tasking), but a longer exercise program may be necessary to fully improve upon the complex neuronal connections associated with dual task walking.

In contrast, it was hypothesized that an internal focus of attention during completion of a goal-based exercise program might interfere with dual task walking performance since this training was expected to increase reliance on conscious control of movement. Interestingly, this hypothesis was supported, in that dual tasking step length and velocity significantly decreased from pre assessment to post in only the Internal group. The percentage of time spent in double

support while dual tasking also increased in the internal group from pre assessment to post (which might indicate worse dynamic stability [72–74]), but this only demonstrated a trend towards significance (p=0.081). It is also important to note that error on the secondary task did not increase in the internal group after the intervention. These findings might suggest that an internal focus of attention during goal-based exercise increased reliance on a less damaged compensatory conscious control system, in that control of gait became more consciously demanding after the internal focus of attention exercise [4–6,23,25–28]. This may have left participants more susceptible to deterioration in gait parameters when attentional focus was directed away from one's own movements after the exercise program. These findings align with those reported by Sage and Almeida (2009) in which individuals with Parkinson's disease improved conscious movement control, but walked with a greater step length variability after a 12-week PD-SAFEx™ program that directed attention towards sensory information (similar to the directions in the present study provided to the Internal group). Other goal-based exercise studies that have not found increased gait demand on conscious control [64,75,76] may have not instructed participants to focus attention internally on sensory information, and therefore, may not have increased the degree of reliance on compensatory conscious control systems in the associated individuals with Parkinson's disease. Nonetheless, it would appear that internal focus of attention exercise increased one's reliance on conscious control networks, hindering dual task performance, whereas after an external focus of attention exercise program, no changes to notwork predominance (conscious or automatic) seemed to emerge. To gain further understanding of the potential effects that the differing exercise instructions had on the underlying function of automatic and conscious control networks, the second aim of the study

explored the influence of externally and internally focused exercise on UPDRS-III scores that reflect basal ganglia function [67], central to automatic control.

Since automatic processes rely on basal ganglia function, particularly dorsal striatal areas more affected by the progressive pathology of Parkinson's disease [2,4–6], it was expected that goal-based exercise combined with an external focus of attention (promoting use of automatic systems) would provide greater improvements to Parkinson's disease motor symptoms compared to internally focused exercise (believed to promote the use of ventral conscious control networks less affected by disease progression). In support of this hypothesis, it was found that UPDRS-III scores improved significantly from pre assessment to post in only the external focus of attention exercise group (UPDRS-III changes: External OFF = -5.4, ON = -4.58; Internal OFF = -2.56, ON = -3.92; control OFF = +0.05, ON = +0.95) (Fig 4). Although there was no interaction with medication state, anecdotally, it appeared that the OFF medications UPDRS-III improvement in the external group was the driving force for the interaction. The OFF medication improvement in UPDRS-III scores in the external group was also the only change to reach clinical significance (greater than a five point change)[77]. These results might suggest that since the UPDRS-III assessment reflects functionality of the basal ganglia (especially OFF medications in which dopamine replacement is not masking endogenous functioning), the external focus of attention exercise was able to significantly improve basal ganglia function, whereas focusing internally while completing the exercise program was not. The reason for the differing effects of the exercise interventions on UPDRS-III scores may be the result of recruiting opposing networks that project through the basal ganglia. For instance, our recent work (see Beck and Almeida, 2016) suggests that when an external focus of attention is adopted, one might recruit automatic processes that project through the dorsal region of the striatum (from the sensorimotor cortex),

the same area of the basal ganglia where degeneration initiates and is more severe compared to the ventral aspects of the striatum [4–6]. Therefore, combining goal-based exercise with an external focus of attention may have increased sensorimotor drive [57] into the more damaged dorsal area of the basal ganglia, potentially promoting improvements to these impaired circuits that were revealed as improvement to motor symptoms [26,78–81]. Unexpectedly, these improvements to basal ganglia functioning after an exercise program that instructed external focus did not foster improvements to dual task walking, as previously mentioned. This may be due to vast brain regions that contribute to walking, especially dual task walking, in addition to the automatic system that includes the basal ganglia [82]. The automatic control networks that comprise basal ganglia functioning may have been enhanced by the external focus of attention exercise, but erroneous functioning in the remaining areas of the brain necessary for dual tasking [18] may have masked the potential benefits to automatic system processing. It is important to note, however, that although improvements to dual task walking were not found in the External group, this group still received benefits to motor symptoms while protected from detriments to dual task walking that were found in the internal focus of attention exercise group. This may also be further explained by the long-term progression of disease pathology.

The results from a recent study by Beck and Almeida (2016) suggest that an internal focus of attention may recruit conscious control processes that project through the ventral region of the striatum [59]. Thus, if ventral areas of the striatum were relatively preserved in participants randomized to the internal focus of attention exercise group, there may not have been opportunity for improved functioning through these ventral circuits that may be without a large degree of dysfunction associated with movement [83]. In general, combining goal-based exercise with an internal focus of attention may have increased neuronal drive into less damaged

ventral areas of the basal ganglia as opposed to more dorsal impaired areas, thus impeding potential for greater improvements to basal ganglia functioning that the external focus of attention exercise provided for Parkinson's disease. This is further supported by increased dual task walking impairment found at post assessment in the Internal group, which suggested that recruitment of the ventral striatum areas involved in conscious control of movement increased reliance on these circuits for movement control. To add some confirmation to these suggestions, we lastly aimed to investigate if changes to dual task walking behaviour and symptom severity (as a result of the goal-based exercise program) persisted for 8 weeks following cessation of the exercise program.

If changes to neuronal connections took place (neuroplasticity) after the present intervention to either automatic and/or conscious control networks, one might expect these changes to persist throughout an 8 week washout [26,61,60,62–65]. The results from Part B of the present study demonstrate that from pre assessment to washout, both groups demonstrated significantly decreased step time and percentage of time in double support while single and dual task walking. However, as can be observed in figure 5, the External group demonstrated increased number of errors on the secondary task by only 8.23%, whereas the Internal group increased number of errors on the secondary task by 53.04%. This suggests that at washout, the External group prioritized the secondary task and demonstrated significant improvements to dual task walking. In contrast, the internal group prioritized walking instead of the secondary task, which most likely reflects that improvement to step time and percentage of time spent in double support was the result of consciously controlling gait, and not representing improved dual task ability at washout assessment compared to pre. These findings might suggest that improvements to dual task ability induced by external focus of attention exercise could have been subject to a

delayed effect, in that the exercise program may have provided the training foundation necessary to enhance automatic processes, but more time was needed to further establish an efficient use of this information. This is speculative, and requires further investigation. However, without collecting gait data from the control group at washout, a practice effect cannot be ruled out since the washout assessment was the third time participants were subject to the dual task protocol. Regardless, to confirm where the neurological improvements may have taken place in the basal ganglia after external and internal focus of attention exercise programs for individuals with Parkinson's disease, future work should utilize three-dimensional [^{18}F] radiolabeled N-(3-fluoropropyl)- 2 β -carboxymethoxy-3 β -(4-iodophenyl) nortropane positron emission tomography to investigate post-synaptic functioning at the dorsal and ventral striatum. This would provide evidence to whether external and internal focus of attention exercise can improve functioning at the dorsal and ventral striatum, respectively.

The final important finding to report was a significant main effect of evaluation time, which demonstrated that UPDRS-III scores (ie. participant motor symptom severity) were significantly lower at post assessment compared to pre, and persisted at this level 8-weeks after the exercise program had ceased. What is most unique about these findings is that despite our instructions to participants to refrain from changing aspects of their dopaminergic medication regime, participants required significantly less dopaminergic medications consumed each day from pre assessment to washout. Therefore, improved symptom severity persisted for 8 weeks after cessation of the exercise program despite decreased levels of dopamine consumed each day. Due to a realm of unpleasant side effects that may accompany medications, these findings are novel and carry great importance.

CONCLUSION

Minimal evidence was found to suggest that external focus of attention exercise could provide benefits to dual task walking in Parkinson's disease. However, dual task walking ability did significantly improve 8-weeks after exercise cessation (compared to pre assessment), suggesting that externally focused exercise may have provided a foundation for continued improvements to dual task walking over the 8-weeks following the intervention. Internal focus of attention exercise proved detrimental to dual task walking. Finally, although benefits to motor symptoms were found after both externally and internally focused exercise, focusing externally on the movement of a manipulated object while exercising provided greater improvements to UPDRS-III scores in Parkinson's disease.

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CHAPTER 3: GENERAL DISCUSSION

The purpose of the present study was to investigate whether combining a goal-based exercise program with an external focus of attention might improve dual task walking in individuals with Parkinson's disease. We hypothesized that if an external focus of attention promotes the use of one's automatic control networks [1–7], then completing a goal-based exercise program while focusing externally on labels attached to individuals' limbs might improve dual task walking in those with Parkinson's disease. In contrast, promoting an internal focus of attention during goal-based exercise was expected to hinder dual task walking performance since this training might increase reliance on conscious control of movement [1–7]. After the completion of an 11-week external focus of attention exercise program, dual task walking did not significantly improve after the exercise program, but rather gait parameters throughout single and dual task walking did not change from pre assessment to post. In contrast, dual task walking was negatively effected by the internal focus of attention exercise program, in that step length and velocity significantly decreased while dual task walking from pre assessment to post. Interestingly, after an 8-week washout period, where individuals in the exercise program were not asked to attend exercise sessions, both the external and internal focus of attention exercise groups demonstrated improvements to dual task walking, in that step time and percentage of time in double support significantly decreased from pre assessment to the washout. However, the internal group increased error on the secondary task by 53% while walking, whereas the external group increased error by 8% (from pre assessment to washout). This would indicate that the internal group prioritized their walking as opposed to the secondary task, and therefore internal focus of attention exercise did not actually improve dual task walking, but rather increased the requirement for conscious control of gait. In contrast, since the external

group demonstrated significantly improved gait while dual tasking at washout compared to pre, and the error on the secondary task did not change a meaningful amount, external focus of attention exercise did improve dual task walking in Parkinson's disease, although there was a delayed effect. These changes in dual tasking ability from pre assessment to post to washout are interesting, but the potential mechanisms underlying these changes are various. To determine whether these changes were mediated by dopamine modulation in the basal ganglia that is critical for automatic control processes, motor symptom severity was measured.

Furthermore, since automatic control processes rely on basal ganglia function [8–16], it was expected that goal-based exercise combined with an external focus of attention would lead to greater motor symptom improvements than an internal focus of attention, which may promote the use of conscious control processes less influenced by the basal ganglia. In support of these hypotheses, UPDRS-III scores significantly decreased from pre assessment to post (improved) in only the external focus of attention exercise group (Fig 4), potentially signifying improved basal ganglia (which are implicated in automatic control networks) function [17]. Separate analyses (subset of each group that completed pre and post assessment) also demonstrated a main effect of time, in which both exercise groups showed significant improvements from pre assessment to post that persisted to the washout period. Although these findings are behavioural, they do align with findings from previous literature, and allow for inferences to be made regarding the mechanisms underlying external and internal focus of attention exercise.

THE MECHANISM BEHIND EXTERNAL AND INTERNAL FOCUS OF ATTENTION EXERCISE

In general, it would appear that there are two primary circuits that are at play (Please refer to Fig 7 below). Instructing participants to focus externally on the manipulation of an object

(whether it be controlling a platform underneath one's feet or pushing coloured labels attached to their limbs [Chapter 2]) during movements may have promoted recruitment of automatic control networks that project through the dorsal areas of the striatum [7,8,15,16,18–20]. These dorsal areas of the striatum are primarily involved in the basal ganglia motor loops [8,10,11,21–23], and typically more compromised in Parkinson's disease in the initial stages [24–26]. Despite the damage to dorsal striatal areas, previous work suggests that individuals with Parkinson's disease are able to effectively recruit these automatic control areas [20,27]. Thus, during exercise where an external focus of attention was used, the dorsal striatum may have been recruited, potentially promoting changes somewhere in the complex circuitry involved in automatic processing, providing benefits to symptoms of Parkinson's disease, as well as delayed improvements to a measure that reflects automatic processing (ie. dual tasking).

In contrast, instructing individuals to focus internally on limb movements (such as pushing their knee up during the exercise program) may have promoted recruitment of conscious control networks that project through ventral areas of the striatum [7,8,15,16,18–20]. These ventral areas comprise more cognitive and limbic loops that pass through the basal ganglia [8,10,11,21–23], and are typically more preserved in the earlier stages of Parkinson's disease [24–26]. Therefore, the effect of exercise may have been solidification of conscious control networks that pass through the ventral striatum [28], explaining the greater demand on conscious control that gait posed after the internally focused intervention, supported by the slower walking with shorter steps while dual task walking at post assessment compared to pre. The reasoning for only subtle improvements to UPDRS-III were most likely a potential ceiling effect, in the sense that there may not have been as great of a capacity for improvement to the less damaged ventral striatum (compared to dorsal striatum). With reference to previous research, changes in

behaviour after the external and internal focus of attention exercise programs may have been due to neurological changes within the basal ganglia.

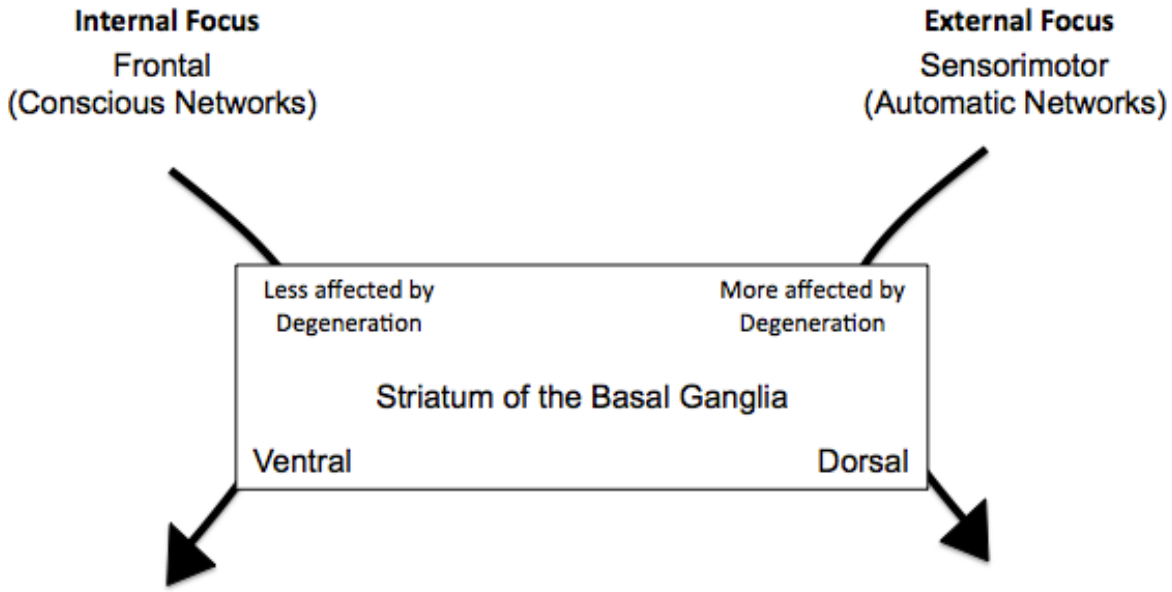

Fig 7. Theoretical framework for the mechanism underlying an external and internal focus of attention during movement in Parkinson's disease.

Previous work has demonstrated that after an exercise program that improved UPDRS-III score in individuals with Parkinson's disease, ability to inhibit excitatory stimulation administered through transcranial magnetic stimulation (a direct measure of basal ganglia functioning) also improved [29]. When excitatory magnetic stimulation is applied through transcranial magnetic stimulation into the motor cortex, prior to an efferent signal, there is a cortical silent period in which the brain attempts to inhibit the incoming excitation [30]. This inhibition that produces the cortical silent period is interceded by GABA-B receptors mediated

by the basal ganglia [31]. It is therefore no surprise that the cortical silent period is consistently shorter in individuals with Parkinson's disease [30]. In light of this, Fisher and colleagues (2008) proposed that the lengthening in cortical silent period that they found after an exercise program was the result of improved propagation through the basal ganglia. In relation to the findings from the present study, this might indicate that improved UPDRS-III scores found at post assessment compared to pre (Part A) in only the external focus of attention exercise group was the result of improved basal ganglia functioning. Since an external focus of attention promotes recruitment of automatic control processes that largely implicate the basal ganglia, goal-based exercise combined with an external focus of attention may have facilitated greater motor symptom improvements than an internal focus of attention. Improvements to basal ganglia functioning after exercise may be the result of many different events at the microscopic level. Despite the degeneration of the basal ganglia that occurs in Parkinson's disease, previous work has demonstrated that neuroplastic changes in this sub-cortical area of the brain affected in Parkinson's disease can take place after exercise.

The mechanism underlying improved basal ganglia function may be attributed to neuro-restorative and protective properties of a brain-derived neurotrophic factor [32] found to increase in Parkinson's disease with exercise [33]. Since individuals with Parkinson's disease possess preserved nerve-growth factor binding sites within the striatum despite the neurodegeneration [34], this mechanism holds merit. Exercise has the potential to foster numerous additional physiological changes in the basal ganglia, such as increasing striatal dopamine [35], increasing the expression of D1 and D2 dopamine receptors (post-synaptic dopamine receptors of the striatum) while down-regulating the expression of dopamine active transporters (that promote dopamine reuptake back into the presynaptic substantia nigra cell that produces dopamine)

[36,37], enhancing the binding potential of dopamine to D2 receptors of the dorsal striatum [38], and even increasing the structural volume of the striatum [39]. Therefore, the improvements to symptom severity found after external focus of attention exercise may have been the result of multiple neuroplastic changes in the basal ganglia presented above. For example, since external focus of attention exercise is believed increase sensorimotor drive [7] and recruit the damaged dorsal striatum, D2 receptor up-regulation and dopamine active-transporter down-regulation may have taken place in this area, providing benefits to motor symptoms and eventually functioning of automatic control processes since dual tasking ability improved at washout assessment compared to pre. If this were the case, we might expect that if a transcranial magnetic stimulation protocol were utilized before and after the present study, such as that employed by Fisher et al. (2008), a lengthening of the cortical silent period might be found after the external focus intervention, but not the internal focus intervention. In contrast, since internal focus of attention exercise is believed to recruit the preserved ventral striatum, D1 receptor up-regulation at the ventral striatum and dopamine active-transporter down-regulation in this area may not provide further benefits (ceiling effect). However, cholinergic activity in circuitry between the frontal areas, such as the anterior cingulate cortex, and the ventral striatum may have strengthened after internal focus of attention exercise [28]. This is supported by previous work that has demonstrated greater specialization of the anterior cingulate cortex in instructors of Tai Chi (goal-based exercise in which attention is guided towards one's movement, similar to the internal instruction) compared to a control group [28]. More effective anterior cingulate cortex specialization would foster improved error detection [40] and potentially promote greater reliance on conscious control, providing explanation for impaired dual tasking ability after internally focused exercise.

SHOULD AN EXTERNAL OR INTERNAL FOCUS OF ATTENTION EXERCISE BE APPLIED TO A CLINICAL SETTING?

Goal-based exercise combined with an external focus of attention was able to significantly improve motor symptoms and eventually, dual task walking ability to an extent. Despite these delayed improvements to dual task walking, if individuals with Parkinson's disease were interested in enhancing dual task performance more efficiently without the aim to improve symptoms, external focus of attention exercise may not be as effective as other therapeutic strategies. For example, previous work has demonstrated that one dual task training (combination of gait training and working memory language tasks) session led individuals with Parkinson's disease to increase step length and velocity while dual tasking [41,42]. Longer dual task gait training interventions [43–45] have found similar results. Most interesting, dual task training significantly decreased stride time variability while walking and completing a secondary task [45], which is typically not improved by dopaminergic medication [46,47]. Most recently, a well-conducted single-blind randomized controlled trial with longer duration (10-weeks) found that training balance while dual tasking in Parkinson's disease improved performance on the secondary task significantly without greater interference to walking [48]. The findings from the present study suggest that directly training one's ability to dual task might provide more effective improvements to dual tasking ability in Parkinson's disease compared to an external focus of attention exercise, but without the level of benefits to motor symptoms that were demonstrated with this intervention. For instance, severity of motor symptoms was significantly lowered by the end of the external focus of attention exercise program, and persisted 8-weeks after the program had ceased. This was even the case despite a significant decrease in dose of dopaminergic medications consumed each day by participants. Due to various side effects that accompany

medications for Parkinson's disease, these findings carry clinical importance. Improving upon the severity of symptoms while decreasing the amount of unpleasant side effects are goals of any physician. But how do these benefits to motor symptom severity compare with other previously conducted goal-based exercise programs?

To date, thirty-two exercise studies classified as goal-based with at least a quasi-randomization protocol have been conducted that assessed UPDRS-III scores in Parkinson's disease [49–80]. Twenty of these studies reported a significant improvement in motor symptom severity. Cugusi et al. (2015), Frazzita et al. (2012), Ganeson et al. (2014, 2015), Monteiro et al. (2016), Picelli et al. (2012) and Sale et al. (2013) all reported significant improvements in UPDRS-III scores after gait training exercises (reported range of improvement from 5.8 - 16.0 points). Studies conducted by Dashtipour et al. (2015) and Ebersbach et al. (2014) demonstrated that emphasis on increasing movement amplitude (LSVT BIG) also significantly improves UPDRS-III scores (6.8 and 6.6 point improvements, respectively). Moreover, Sage and Almeida (2011) further showed that focusing attention on sensory feedback during exercise significantly improved symptom severity, more so than aquatic, aerobic, and strength training exercises (6.7 points). Interestingly, various forms of dancing, including Tango and Irish set dancing, have been found to improve motor symptom severity as well (ranging from 4.1 – 12.55 points) [56,63,71]. UPDRS-III improvements were also found after simple physical therapy exercises with various modalities of intervention (ranging from 4.1 – 13.0 point decreases) [54,66,69,70,72,79]. Notably, the goal-based intervention with the largest sample size and most effective methodology investigated the influence of Tai Chi on balance and fall prevention in Parkinson's disease, reporting an 8.05-point decrease with no associated adverse effects [61]. Although these goal-based exercise interventions appear to provide significant improvements,

these studies were examined carefully since multiple limitations were evident and many confounding effects could have influenced results. Thus, comparing across studies provides only superficial indication as to how effective the present intervention was for motor symptom improvements.

In general, the findings from the current study would suggest that adopting an external focus of attention (and internal focus of attention to a lesser extent) during goal-based exercise provides benefits to UPDRS-III scores similar to those published by other groups. However, previous work, such as that by Sage and Almeida (2010), has demonstrated that directing focus towards sensory information (homologous to the internal focus of attention exercise intervention) provided significant benefits to motor symptoms. Potential reasoning for contradicting results between the present study and previous work that has promoted an internal focus of attention might be due to the mechanism proposed in figure 7 above. Depending on the severity of disease progression (ie. more or less degeneration that has begun to effect ventral striatum areas) and the instruction provided by the instructor (a precise instruction for an internal focus as opposed to an ambiguous instruction), variable improvements may be found. For example, a group of individuals with Parkinson's disease who were further along in the disease progression (greater ventral striatum degeneration) and instructed to focus attention internally might receive similar benefits to motor symptoms as a group of individuals with Parkinson's disease that had less severe symptoms and were instructed to focus externally throughout the intervention. Whereas, a group of individuals with Parkinson's disease who have only minor motor symptoms would be predicted to not receive a significant benefit from focusing internally during exercise (based on the proposed mechanism). Thus, contradicting findings across exercise intervention studies may very well be the result of differing symptom severities across studies, as well as variable

instruction that promotes recruitment of striatal projections. Another potential confounding influence might be dopaminergic medication. Until the present study, no goal-based intervention has investigated the effect of the exercise program on symptoms while in the OFF medication state, and therefore some improvements may have been influenced by variability associated with medications.

Nevertheless, gait training, LSVT BIG, PD-SAFEx, Tai Chi, dancing, and physical therapy were grouped together as goal-based exercise programs since they aim to improve performance of a specific task [81]. Emphasis of these modalities of intervention is aimed toward improvement of motor control including gait, postural stability, coordination, body awareness, and others. However, due to the variation in aspects emphasized between interventions, as well as limitations of protocol designs, it cannot yet be concluded what qualities of these goal-based exercise programs were responsible for improving motor symptom severity in Parkinson's disease. This fact highlights the importance of the present research in which a randomized controlled trial with blinded assessments and a washout period was utilized to focus on the rudimentary aspect of the movements, controlling for location of attention.

It should be noted that although the internal focus of attention exercise program did not provide benefits to gait, and less improvement to motor symptom severity (compared to externally focused exercise), this was not all that surprising since we would expect an internal focus to recruit ventral striatal areas that comprise cognitive and limbic areas, in contrast to the external focus that causes recruitment of dorsal motor areas. However, it does anecdotally appear that internal focus of attention exercise provided improvements to how individuals felt. For example, at post assessment, the internal focus of attention exercise group reported lower

numbers on the PDQ-39 compared to pre (Table 3), suggesting that these individuals reported an improvement to their perceived quality of life. Therefore, although an external focus of attention improved upon dual task walking and symptom severity, if individuals wished to improve how they felt affectively in general, an internal focus of attention may be a suitable option.

In conclusion, since no adverse events related to the exercise program were reported, the findings from the present study suggest that an external focus of attention exercise could be beneficial for improving upon dual task walking and motor symptoms in Parkinson's disease.

THESIS LIMITATIONS

A few limitations were evident that were inherently difficult to avoid. First, the primary investigator instructed all participants through the exercise interventions (both External and Internal), and therefore, one might be concerned with experimenter bias associated with preconceived hypotheses. However, by training both exercise groups, the instructor was able to provide identical time and repetition prescription aspects to the exercise, which might decrease the potential for bias to emerge. Also, blinded research assistants and a movement disorders specialist (for UPDRS-III assessment) conducted pre, post, and washout assessment measures, further minimizing the chance of bias. Second, although participants were consistently asked to focus their attention on the movement of coloured labels (External) or their sensory information (Internal), it could not be confirmed that these strategies were efficiently adopted, especially since significant differences between groups after the intervention were not found. Although, the different attentional methods of exercise intervention transferred to dissimilar changes in dual task ability and symptom severity, and since participants were not demographically different at pre assessment, it can be concluded that the manipulations did have an effect, and were therefore

adopted. Third, unlike a previous study that investigated how focus of attention exercise may influence static and dynamic balance in Parkinson's disease [82], a third exercise group which did not receive attentional instruction was not included in the present study. The purpose of this was two-fold: i) to maximize the number of individuals in completely unique manipulations, and ii) differences between an Internal focus of attention and control were not expected since individuals with Parkinson's disease naturally recruit conscious control networks (ie. focus internally) to compensate for impaired automatic processes. Fourth, since the control group did not complete the washout assessment, it cannot be clear whether the improvements to dual task walking found in the external focus of attention group (at washout compared to pre assessment) were the result of improved automatic control networks, or a simple practice effect. Last, ruling out a placebo effect is very difficult, if not impossible, in exercise studies. Participants were obviously aware that they were randomized to an exercise group that one would expect to naturally provide benefit. However, participants were not made aware of the research hypotheses associated with the present study. Therefore, expectation of improvement would have been the same in both exercise groups.

FUTURE DIRECTIONS

Future work should explore synaptic function at the striatum through [^{18}F]FP-CIT PET before and after external and internal focus of attention exercise to gain an objective understanding with regards to the influence these interventions have in Parkinson's disease. This will allow for the design of more precise interventions so that maximal mitigation of dual tasking ability and motor symptoms might be achieved. Furthermore, it might be expected that since the frontal loops of the basal ganglia that are recruited during an internal focus of attention are

closely linked with limbic centers underlying emotion and anxiety processing, internally focused exercise may provide benefits to clinical anxiety in individuals with Parkinson's disease. Future studies should investigate the influence of external and internal focus of attention exercise on a very prevalent non-motor symptom associated with Parkinson's disease, anxiety.

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