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The Influence of Dopamine Replacement on Movement Impairments During Bimanual Coordination in Parkinson's Disease (PD)

Matt Brown
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The influence of dopamine replacement on movement impairments during bimanual coordination in Parkinson's disease (PD)

Matt Brown

Honours Bachelor of Science in Kinesiology and Physical Education, Wilfrid Laurier University, Canada, 2008

Thesis

Submitted in partial fulfillment of the requirements for the degree of Master of Science in Kinesiology and Physical Education

Department of Kinesiology and Physical Education
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Abstract

The purpose of the current thesis was to investigate the influence of dopamine replacement on performance during bimanual coordination in individuals with Parkinson's disease (PD). There has been conflicting research on the cause of movement impairments such as coordination deficits, slowed switching and upper limb freezing that occur during coordinated movements. It is unclear whether decreased function of the dopaminergic system after withdrawal from dopamine replacement is responsible for these deficits. Healthy age-matched control participants were compared to PD participants in two experiments to determine the movement impairments that occurred during three-dimensional wrist flexion-extension bimanual coordination as a result of PD. In addition, individuals with PD were compared without ('off') and with ('on') dopamine replacement in both experiments to determine whether modulation of the dopaminergic system influenced coordinated movements.

In Experiment 1, continuous bimanual coordination was performed in in-phase (simultaneous wrist flexion and extension) and anti-phase (flexion of one wrist while extending other wrist) with movements externally paced with increasing across seven cycle frequencies (0.75 to 2 Hz). Visual feedback was also manipulated in one of three sensory conditions: *no vision*, *normal vision* or *augmented vision*. Visual feedback, phase and cycle frequency manipulation was performed to determine whether other deficits (e.g. sensory and/or attentional deficits) may influence coordinated movements. Despite reduced amplitude of movements in both limbs of individuals with PD (PD 'off'), coordination deficits were not observed in PD compared to healthy control participants.

In addition, there was an increased occurrence of upper limb freezing (ULF) when cycle frequency demand was greater. Dopamine replacement did increase the amplitude of movements in individuals with PD but did not influence coordination performance or the occurrence of ULF.

In Experiment 2, coordinated movements were initiated in either in-phase or anti-phase and participants were required to voluntarily switch to the other phase pattern when an auditory cue was presented. Trials were performed at one of two cycle frequencies (1 or 2 Hz) and one of two sensory conditions (*no vision* or *normal vision*) to determine whether other deficits (e.g. sensory and/or attentional deficits) may influence coordinated movement. In addition, a separate block of trials were performed in anti-phase coordination with an auditory cue that did not require a switch. Non-switching trials were included to investigate whether the presence of a distracting cue could evoke ULF comparable to when switching between movements was required. PD ‘off’ participants demonstrated slower switching, more delayed responses and deficits in coordination performance when compared to healthy control participants. The increased demand of cycle frequency particularly when initiating anti-phase coordination, after voluntary switching and with the presence of the auditory cue without switching contributed to a large occurrence of ULF in individuals with PD. Dopamine replacement improved the ability to switch between phase patterns but had no overall influence on coordination performance or the occurrence of ULF.

Overall, the results of the current thesis demonstrated that dopamine replacement can improve motor symptoms during coordinated movements (e.g. hypometria and bradykinesia) but does not contribute to coordination performance or ULF in individuals

with PD. As a consequence, it was concluded that coordination deficits and ULF are not caused by the dysfunctional dopaminergic system but rather associated to secondary impairment caused by PD. The movement impairments caused by secondary dysfunction of PD were proposed to be associated with increased attentional demands and possible executive dysfunction related to fronto-striatal pathways that cannot be modulated by dopamine replacement. Thus, treatment of complex movement impairments such as coordination deficits and ULF may benefit from rehabilitation or non-dopamine therapies that focus on the global dysfunction caused by PD.

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Chapter 1- Prologue

1.1 Problem statement

Parkinson's disease (PD) is a progressive neurodegenerative disorder. It results from diminished dopamine release from the substantia nigra to the basal ganglia (Graybiel, Hirsch, & Agid, 1990, Hirsch, 1994, Hirsch, Graybiel, & Agid, 1988). PD is characterized by several motor symptoms including hypometria (reduced amplitude), bradykinesia (slowness) and freezing (a period of time when no movement occurs despite voluntary movement intention). Importantly, the basal ganglia are considered critical structures responsible for the poor execution of simultaneous movements known as bimanual coordination or inter-limb coordination. However, the contribution of the dopaminergic system in proper execution of coordinated bimanual movements is poorly understood. Individuals with PD have displayed coordination deficits (Almeida, Wishart, & Lee, 2002, Byblow, Summers, Lewis, & Thomas, 2002) and upper limb freezing (Almeida, Wishart, & Lee, 2003, Nieuwboer et al., 2009) during execution of continuous bimanual coordination. Reductions in amplitude (Byblow et al., 2002, Swinnen et al., 1997) and frequency of movements (Almeida et al., 2002, Swinnen et al., 1997) have also been demonstrated and provide some evidence that the dopaminergic system and these dopa-responsive motor symptoms such as hypometria and bradykinesia may contribute to the poor execution of bimanual coordination in PD. However, coordination deficits and freezing were even more apparent after the inclusion of a cued intentional change in coordination patterns during rhythmic coordinated movements (Almeida et al., 2003, Byblow et al., 2002). This may be representative of deficits in central programming or

executive function that are not directly related to dopaminergic system dysfunction. Furthermore, these movement impairments could be explained by deficits related to attentional demands of the task (Almeida et al, 2003) or result of disrupted proprioceptive processing or sensorimotor integration (Abbruzzese & Berardelli, 2003, Demirci, Grill, McShane, & Hallett, 1997, Klockgether, Borutta, Rapp, Spieker, & Dichgans, 1995, Lim, Hamm, Byblow, & Kirk, 2005, Rickards & Cody, 1997). It is unclear how the dopaminergic system is involved in the different aspects that are essential to the execution of coordinated movements. These may be caused by dysfunction of the dopaminergic system or other basal ganglia related dysfunction. Thus, it is important to study how basal ganglia dysfunction with and without dopaminergic modulation influences the different parameters that are necessary for bimanual coordination.

1.2 Rationale

Although the influence of dopaminergic replacement on continuous bimanual coordination has not been studied in PD, certain aspects of movement have been shown to improve with treatment. Based on clinical evaluations, motor symptoms such as hypometria and bradykinesia are typically responsive to dopaminergic treatment (Deleu, Northway, & Hanssens, 2002, Espay et al, 2009, Factor, 2001, Talati, Reinhart, Baker, White, & Coleman, 2009). In addition, sequencing of unimanual movements (Benecke, Rothwell, Dick, Day, & Marsden, 1987b) and reach-to-grasp upper limb movements (Schettino et al, 2006) have been shown to improve with dopaminergic replacement. However, freezing of gait (FOG) does not reliably respond to dopaminergic modulation (Nomoto & Nagai, 2006, Schroeteler, Ziegler, Fietzek, & Ceballos-Baumann, 2009). Thus, performance during bimanual coordination may be influenced by improvements in

amplitude and frequency. Manipulating dopamine replacement in PD can provide a unique approach to examine the influence of the dopaminergic system on the various aspects that influence the execution of coordinated bimanual movements. A more thorough understanding of the deficits and the role of the dopaminergic system in bimanual coordination can contribute to improved treatment (such as medication and upper limb rehabilitation) as well as possible diagnostic tools for PD.

1.3 Outline of thesis

The current thesis intends to determine how the dopaminergic system contributes to the execution of a coordinated movement (bimanual coordination). Coordination performance (accuracy and stability), amplitude of movements and frequency of movements were all measured since all of these measures may have the potential to contribute to performance (or impairments) during bimanual coordination. The aim is to determine what factors alone or in combination with dopamine replacement may influence bimanual coordination including sensory feedback, phase and/or cycle frequency. This thesis was structured to answer this detailed problem with multiple research questions that are presented in the subsequent paragraphs.

Chapters two through four present two experiments that evaluate coordination performance during three-dimensional bimanual wrist flexion-extension using haptic devices. Each of the two experimental studies manipulated the dopaminergic system of the basal ganglia by testing individuals with Parkinson's disease (PD) both 'off' and 'on' their regular dopamine medication. The manipulation of dopamine replacement was investigated to understand how the dopaminergic system contributes to performance during bimanual coordination (e.g. coordination performance, frequency and amplitude).

Additionally, sensory feedback, phase and cycle frequency were manipulated in both experimental studies to examine their influence to bimanual coordination in combination with the dopaminergic system

Chapter two presents a comparison of continuous, coordination performance with between group (PD 'off' and controls 1st session) and within-group (PD 'off' vs 'on') designs. Cycle frequencies, coordination patterns (in-phase and anti-phase) and sensory conditions (no vision, normal vision and augmented vision) were manipulated across trials. This permitted an evaluation of the effect of the different factors related to basal ganglia dysfunction that could influence coordination, frequency and amplitude with a specific interest in the dopaminergic system. Chapter three describes the performance of a voluntary switch in phase pattern (e.g. in-phase to anti-phase or anti-phase to in-phase) and subsequent continuous coordination performance of individuals with PD and healthy control participants. A focus of this chapter is how dopaminergic modulation affects the temporal component of the switch and the successful completion of the switch. This was conducted to isolate the contributions of bradykinesia compared to hypometria or freezing to sequencing movements during bimanual coordination. Chapter four presents upper limb freezing (ULF) in PD that was a primary focus of both experimental studies. The amount of freezing is presented during continuous bimanual coordination (from study #1) and during continuous bimanual coordination before and after a voluntary change in movement (from study #2). The occurrence of freezing episodes is compared across different parameters with the goal to develop a better understanding the etiology of upper limb freezing. In addition, clinical characteristics of individuals who displayed ULF (*upper limb freezers*) are presented.

Chapter five provides a detailed synthesis of the most significant findings of the current thesis. This involved examining the major findings from Chapters 4, 5 and 6 and identifying the main conclusions. There was a specific interest in how the dopaminergic system is involved in the execution of continuous coordinated bimanual movements and change in movements. In addition, sensorimotor integration and ULF are discussed. The implications of the findings, the limitations of the current thesis and future directions of research involving bimanual coordination, dopaminergic modulation, sensory feedback and freezing in PD are presented.

Appendix A attempts to examine muscle activity from surface electromyography (sEMG) during continuous bimanual coordination. The main focus of this chapter is to detect if irregular timing of muscle activity is associated with ULF. This would help clarify if a physiological link exists between upper and lower limb freezing. A secondary focus is to determine if sEMG could be used to help detect ULF in PD. A thorough explanation of the methods, limitations of these methods for examining sEMG in PD and future directions are provided.

1.3.1 Primary research questions for thesis

- Does withdrawal of dopamine replacement in combination with sensory feedback, phase and/or cycle frequency, result in movement impairments including upper limb freezing, coordination, amplitude or frequency deficits during bimanual coordination in individuals with Parkinson's disease compared to healthy older adults?

- Can dopamine replacement in combination with sensory feedback, phase and/or cycle frequency, improve movement impairments during bimanual coordination in individuals with Parkinson's disease?

1.3.2 Specific research questions for chapters

Chapter Two

- Do individuals with PD have coordination (accuracy and stability), frequency or amplitude deficits compared to healthy older adults? Are movement impairments related to sensory, phase and/or cycle frequency manipulations?
- If coordination, frequency or amplitude deficits are present, do they always occur simultaneously or can they exist separately?
- How does dopamine replacement affect frequency, amplitude and coordination (accuracy and stability) in individuals with PD? Is there a relationship between dopamine replacement and sensory, phase and/or cycle frequency manipulations?
- Are practice effects (as revealed by coordination performance) present during two consecutive sessions in healthy older adults? If so, how might this influence interpretations using the current design to examine dopamine replacement on individuals with PD?

Chapter Three

- Do individuals with PD have difficulty voluntarily switching between different coordination patterns compared to healthy older adults? Specifically, are switches slower, delayed or unsuccessful in PD? Is this related to sensory, phase and/or cycle frequency manipulations?

- How does a cued and intentional change in movement influence the subsequent coordination accuracy and stability in PD and healthy older adults?
- Does dopaminergic modulation influence switching performance or coordination performance after a switch in PD? Is the influence of dopamine replacement related to sensory, phase and/or cycle frequency manipulations?

Chapter Four

- Are upper limb freezing episodes present during continuous, bimanual coordination in PD?
- Does cycle frequency, phase or type of sensory feedback affect the amount of freezes? Does an intentional change in movement increase the amount of freezes? Does an attentionally demanding external cue in the middle of continuous coordination evoke ULF?
- What mechanism can explain the occurrence of ULF in PD?
- Does dopamine replacement influence the amount of freezes similar to other motor symptoms in PD?
- What factors are characteristic of *upper limb freezers*? Is there any evidence for a relationship between upper and lower limb freezing?

Appendix A

- Can surface electromyography (sEMG) reliably examine muscle activity in the forearms of individuals with PD during bimanual coordination? Are there factors that limit its' use in PD?

- What methods of processing and analyzing sEMG would be most accurate to examine this muscle activity in PD?
- Is there irregular timing of muscle activity in the primary agonist and antagonist prior to a ULF? If so, is this a physiological link between individuals with PD that display freezing of gait (FOG) and upper limb freezing?

1.4 The basal ganglia and Parkinson's disease (PD)

1.4.1 An overview of the basal ganglia in PD

The basal ganglia are a group of neural substrates that function together to contribute to movement control. The system is composed of the caudate nucleus and putamen (together forming the striatum), substantia nigra compacta (SNc), substantia nigra reticulata (SNr), globus pallidus internal/medial (GP_i), globus pallidus externa/lateral (GPe) and subthalamic nucleus (STN). Their primary output is to the thalamus and ultimately, the motor cortices including the supplementary motor areas (SMA), premotor cortex and primary motor cortex by thalamocortical pathways (Alexander & Crutcher, 1990, Alexander, Crutcher, & DeLong, 1990, Crossman, 2000). Smaller projections also extend from the GP_i to the pedunculopontine nucleus (PPN) (Crossman, 2000). In addition to having several output projections, there are multiple structures that input to the basal ganglia as part of the glutamatergic corticostriatal pathway such as the primary motor cortex, supplementary motor area (SMA) and dorso-lateral prefrontal motor cortex (Alexander & Crutcher, 1990, Alexander et al., 1990, Crossman, 2000). In addition to those motor areas, these corticostriatal pathways also include projections from oculomotor, limbic and somatosensory areas (Alexander &

Crutcher, 1990, Alexander et al , 1990) There also exists thalamostriatal pathways that project from the intralaminar nuclei of the thalamus to the striatum (Crossman, 2000) Until recently, these thalamostriatal projections have not been considered to have a prominent functional role in PD (Smith et al , 2009) However, there is evidence that these projections may relay sensory feedback for sensorimotor integration or attentional information back to the striatum (Smith et al , 2009)

PD is a progressive neurodegenerative disorder characterized by a substantial loss of dopamine-producing cells in the SNc This results in a dysfunctional basal ganglia due to a lack of dopamine release to the striatum from the nigrostriatal pathways (Graybiel et al , 1990, Hirsch, 1994, Hirsch et al , 1988) The lack of dopamine available to the basal ganglia increases activity in striatum This can influence the basal ganglia function by direct and indirect pathways The direct pathway involves decreased activity in the GP1 and SNr resulting in decreased inhibition (increased activity and excitatory output) of the thalamus The indirect pathway involves decreased activity of the GPe followed by decreased inhibition (increased activity) of the STN Due to its excitatory nature, increased STN activity results in increased activity in the GP1 and SNr that results in greater inhibition of the thalamus Ultimately, there is a dysfunction in the excitatory activity of the thalamus (Graybiel et al , 1990, Hamani & Lozano, 2003)

However, evidence supports that other pathways (secondary dysfunction) are affected by the dysfunction of the nigrostriatal pathway such as the projections between GP1 and PPN (Nandi, Stein, & Aziz, 2002) and corticostriatal pathways that project between the motor cortex (e.g. SMA) and basal ganglia (Sabatini et al , 2000) For example, the SMA receives input into exclusively its central portions and non-exclusively

into its rostral portions from the nuclei in the thalamus that receives their input from the GP₁ (Cunnington, Bradshaw, & Iansek, 1996) This could have important implications for movement as the frontal cortex is involved in both movement and executive function (Alexander & Crutcher, 1990, Alexander et al , 1990, Playford et al , 1992) The dysfunctional basal ganglia and associated structures evident in PD result in the cardinal hypokinetic motor symptoms of bradykinesia, akinesia, rigidity, resting tremor and postural instability (DeLong, 1990) Additionally, secondary motor complications result from PD such as gait disturbances (Morris, Iansek, Matyas, & Summers, 1998) In addition to gait disturbances, the basal ganglia have been connected to many aspects of voluntary limb movements (Stelmach & Phillips, 1991) and cognitive function (Duchesne, Soucy, Masson, Chounard, & Bedard, 2002) However, the relationship between the basal ganglia and bimanual coordination is not clear

The basal ganglia have been proposed to have several roles in executing complex voluntary movements that are relevant for bimanual coordination The basal ganglia have been argued to contribute to the initiation and sequencing of motor programs (Contreras-Vidal & Stelmach, 1995) They have also demonstrated roles in the initiation and regulation of force control (Stelmach & Worringham, 1988) and timing parameters (Harrington, Haaland, & Hermanowicz, 1998) Additionally, the striatum has been found to be important in guiding responses with information from external stimuli in rat models (Bailey & Mair, 2006) It has also been suggested that a central pattern generator in the midbrain is responsible for generating coordination patterns but works in conjunction with higher cortical areas and the basal ganglia to control rhythmic coordination (Asai, Nomura, Abe, Matsuo, & Sato, 2003, Asai, Nomura, Sato et al , 2003) All of this

evidence supports that the basal ganglia have an important contribution to initiation of coordination patterns and the subsequent control of the limbs and timing required for rhythmic inter-limb coordination. However, the basal ganglia are not the only neural substrates responsible for these movement parameters. The SMA is responsible for preparation and selection of movements (Cunnington et al , 1996). In addition, the SMA contributes to the initiation and execution of movement. Studies have demonstrated that the SMA is particularly important during internally-guided voluntary movements (Cunnington et al , 1996, Cunnington, Iansek, Bradshaw, & Phillips, 1995). However, there is also evidence that the SMA has increased activation during externally-cued movements (Debaere et al , 2001). Thus, there appears to be a prominent relationship between the SMA and basal ganglia for bimanual coordination.

The most prominent theory proposes that the basal ganglia indirectly influences coordinated movements through the SMA (Cunnington et al , 1995, Williams et al , 2002). This hypothesis has been supported due to the increased activation in the SMA that has been confirmed during inter-limb coordinated movements (Debaere et al , 2001). Research has demonstrated that dysfunction related to PD can influence activation in the SMA that may be normalized with dopamine replacement (Dick et al , 1987, Dick et al , 1989). Debaere *et al* (2001) verified that the SMA and cingulate motor cortex have increased activation when coordinated movements become increasingly unstable such as during anti-phase coordination. The connections between the basal ganglia and SMA have been proposed to have an important contribution to learning and automatization stages of bimanual skill acquisition (e.g. learning a 1/2 multifrequency in-phase pattern) (Puttemans, Wenderoth, & Swinnen, 2005). These authors demonstrated the both the

putamen and anterior cerebellum were important structures for learned coordination tasks. Overall, the basal ganglia have a role in initiating and executing bimanually coordinated movements. Based on the evidence, its role in movement initiation and execution is largely influenced by the SMA in the frontal cortex.

1.4.2 The basal ganglia and sensory feedback

One of the potential functions of the basal ganglia is to aid in processing and integrating sensory feedback for movement which is referred to as sensorimotor integration (Abbruzzese & Berardelli, 2003, Demirci et al, 1997, Lim et al, 2005, Lim, Hamm, Byblow, & Kirk, 2006, Moore, 1987). Several studies that have examined sensory feedback during voluntary upper limb movements have supported that proprioceptive (kinesthetic) processing is disrupted in Parkinson's disease. For example, when the hands were passively moved without vision, individuals with PD were more likely to terminate movements earlier and short of the required goal with the passive limb blocked on a digitizing tablet (Klockgether et al, 1995). They concluded that individuals with PD have a kinesthetic deficit that may be more evident at slow cycle frequencies. They suggested that this deficit could be the result of altered afferent input from the periphery, increased fusimotor drive (increased Ia afferent drive through gamma motor neurons due to rigidity in muscles) or abnormalities in processing this information in the basal ganglia. During a bimanual triangle drawing coordination task on digitizing tablets, individuals with PD showed a marked drift away from the goal by increased changes in continuous X-Y positions over time when blindfolded (Swinnen, Steyvers, Van Den Bergh, & Stelmach, 2000). However, no differences were observed in the frequency or amplitude of bimanual movements. They determined that the drift was related to changes

in shoulder and elbow angles that were related to decrease in kinesthetic input or decreased processing of proprioceptive information. Several studies using more advanced techniques have also supported a proprioceptive deficit in PD. Investigation of antagonist tendon vibration on flexor carpi radialis during wrist flexion-extension without vision of the moving limb showed that PD undershot the mean ($+SD$) trajectory amplitude more than healthy controls (Rickards & Cody, 1997). They proposed that this was the result of a proprioceptive deficit that can contribute to motor impairment in PD. A study by Schrader *et al* (2008) investigated the relationship between cortical excitability using transcranial magnetic stimulation (TMS) and proprioceptive processing of primary muscle spindles using muscle vibration (MV). TMS was used to examine both cortical inhibition (short-latency intracortical inhibition and cortical silent periods) and excitation (intracortical facilitation) in relation to changes in cortical excitability that is typical with MV. They found that PD did not demonstrate the expected increase in motor evoked potential (MEPs) with MV that was found in healthy controls (Schrader *et al*, 2008). They proposed that this was related to a deficit in processing proprioceptive related to the changes in the basal ganglia and subsequent dysfunction of the thalamocortical pathways.

Although there is currently a considerable amount of evidence for a specific proprioceptive deficit in PD, several authors continue to debate whether there may be a more generalized deficit in processing and integrating multiple forms of sensory feedback for movement (Abbruzzese & Berardelli, 2003, Demirci *et al*, 1997, Lim *et al*, 2005, Lim *et al*, 2006, Moore, 1987, Schneider, Diamond, & Markham, 1987). This may be related to central processing or an inability to adequately gate sensory information (J. W. Brown, Bullock, & Grossberg, 2004, Nowak & Hermsdorfer, 2006). In addition, this

could be a consequence of increased sensory demands or *sensory overload*. This is an important concept to understand since bimanual coordination tasks in PD often require processing and integrating multiple forms of sensory feedback.

1.4.3 Augmented sensory feedback in Parkinson's disease

As a consequence of the proposed proprioceptive deficit in PD, studies have compared upper limb movements with and without vision available to determine whether vision alone can improve movement. Research by Schettino *et al* (2006) investigated individuals with PD during reach-to-grasp with and without vision. It was found that PD had more errors (revealed by failed or incorrect grasps) compared to healthy controls without vision but no difference was observed when full vision was provided (Schettino *et al*, 2006). As described above (1.4.2), Swinnen *et al* (2000) found that PD demonstrated more drift during bimanual triangle drawing when blindfolded compared to healthy controls. No differences were observed between PD and healthy controls when vision of the moving limbs was provided. Although visual feedback alone has been shown to return upper limb movements to that of healthy controls, recent research has incorporated the use of different forms of augmented visual feedback during bimanual coordination in PD (Almeida *et al*, 2002, 2003). However, due to the possible deficits in sensorimotor integration, it is unclear if augmented feedback improves or hinders inter-limb coordination in PD.

Augmented visual feedback has been provided in various forms on a computer monitor (Almeida *et al*, 2002, 2003, Horstink, Berger, van Spaendonck, van den Bercken, & Cools, 1990, Lazarus & Stelmach, 1992, Palmer *et al*, 2009, Verschueren, Swinnen, Dom, & De Weerd, 1997). This form of feedback has often been provided as a

real-time display on a computer monitor of a discrete figure such as orthogonal or Lissajous figure (Almeida et al , 2002, 2003, Lee, Swinnen, & Verschueren, 1995, Wishart, Lee, Cunningham, & Murdoch, 2002) Other forms of augmented visual feedback exist including a visual representation of the hands (Debaere, Wenderoth, Sunaert, Van Hecke, & Swinnen, 2003), angular displacement patterns of the limbs (Swinnen, Walter, Lee, & Serrien, 1993) and horizontal lines representing the desired goal and a moving line which moves in accordance with the movement of the limbs (Palmer et al , 2009) Theoretically, augmented visual feedback may be beneficial to individuals with PD Research that examined augmented visual feedback during bimanual coordination using fMRI in healthy adults found that there is increased activity in a cerebellar network compared to the basal ganglia (Debaere et al , 2003) They suggested by using this source of feedback that the basal ganglia were bypassed In younger adults research has shown that augmented visual feedback improves coordination (Bogaerts, Buekers, Zaal, & Swinnen, 2003, Debaere et al , 2003, Lee et al , 1995) Typically, this type of feedback helps older individuals improve coordination accuracy and stability during learning of new coordination patterns such as a 90 ° pattern (Swinnen et al , 1993, Wishart et al , 2002) Augmented visual feedback was shown to improve coordination accuracy in the acquisition of a new 90° coordination pattern in PD but learning could not be transferred when the feedback was not available (Verschueren et al , 1997) Unfortunately, in tasks that do not focus on motor learning (considering both the in-phase and anti-phase are intrinsic coordination patterns, see section 2.3.1) there remains little experimental support that augmented visual feedback can improve coordination performance In addition, there is evidence that augmented visual feedback

decreased the ability to couple the limbs during bimanual movements in healthy populations (Cardoso de Oliveira & Barthelemy, 2005, Puttemans, Vangheluwe, Wenderoth, & Swinnen, 2004)

Cardoso de Oliveira *et al* (2005) examined discrete reversal bimanual arm movements (moved to and from separate targets) with and without visual feedback on a computer monitor. It was found that augmented visual feedback compared to normal vision of moving limbs resulted in decoupling of the movement amplitudes but not the temporal coupling across the limbs (Cardoso de Oliveira & Barthelemy, 2005)

Puttemans *et al* (2004) examined augmented visual feedback (real-time representation of the limbs on a computer monitor) compared to normal vision in the acquisition of new bimanual line or star patterns in healthy adults. They found difficulties in acquiring the bimanual movements with augmented visual feedback. They concluded that this may have been a consequence of disturbed natural and spontaneous attentional processes with augmented visual feedback. Thus, augmented visual feedback may influence bimanual coordination due to difficulties with sensorimotor integration (see section 1.4.2) or attentional processes. During bimanual coordination with augmented visual feedback, individuals with PD were more variable and less accurate during anti-phase coordination especially as cycle frequency increased (Almeida *et al* , 2002, 2003). Although the authors did not directly attribute augmented visual feedback to causing difficulties with coordination, they suggested that external cueing does not necessarily improve coordination (Almeida *et al* , 2002, 2003). It was suggested that external cueing may impose increased attentional demands. This research has been supported by Brown and Jahanshahi (1998) that examined unimanual compared to bimanual placing of pegs on a

pegboard and/or repetitive finger tapping. It was found that PD participants had decreased performance on both tasks relative to healthy control participants but were improved during the bimanual combined task (finger tapping with peg placing). It was suggested that the removal of attention from placing the pegs and focusing on the finger tapping increased the automatic execution of both tasks. Finally, it was proposed that this could have been a consequence of limited attentional resources to allocate between tasks (R. G. Brown & Jahanshahi, 1998). Similarly, Horstink *et al.* (1990) examined the simultaneous execution of squeezing a rubber bulb with triangle drawing (or writing the letter e) in PD. They demonstrated a decreased amplitude of squeezing that they concluded was a decreased ability of PD to shift attention between the tasks (Horstink *et al.*, 1990). The hypothesis of decreased attentional resources and ability to shift attention in PD has been supported by other research (Cools, Rogers, Barker, & Robbins, 2010, Hoehnerman, Moont, & Schwartz, 2004). Thus, it may be possible that the attentional demands or sensorimotor integration required for augmented visual feedback decreases performance during bimanual coordination in PD. This issue is further complicated in PD by the incorporation of rhythmic pacing from metronomes to externally cue the timing of coordinated movements (Almeida *et al.*, 2002, 2003, Byblow *et al.*, 2002, Johnson *et al.*, 1998).

Internal timing deficits have been commonly reported during upper limb movements in PD (Freeman, Cody, & Schady, 1993, Nakamura, Nagasaki, & Narabayashi, 1978, O'Boyle, Freeman, & Cody, 1996, Pastor, Jahanshahi, Artieda, & Obeso, 1992, Yahalom, Simon, Thorne, Peretz, & Giladi, 2004, Ziv *et al.*, 1999). O'Boyle *et al.* (1996) examined self-paced finger tapping in individuals with PD. It was

found that PD participants had increased tapping variance and faster tapping relative to the required frequency during self-paced tapping compared to healthy control participants. Pastor *et al* (1992) examined rhythmic flexion-extension movements of the wrist. It was found that individuals with PD showed less accurate timing at 2 and 2.5 Hz (not at 0.5, 1 or 1.5 Hz) compared to healthy control participants. In addition, they demonstrated that individuals who had moderate or severe PD were less accurate at all frequencies. They concluded that these deficits were related to impairment in the internal timekeeper (internal timing deficits) (Pastor *et al* , 1992). Internal timing deficits have been supported by other rhythmic unimanual tapping research in PD (Nakamura *et al* , 1978, Ziv *et al* , 1999). Yahalom *et al* (2004) investigated a series of unimanual finger tapping in individuals with PD that included self-paced, fast as possible, tap in rhythm and changing rhythms with a metronome. They observed that PD participants had difficulty internally generating fast rhythmical movements (slowed tapping) but externally or self-paced movement were preserved. Research by Konczak *et al* (1997) examined the execution of unimanual and bimanual finger and lip tapping with and without external cueing in individuals with PD. It was found that PD participants had increased variability and reduced amplitude in tapping but not frequency that was largely influenced by hastening (increased frequency of tapping). It was concluded that this was due to deficits in an internal cueing mechanism and external cueing did not improve these impairments suggesting that it may have negative effects of repetitive movements (Konczak, Ackermann, Hertrich, Spieker, & Dichgans, 1997). The use of augmented auditory feedback has been controversial in individuals with PD during bimanual coordination. Pacing was provided from a metronome for half of the 20-second trials.

during an bimanual coordination task, and no difference in coordination, cycle frequency or size of movements was seen with the metronome (Almeida et al , 2002) Similarly, no effects of auditory cueing were seen on temporal, spatial, pattern switching or coordination in a bimanual coordination task (Byblow, Summers, & Thomas, 2000) Furthermore, no differences were seen in temporally regulating symmetrical bimanual triangle drawing with or without a metronome (Swinnen et al , 2000) Based on this evidence, it appears that auditory cueing does not negatively influence coordination performance in PD However, research by Johnson *et al* (1998) demonstrated that external cues from a metronome improved accuracy and stability of bimanual coordination during in-phase coordination but caused individuals with PD to switch from anti-phase to in-phase during anti-phase trials It was suggested that this may have increased the complexity of the task (Johnson et al , 1998) However, this may also have been the contribution of increased attentional demand as proposed by Almeida *et al* (2003) Thus, it remains unclear whether external auditory cueing negatively affects coordination performance in PD as it may increase attentional demands or affect coordination through the proposed sensorimotor integration deficits This would be largely dependent on the other sources of sensory feedback provided such as augmented visual feedback

Overall, it remains controversial as to whether the addition of augmented feedback results in improvements in coordination performance in PD It is possible that external auditory cueing regulates the internal timekeeper deficit that has been proposed in PD In addition, augmented visual feedback may reduce the complexity of the movement (Wenderoth et al , 2009) or use circuitry that by-passes the basal ganglia

However, these forms of sensory feedback may be influenced by difficulty in integrating multiple forms of sensory feedback for movement (deficit in sensorimotor integration) in PD. Alternatively, multiple sources of feedback may require additional attentional resources or shifting between resources that could contribute to decreased coordination performance in PD. Providing an answer to this problem is important for determining how the basal ganglia is involved in the use of sensory feedback for bimanual coordination and how this ultimately affects coordination performance in individuals with PD.

1.5 Bimanual coordination

1.5.1 Dynamics of bimanual coordination

Coordination dynamics have been studied extensively in healthy adults. Studies investigating inter-limb coordination have found that the limbs are attracted temporally to work together as a single synergistic unit (Kelso, Southard, & Goodman, 1979b). This has been found across different movement systems (Kelso & Tuller, 1984). Two stable, intrinsic coordination patterns (in-phase and anti-phase) exist in the human motor system and have often been used to evaluate bimanual coordination from the perspective of motor control (Haken, Kelso, & Bunz, 1985, Kelso, 1984, Kelso, Southard, & Goodman, 1979a, Schoner, 1990, Yamanishi, Kawato, & Suzuki, 1980). In-phase is a symmetrical pattern that requires the synchronized use of homologous muscles in both limbs (Schoner & Kelso, 1988d). Contrary to in-phase, anti-phase is an asymmetrical pattern that requires the use of non-homologous musculature (Schoner & Kelso, 1988d). The relative phase is a dynamic measurement that measures the phase difference between the two limbs in degrees ($^{\circ}$) (Haken et al., 1985). Accurate in-phase coordination is represented

by a relative phase of 0° (or 360°) Perfectly synchronized anti-phase coordination is characterized by a relative phase of 180° (Schoner & Kelso, 1988c)

The existence of these patterns was originally proposed to allow individuals to limit the degrees of freedom and naturally reduce the complexity of movements (Kelso & Schoner, 1988) This was supported by research that examined other phase relationships such as the 90° out of phase pattern As cycle frequency was increased, variability in the phase relationship increased and people were naturally attracted to and shifted into either in-phase or anti-phase (Kelso, 1984) This phase transition represented the inherent stability of both the in-phase and anti-phase relative to other patterns Although anti-phase was more stable than other coordination patterns, participants appeared to be naturally drawn to a shift to in-phase, as cycle frequency was increased preceded by increased variability in relative phase (Kelso, Scholz, & Schoner, 1986) Based on this evidence, anti-phase may be considered stable coordination pattern but in-phase is the most stable pattern that has been found in the human motor system

Spontaneous and intentional transition between phases is an important aspect of coordination dynamics Spontaneous transitions from anti-phase to in-phase have documented at varying cycle frequencies from person to person and between different tasks (Byblow, Carson, & Goodman, 1994, Byblow & Goodman, 1994) Spontaneous switches for healthy young adults were performed at a mean frequency of 2.34 Hz for free movement and 1.83 Hz with resistive loading (Kelso, 1984) Older adults demonstrated similar switching frequencies of 2.41 Hz in non-loading situations (Byblow et al., 2002) It has traditionally been argued that spontaneous pattern switching occurs to simplify the demands on the motor system by using homologous rather than different

musculature (Johnson et al , 1998, Kelso, 1984, Kelso & Schoner, 1988) Recently, some well designed experiments comparing congruent with incongruent muscles in a wrist flexion-extension, finger tapping and bimanual circle drawing found that the attraction for symmetry during in-phase was due to the perceptual spatial symmetry rather than any other motor explanation such as the simplicity to the motor system of using homologous muscles (Mechsner, Kerzel, Knoblich, & Prinz, 2001) The examination of voluntary (intentional) pattern switches allows examination of the intention to change behaviour but is highly dependent on the inherent pattern stability (Scholz & Kelso, 1990, Schoner & Kelso, 1988a) Switch time has been shown to be longer from in-phase to anti-phase compared to the reverse (Serrien & Swinnen, 1999) The slowed switching has been argued to be a result of the difficulty in transitioning from a high to low stability coordination mode The attraction to particular coordination patterns and the behavioural outcomes with cycle frequency and changing are well understood in healthy adults

1.5.2 Coordination performance in Parkinson's disease (PD)

A wide variety of deficits have been found in individuals with PD during bimanual coordination Coordination accuracy and variability as revealed by the relative phase (see section 1.7.4 for relative phase calculation) were found to be worse in PD participants during both in-phase and anti-phase but it was more pronounced in anti-phase when producing a cyclical movement towards and away from the midline of the body (Serrien, Steyvers, Debaere, Stelmach, & Swinnen, 2000) PD participants were found to have less accuracy and more variability during anti-phase (but not in-phase) during a medial-lateral sliding task and a pronation-supination task of the forearms while grasping handles (Almeida et al , 2002, Byblow et al , 2000) More variability was seen

in the relative phase during both anti-phase and in-phase but more so in anti-phase in individuals with PD. Accuracy of relative phase was not measured during a task that required flexion-extension of the forearms with the hands resting flat (van den Berg, Beek, Wagenaar, & van Wieringen, 2000). In-phase was found to be less accurate and more variable at both 1 and 2 Hz and anti-phase was less accurate at 1 Hz in individuals with PD. Additionally, both PD and age-matched control participants performed poorly during anti-phase at 2 Hz during a rotational task with manual cranks (Johnson et al., 1998).

Accuracy and variability deficits in coordination have not been universally found. Individuals with PD were less accurate but no differences were seen in variability in both isodirectional (in-phase) and non-isodirectional (anti-phase) coordination during cyclic movements in the sagittal plane (Swinnen et al., 1997). It is not clear why this study did not find any differences in variability between groups but it may have been a result of the age of the participants. Mean age of PD participants was 67.8 years whereas the healthy controls mean age was 76.4 years. It has been found that coordination is lost with the aging process (Wishart et al., 2002). Thus, the lack of difference between groups may have been a result of the aging deficits in the control group. Accuracy and stability of coordination was not different in PD compared to healthy control participants (Byblow et al., 2002). It was proposed that this was a result of individuals with PD using preferred frequencies of 1.02 Hz for compared to 1.56 Hz in healthy controls during a pronation-supination task. Similarly, no differences in relative phase were observed in individuals with PD using a frequency of 0.6 Hz with wrist flexion-extension movements (Byblow, Lewis, & Stinear, 2003). These experiments suggest that the cycle frequency demand is

critical to establish deficits. Coordination performance has also been investigated using the number of successful trials. Individuals with PD were shown to have more unsuccessful trials during in-phase at high frequencies and anti-phase at low frequencies than healthy age-matched controls during bimanual circular drawing (Ponsen et al., 2006). No differences in unsuccessful trials were found between groups during anti-phase at 1.75 Hz. It was suggested that this could have occurred due to a lack of amplitude requirements.

Overall, it appears that deficits in coordination accuracy and variability are most evident and more pronounced during anti-phase at cycle frequencies around 1 Hz but they have also been found in some studies during in-phase with high-cycle frequency demand (e.g. above 1 Hz) in individuals with PD. However, coordination deficits have not been universally found in individuals with PD. Several factors such as slow cycle frequencies, small amplitude requirement and age-related deficits in coordination (e.g. anti-phase at fast cycle frequencies) may have contributed to a lack of coordination deficits in individuals with PD. In addition, the relationship between sensory feedback and attentional demands (see sections 1.4.2 and 1.4.3) may also contribute to whether coordination deficits are observed in individuals with PD. Hence, careful consideration is needed to understand the circumstances that they occur since this could provide important insight into the role of the basal ganglia in bimanual coordination.

1.5.3 Amplitude and frequency during bimanual coordination in PD

Coordination involves the temporal and spatial coupling of the limbs (Swinnen, 2002). However, the individual assessment of amplitude and frequency are important to consider in bimanual coordination in individuals with PD due to the possible

contributions of motor symptoms including bradykinesia (slowness of movement) and hypometria (reduced size of movement) (see section 1.4.1) to voluntary movement. In addition to coordination deficits, impairments in amplitude and frequency have been documented in individuals with PD while performing bimanual tasks. Smaller amplitudes were seen during both in-phase and anti-phase at a frequency of 1 Hz (Swinnen et al., 1997). In addition, smaller amplitudes were observed during symmetrical (in-phase) triangle drawing, but only symmetrical patterns were used (Swinnen et al., 2000). Byblow *et al.* (2002) found smaller amplitude of movements predominantly with increasing the frequency from below to above the spontaneous transition frequency in individuals with PD. Serrien *et al.* (2000) observed more variable amplitudes across all conditions for individuals with PD. Swinnen *et al.* (2000) demonstrated that amplitude of movements were more variable in symmetrical triangle drawing in individuals with PD. However, conflicting evidence has also found that amplitudes were not more variable during a cyclical flexion-extension task in individuals with PD (Swinnen et al., 1997). The reason for this finding is unclear but it was suggested that the novel task used in this experiment could have resulted in variability of amplitude to be high across all participants.

Frequency deficits have also been found in individuals with PD during bimanual coordination tasks. The frequency of movements in PD participants was found to be slower than healthy control participants only at a frequency of 1.75 Hz but not at 0.75 or 1.25 Hz (Almeida et al., 2002). Longer cycle durations were found in PD participants either when both arms moved 80 degrees or when one moved 80 while the other moved 40 degrees but not during movements of 40 degrees (Serrien et al., 2000). Swinnen *et al.*

(1997) also found longer cycle durations during both in-phase and anti-phase coordination at 1 Hz in individuals with PD. In addition, Swinnen *et al* (2000) observed longer cycle durations during symmetrical triangle drawing when there was a goal of 1.5 seconds per cycle in individuals with PD. Johnson *et al* (1998) found the velocity of movements to be more variable at 1.0 Hz in both in-phase and anti-phase coordination in individuals with PD. Lazarus and Stelmach (1992) observed a slower and longer time to reach peak velocity as well as a longer time to reach peak negative and positive acceleration in individuals with PD. Ponsen *et al* (2006) demonstrated that PD participants had more variable frequency of movements at higher cycle frequencies and to a greater extent during anti-phase. Finally, more variability was observed in cycle durations in PD participants during a cyclical flexion-extension task (Swinnen *et al* , 1997) and during in-phase triangle drawing (Swinnen *et al* , 2000).

Overall, it appears that PD participants have deficits in amplitude and frequency during bimanual coordination. Collectively, the results from previous experiments demonstrate a potential deficit in the amplitude and frequency of movements that may be representative of the motor symptoms of hypometria (reduced amplitude) and bradykinesia (slowness) in PD.

1.5.4 Phase switching during bimanual coordination in PD

As previously described (see section 1.5.1), individuals are naturally drawn to in-phase coordination and will perform a spontaneous shift from anti-phase or other less stable coordination patterns. Spontaneous transition frequencies were found to be lower in individuals with PD compared to healthy older adults (1.76 Hz compared to 2.41 Hz) (Byblow *et al* , 2002). Spontaneous transitions from anti-phase to in-phase were also

found to occur more often in individuals with PD (Byblow et al , 2000, Ponsen et al , 2006)

Individuals with PD have been shown to have difficulty in sequencing between movements (Benecke, Rothwell, Dick, Day, & Marsden, 1987a, Harrington & Haaland, 1991) Intentional pattern switching requires sequencing movements and performing a voluntary change between two coordination patterns rather than spontaneous switch Voluntary pattern switches especially from in-phase (stable) to anti-phase (less stable) pattern caused for longer transitions and longer initiation of the voluntary switch in individuals with PD (Almeida et al , 2003, Byblow et al , 2003, Byblow et al , 2000) After switches to anti-phase (from in-phase,) there was less accuracy and more variability in coordination performance in individuals with PD (Almeida et al , 2003) Thus, the inclusion of a pattern switch during the performance of a coordinated movement adds an additional demand on the motor system It can provide further insight into the role of the basal ganglia in the execution of bimanual coordination

1.5.5 Freezing during bimanual coordination in PD

Akinesia (absence of movement) has been proposed to represent a complex PD motor symptom that incorporates exacerbated forms of hypometria, bradykinesia and freezing (Imai, 1996) Freezing has been described as one of the most debilitating symptoms of PD since it can severely alter the ability to perform everyday tasks and remains one of the most challenging features of PD (Imai, 1996) A period of time during which no movement occurs despite the intention to move is characteristic of freezing The term motor block has also been used in alternative to freezing to refer to any sudden stop in movement or inability to initiate movement (Giladi et al , 1992) Freezing is

similar to the hastening that has been found to occur in the lower limbs during gait (Giladi et al , 2001, Lambertı et al , 1997) Freezing was originally documented in gait initiation, during continuous walking, during turning and walking through narrow doorways (Almeida & Lebold, 2010, Giladi et al , 2001, Lambertı et al , 1997) Freezing has also been found in other tasks such as speech, unimanual finger tapping and handwriting (Nakamura et al , 1978, Popovic, Dzoljic, & Kostic, 2008, Ziv et al , 1999) Manual motor blocks (MMBs) were examined during a unimanual finger tapping task (Ziv et al , 1999) MMBs were identified to occur more often and for longer durations in PD but were not exclusive to individuals with PD Correlations with MMBs were only found between freezing of gait but not with any other symptoms or disease duration and levodopa did not reduce the amount of MMBs

Freezing has been also been shown to occur during continuous bimanual coordination in the upper limbs (Almeida et al , 2002) and after pattern switching in upper limbs during coordination tasks (Almeida et al , 2003) using a medial-lateral sliding task Using a computer algorithm to detect freezing, individuals with PD were found to freeze in their upper limbs in 8.1% of anti-phase trials (Almeida et al , 2002) A successive study by Almeida *et al* (2003) using the same definition and computer algorithm, documented upper limb freezing in 52.9% of trials after a pattern switch predominantly from anti-phase to in-phase

Recently, research has been conducted to examine upper limb freezing episodes (FO-UL) using visual examination of displacement profiles during a bimanual rhythmic task using digitizing tablets (Nieuwboer et al , 2009) They detected 25 FO-UL episodes (10.4% of trials) all during anti-phase Neither cycle frequency (between 1.08 and 1.71

Hz) nor amplitude (2 or 4 cm) significantly influenced the amount of freezing episodes. A trend revealed that visual cueing may result in less freezing compared to without visual cues in non-freezers but the opposite was found in freezers. Finally, they found that the amount of FO-UL were correlated with scores on a freezing of gait questionnaire but no correlation was found with age, Hoehn and Yahr stage, UPDRS score or Mini Mental State Examination (MMSE) (Nieuwboer et al , 2009)

Early research into the mechanism of unimanual movement interruptions proposed that PD have a deficit in internally-cueing continuous, repetitive movements that was referred to as a dysfunctional *motor pacemaker* (Ziv et al , 1999). Similarly, hastened tapping was argued to represent an internal or intrinsic oscillation that did not allow for maintenance of synchronized tapping (Nakamura et al , 1978). Freezing during bimanual coordination cannot be explained by the same internal-cueing deficit since episodes have been identified with external cueing. They have been argued to occur due to increased attentional demands presented by the task through pattern difficulty during anti-phase coordination and cycle frequency (Almeida et al , 2002). Furthermore, it was suggested that the attentional demand of anti-phase, externally paced movements in combination with switching between patterns resulted in increased movement impairments during bimanual coordination (Almeida et al , 2003). Similar results by Nieuwboer *et al* (2009) demonstrated that only the demand of anti-phase coordination resulted in freezing. However, this same effect was not seen with small amplitudes and increasing cycle frequency. In addition, they demonstrated that visual cueing decreased the amount of freezing (Nieuwboer et al , 2009). Thus, the mechanism for upper limb freezing warrants further investigation since the current explanations of a dysfunction

internal timing mechanism or increased attentional demands cannot fully explain previous research

1.6 The possible contributions of the dopaminergic system to bimanual coordination

1.6.1 Dopamine replacement on primary motor symptoms and freezing

Early research identified the relationship between dopamine and Parkinsonism (Carlsson, 1959, Hornykiewicz, 1963, 1966) This led researchers to explore dopamine as a therapeutic treatment for PD (Bernheimer, Hornykiewicz, & Birkmayer, 1963, Cotzias, 1968, Cotzias, Papavasiliou, & Gellene, 1968) Historically, this treatment has been provided primarily in the form of levodopa (L-dopa) (Caraceni & Musicco, 2001, Cotzias, 1968, 1969, Cotzias, Duby, Ginos, Steck, & Papavasiliou, 1970, Cotzias et al , 1968, Cotzias, Papavasiliou, & Gellene, 1969a, 1969b, Factor, 2001) However, various forms of dopamine analogues were identified (Cotzias et al , 1970) and slowly other variations and alternatives to L-dopa were developed (Papavasiliou et al , 1972, Yahr & Duvoisin, 1971) As a consequence, various forms of dopamine replacements have been developed to alleviate the symptoms related to PD including β -monoamine oxidase inhibitors (MAO- β) (Sieradzan et al , 1995, Talati et al , 2009, Tyce, Dousa, & Muentzer, 1990) and dopamine agonists (Bonuccelli & Pavese, 2006, Deleu et al , 2002, Piccoli & Ruggieri, 1995) Although each treatment distinctively manipulates the dopaminergic system, all forms of modulation aim to increase the amount of dopamine available in the basal ganglia These treatments do not replenish levels of dopamine to the expected level of older adults and as the disease progresses the level of medication is often increased As a consequence, there are an increase in complications such as dyskinesia and motor

fluctuations are often inevitable (Almeida & Hyson, 2008, Caraceni & Musicco, 2001, Fahn, 2008)

Although individual variability exists for motor symptom improvement for the various forms of dopamine replacement, the primary motor symptoms of PD have been shown to improve with dopamine replacement. These include rigidity (Andrews & Burke, 1973), resting tremor (Burleigh, Horak, Nutt, & Frank, 1995, Duffau, Tzourio, Caparros-Lefebvre, Parker, & Mazoyer, 1996, Strian, Benkert, & Micheler, 1972), bradykinesia (Kaufmann, Butz, & Wiesenda M, 1970, Spiegel, Szekely, & Zivanovi, 1968, Utterbac, Pozos, & Stiles, 1971) and postural instability (Chaco & Abramsky, 1971, Folkerts & Njikikt, 1972). Improvement in total motor symptoms (Siderowf, Stern et al, 2002, Yamamoto et al, 1997) and specific motor symptoms such as upper limb amplitude and bradykinesia (Espay et al, 2009, Kishore et al, 2007) have been further revealed by clinical evaluations on the motor subsection of the Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn & Elton, 1987). This clinical tool has been shown to have very high test-retest reliability for motor symptoms in PD (Siderowf, McDermott et al, 2002). However, despite the improvement of most motor symptoms with dopamine replacement there is much debate about the responsiveness of akinesia (freezing) to dopamine replacement (Bloem, Hausdorff, Visser, & Giladi, 2004, Iansek, Huxham, & McGinley, 2006, Imai, Nakamura, Kondo, & Narabayashi, 1993, Narabayashi, Kondo, Nagatsu, Hayashi, & Suzuki, 1984, Nomoto & Nagai, 2006, Okuma, 2006, Schaafsma et al, 2003, Schroeteler et al, 2009, Ziv et al, 1999).

Research that has examined the influence of dopamine replacement on freezing of gait (FOG) in PD found general improved gait characteristics including speed, stride

length and step size as a result of dopaminergic manipulation that are proposed precursors of freezing of gait (Ianssek et al , 2006) Freezing of gait frequency was found to be more prominent during turning in the 'off' state compared to the 'on' state in PD but not it was still apparent during the 'on' state (Okuma, 2006, Schaafsma et al , 2003) Additionally, they found that total akinetic freezing episodes were only evident in the 'off' state However, several studies have found that dopaminergic modulation does not influence the amount of freezing of gait (Bloem et al , 2004, Imai et al , 1993, Nomoto & Nagai, 2006, Schroeteler et al , 2009) Furthermore, the frequency of upper limb movement interruptions during a unimanual task was not improved with dopaminergic modulation (Ziv et al , 1999) This suggests that freezing does reliably respond to dopaminergic replacement in contrast to other motor symptoms An understanding of the involvement of the dopaminergic system in freezing is necessary for accurate etiology of freezing There has been a proposition that the mechanism for freezing of gait and akinesia may involve basal ganglia dysfunction that does not typically respond to dopamine replacement This includes executive function in the frontal cortex (Dagan, Plotnik, Grundlinger, Giladi, & Hausdorff, 2008, Giladi & Hausdorff, 2006, Giladi, Huber-Mahlm, Herman, & Hausdorff, 2007) that may be mediated by acetylcholine rather than dopamine (Rodriguez-Oroz, Jahanshahi et al , 2009, Rodriguez-Oroz, Lage et al , 2009) In addition, akinesia has been proposed to involve a non-dopaminergic GABA mediated pathway involving the basal ganglia and degeneration of the pedunculopontine nucleus (PPN) (Bloem et al , 2004, Nandi et al , 2002) Thus, it is necessary to determine whether upper limb freezing during continuous, bimanual coordination tasks is responsive to dopaminergic manipulation

1.6 2 Dopamine replacement on complex voluntary movements

The effect of dopaminergic replacement has been controversial in complex voluntary movements. Dopaminergic modulation has been shown to produce secondary improvements in gait including stride length, double support and cadence (Morris, Matyas, Ianssek, & Summers, 1996). Similarly, PD under dopaminergic manipulation can reach a target while walking more accurately than individuals with PD who were non-medicated (Almeida et al, 2005). However, PD participants were less accurate at reaching a target when walking 'off' dopaminergic medications when only proprioception was available. Furthermore, individuals with PD were shown to have an increased step-to-step variability and decreased mean temporal gait as a result of dopaminergic manipulation (Almeida, Frank, Roy, Patla, & Jog, 2007).

There have been few studies that have investigated the effect of dopamine replacement on complex voluntary movements in the upper limbs. Research that involved single limb reach-to-grasp found that individuals with PD 'off' dopaminergic medication have difficulty integrating proprioceptive with visual information to correctly coordinate the reach and grasp components (Schettino et al, 2006). In the same study, dopaminergic manipulation improved the speed of movements but it could not improve the sensorimotor integration problem. Dopamine replacement in PD was not found to influence a unimanual and bimanual task involving squeezing a bulb and key pressing as revealed by similar error rates and force outputs (Palmer et al, 2009). No previous studies have evaluated the contribution of the dopaminergic system for continuous, inter-limb coordination in the upper limbs. Pilot work from this lab examined found that no overall differences in coordination were present with or without dopaminergic

manipulation (M J N Brown & Almeida, 2008)) It was found that there may be differences in the ability for individuals with PD not under the influence of dopaminergic medication (PD 'off') compared to individuals who were under the influence of dopaminergic medication (PD 'on') to use and integrate sensory feedback Specifically, relying on a novel source of augmented visual feedback may result in decreased and more variable coordination in PD 'off' compared to the combination of both vision of the hands and augmented visual feedback Additionally, PD 'off' may have a deficit in coordination that is more influenced by factors such as pattern difficulty such as anti-phase and increasing cycle frequency demand Though these results were preliminary they suggest the dopaminergic system could be involved in sensorimotor integration or potentially allocating attentional demands Further research is necessary to support these findings

Manipulating the dopaminergic system during bimanual coordination in PD can provide critical information into whether and how it is involved in executing simultaneous movements Additionally, dopaminergic manipulation can help discern the relationship between motor symptoms such as hypometria, bradykinesia and upper limb freezing on coordination performance in individuals with PD This would help to distinguish whether difficulties while executing simultaneous movements such as coordination or sensory deficits are accounted by the dopaminergic system or other dysfunction as a result of PD

1.7 Methodology

1.7.1 Instrumentation

There have been a variety of instruments used to perform coordinated movements and collect data in bimanual coordination research in PD. These include measuring arm displacement using linear potentiometers attached to horizontal sliding devices at 200 Hz (Almeida et al, 2002, 2003). Rotational movements of the forearms were measured using custom-made handles mounted on the edge of a table at 200 Hz (Byblow et al, 2002, Byblow et al, 2000). Rotational/cyclical arm movements have been measured with shaft encoders attached to two horizontal rotational levers measuring movement at 150 Hz (Serrien et al, 2000), two horizontal rotational manipulanda measuring at 150 Hz (Swinnen et al, 1997) and manual cranks with two wheels to measure vertical plane rotational movements using code-wheel and optical decoders at 200 Hz (Johnson et al, 1998). Other methods of measuring displacement include digitizing tablets to measure bimanual circle drawing with matching electronic pencils at 99 Hz (Ponsen et al, 2006). Only one previous study has examined wrist flexion-extension using manipulanda that measured sagittal plane displacement at 1000 Hz (Byblow et al, 2003). One of the major limitations of these instruments is that they do not allow for manipulation of the type of movement or degrees of freedom. Furthermore, although these devices may be adequate at measuring coordination performance, new instruments may provide more accurate measurement and increased clinical application. These limitations could be resolved with the use of robotic haptic devices that have recently been used in the field of neurorehabilitation with stroke (Wolbrecht, Chan, Reinkensmeyer, & Bobrow, 2008) and individuals with multiple sclerosis (Casadio, Sanguineti, Solaro, & Morasso, 2007).

Continuous, bimanual coordination in PD has not been evaluated using haptic devices but they can provide several possible advantages. Traditionally, bimanual

coordination has been investigated in either one or two dimensions. Haptic devices provide a unique opportunity to evaluate coordination in three-dimensions that few studies have evaluated at high precision recording (e.g. 1000 Hz). Another major advantage of haptic devices is the ability to not only determine traditional kinematics such as displacement and velocity but also to measure and apply forces including constant, frictional or viscous in three-dimensions. For example, the haptic interface is able to apply constant forces in all three directions to form a virtual path and when participants deviated from the required path, it would apply reactive forces to push people back into it (Mihelj, Nef, & Riener, 2007). This essentially can create any desirable virtual environment and could constrain movements to a single dimension if required.

Aside from being useful as a measurement tool, haptic devices have other important applications. They can be used to create virtual environment for upper limb rehabilitation. Also, haptic devices have been used to evaluate different forms of tremor in PD (Grimaldi, Sattar, Lammertse, & Manto, 2007). Consequently, they could be used as a diagnostic tool in PD. Thus, haptic devices are multifaceted and have many possible applications. This makes them a valuable instrument to measure bimanual coordination in PD. Although these devices have been used for single limb reaching tasks, it is reasonable to propose that the use of two haptic devices simultaneously could be beneficial to evaluate bimanual coordination. A preliminary study investigated the use of haptic devices constrained to two-dimensions in individuals with PD in a single arm task (Bardorfer, Munić, Zupan, & Primožič, 2001). Therefore, haptic devices have the potential to serve as useful tools to measure upper limb functioning in PD.

1.7.2 Upper limb coordination tasks

There remains to be a single standardized movement or task to examine bimanual coordination in PD. Continuous, bimanual coordination is different from discrete bimanual coordination as it requires a rhythmic component and its primary goal is not goal-directed to a discrete location. Though there is often a required movement distance, the primary focus of bimanual coordination is on temporally and spatially coordinating the limbs.

A wide variety of uni-dimensional tasks have been used to study upper limb coordination in PD including arm/wrist flexion-extension movements in the horizontal plane (Almeida et al , 2002, 2003, Nieuwboer et al , 2009, Serrien et al , 2000, van den Berg et al , 2000, Verschueren et al , 1997), forearm movements in the sagittal plane (Swinnen et al , 1997), pronation/supination of the forearms (Byblow et al , 2002, Byblow et al , 2000), and vertical plane movements with manual cranks (Johnson et al , 1998). Previous research has demonstrated that individuals with PD have more difficulty performing a bilateral prehension task with more degrees of freedom (Alberts, Tresilian, & Stelmach, 1998). Additionally, multi-dimensional tasks are more applicable to movements of daily living. Thus, examining bimanual coordination in more than one-dimension may provide a better representation of the actual deficits that occur in individuals with PD.

Movements that have not been constrained to a single dimension include circle drawing (Nieuwboer et al , 2009, Ponsen et al , 2006), triangle drawing (Swinnen et al , 2000) and index finger tapping (Nieuwboer et al , 2009, Verheul & Geuze, 2004). All of these tasks maintain temporal and spatial characteristics between the limbs. Other irregular tasks include drawing triangles with one hand while squeezing a rubber ball

with the other hand (Horstink et al , 1990), key pressing combined with squeezing a rubber bulb (Palmer et al , 2009) and combining isotonic and isometric movements (Lazarus & Stelmach, 1992) These tasks are not traditional continuous, bimanual coordination tasks since they are focused on examining time-sharing and attention of simultaneous movements similar to what is observed in dual-tasks In comparison, continuous bimanual coordination is focused on the spatial and temporal coordination between the limbs

There are several limitations with comparing different bimanual coordination tasks One problem between comparing different tasks is that each requires a varying amount of muscle recruitment and degrees of freedom across different joints in the upper limbs to produce the movement (e g arm horizontal plane movements require the use of shoulder abduction/adduction, elbow flexion/extension and wrist flexion/extension where as finger tapping only requires digital flexion/extension) To resolve this issue, several tasks make use of special apparatus to decrease the degrees of freedom (across different joints) and isolate movements For example, forearms were attached and fastened in a manipulanda to stop any forearm movements (Swinnen et al , 1997, van den Berg et al , 2000, Verschueren et al , 1997) As described above, some researchers would argue against isolating single movements in one dimension since it does not reveal as prominently all deficits that would be found as the degrees of freedom are increased (Alberts et al , 1998) However, research in bimanual coordination in healthy adults using elbow flexion-extension demonstrated that there was increased forearm pendulum-like motion in two-dimensions and three-dimensions with increased frequency of movement (Buchanan & Kelso, 1999, Buchanan, Kelso, DeGuzman, & Ding, 1997) It was

suggested that the systematic increases in degrees of freedom help to stabilize coordination. Ultimately, it is presumed that the more muscles involved in the movement, the better the ability to detect deficits in coordination. Therefore, careful consideration needs to be taken for choosing a movement task that eliminates the ability to recruit different joints but does not constrain the degrees of movement within the specific joint being measured to maximize the ability to detect deficits in PD.

The current thesis used an apparatus that permitted three-dimensional wrist flexion-extension movements with the forearms constrained. This movement allowed unconstrained movement and degrees of freedom at the wrist compared to movement in a single plane. In addition, the movement aimed to isolate the forearm muscles and avoid use of muscles at the elbow and shoulder joints. This was in an effort to identify coordination deficits and freezing in the wrist without compensation by elbow or shoulder joints.

1.7.3 Coordination patterns, cycle frequency and amplitude

Most commonly in-phase and anti-phase are used to examine bimanual coordination in PD (Almeida et al , 2002, 2003, Byblow et al , 2002, Byblow et al , 2000, Johnson et al , 1998, Ponsen et al , 2006, Serrien et al , 2000, Swinnen et al , 1997). These coordination patterns are stable, attractor states that inherently exist (Cohen, 1971, Kelso, 1984). Other studies have used 90° out-of-phase pattern in individuals with PD (Verheul & Geuze, 2004, Verschueren et al , 1997), healthy young adults (Fontaine, Lee, & Swinnen, 1997, Lee et al , 1995) and healthy elderly adults (Wishart et al , 2002). However, patterns other than anti-phase and in-phase (e.g. 90° out-of-phase) are not intrinsic so they require learning and forming new attractor states (Lee et al , 1995,

Schoner, Zanone, & Kelso, 1992, Zanone & Kelso, 1992) Research has also demonstrated that PD could not perform (2 or more trials) in over half of the trials (53%) in a finger tapping task requiring 90° out of phase coordination (Verheul & Geuze, 2004) Thus, the current study used in-phase and anti-phase to evaluate continuous, bimanual coordination to limit motor learning in relation to the coordination pattern and to verify completion of the task

A variety of cycle frequencies have been used to examine bimanual coordination in PD ranging from 0.6 Hz (Byblow et al., 2003), self-paced movements (Byblow et al., 2000) to cycle frequencies of 3.0 Hz (van den Berg et al., 2000) As detailed in section 1.5.1, research in bimanual coordination has demonstrated that as frequency of movement is increased, there is increased variability in coordination and attraction to in-phase coordination (Kelso, 1984) Furthermore, research has found that at frequencies around 3.0 Hz individuals with PD either hasten (increase actual frequency of movement relative to required frequency) or cannot produce the movement in both unimanual finger tapping (Freeman et al., 1993) and during anti-phase coordination (van den Berg et al., 2000) This may be in relation to the timing deficits (see section 1.4.3) or bradykinesia (see section 1.5.3) in individuals with PD The most common frequencies used to evaluate bimanual coordination in PD range from 0.75 to 2.0 Hz Pilot work from this lab evaluated frequencies as low as 0.3375 Hz and found that movements at exceptionally slow cycle frequencies were difficult to remain rhythmic and continuous (M. J. N. Brown & Almeida, 2008) Typically, studies that have evaluated cycle frequency demand on coordination have used separate trials at different frequencies (Almeida et al., 2002, Byblow et al., 2002, Byblow et al., 2000) Dynamic cycle frequency protocols have

previously been used in bimanual coordination to evaluate increased coordination variability and spontaneous phase transitions in healthy young adults (Scholz, Kelso, & Schoner, 1987) and individuals with PD (Byblow et al , 2000) Although the goal of the current study was not to specifically evaluate spontaneous transition frequencies, a dynamic cycle frequency protocol was employed to increase the coordination variability (see Chapter 2 and Experiment 1 in Chapter 4) This increased coordination variability may also contribute to increased occurrence of freezing in individuals with PD as increased variability of step length and step time is characteristic of FOG (Almeida & Lebold, 2010) A previous study systematically evaluated dynamic switching during bimanual coordination between 4 different amplitudes within 60-second trials and found this to be a good method to evaluate continuous coordination (Byblow et al , 2003) Thus, dynamic cycle frequency changes within a single trial will serve as a promising novel paradigm to evaluate continuous coordination deficits and freezing in PD However, this method would not be appropriate when examining changes or voluntary pattern switches in movements (see Chapter 3 and Experiment 2 in Chapter 4) It is suggested that combining these two methods would make evaluating the results more complex since it would be difficult to determine whether increasing cycle frequency demand or the change in movement contributed to the outcomes

Amplitude requirements have varied depending on the type of task Amplitude demands for each limb have ranged from small 2cm movements (Byblow et al , 2000) to large 16 cm movements (Almeida et al , 2002, 2003) Rotational amplitudes have consisted of 40, 60, 80 and 100 ° (Byblow et al , 2003, Serrien et al , 2000) However, other studies have avoided specific amplitude requirements but encouraged large and

consistent movement amplitude (Swinnen et al , 1997) or comfortable amplitudes to maintain the frequency and coordination of movement (Ponsen et al , 2006) Similarly, the current study did not use a specific amplitude requirement but required participants to perform large but comfortable movements with discrete amplitude goals This was done to emphasis the correct frequency and coordination of movement

1.7.4 Outcome measures

All outcome measures were calculated using customized scripts in MatLab and assigned to data spreadsheets The experimenter was only responsible for transferring data into a master spreadsheet in Excel This was done to increase accuracy of data acquisition by limiting the contribution of the experimenter and potential errors in handling the data

Coordination performance

There are no universal outcome measures that have been used to study bimanual coordination Coordination performance has been measured by the inability to perform a task by examining unsuccessful trials (van den Berg et al , 2000) However, this measure does not provide insight into the specific deficits that may be causing the unsuccessful trials Coordination accuracy and stability have most commonly been used to measure coordination performance Three methods have been used to measure the relative phase between the limbs The Hilbert phase has been used to measure only the stability of coordination (Ponsen et al , 2006) The most common way that has been used to calculate accuracy and variability between the limbs was formulated in the form of relative phase (a k a HKB model) (Haken et al , 1985, Kelso et al , 1986) The relative phase determines the position of one limb relative to the other using the formula

$$\theta = \tan^{-1} [(dXR/dt)/XR]$$

Where θ is the relative phase between limbs at each sample, X is the position of each limb within a cycle rescaled to the magnitude [-1,1], (dXR/dt) refers to the normalized and continuous instantaneous velocity (Haken et al , 1985) Several studies examining bimanual coordination in PD have used this to measure coordination performance (Almeida et al , 2002, 2003, Johnson et al , 1998, Serrien et al , 2000, Verschueren et al , 1997) Other studies have used similar relative phase measurements referred to as the pseudo relative phase (Bailey & Mair, 2006, Byblow et al , 2003, Byblow et al , 2002, Byblow et al , 2000) Beek and Beek (1988) developed the pseudo relative phase based on the principal that rhythmic movement is non-linear but externally driven However, the relative phase developed in the HKB model is only based on the assumption that rhythmic movement is non-linear (Beek & Beek, 1988) Although these methods of calculation are similar very few studies have adapted the use of the pseudo relative phase This may be in part that coordination dynamics have been formed based on the principles of the relative phase developed in the HKB model (Kelso, 1984, Kelso, Holt, & Flatt, 1980, Kelso, Holt, Rubin, & Kugler, 1981, Kelso et al , 1986, Kelso, Scholz, & Schoner, 1988, Kelso & Schoner, 1988, Kelso et al , 1979a, 1979b) Therefore, the current study used the relative phase measure from the HKB model rather than the pseudo relative phase to be able to compare the current results with the vast knowledge that exist for dynamic bimanual coordination

Spatial and temporal aspects of movement

The temporal aspect of each limb can be measured in several different ways Velocity measured from the derivative of the displacement has been used as measures of

the temporal component of movement (Johnson et al , 1998) Frequency deviation has been used to calculate the difference between the required frequency and the actual frequency (Ponsen et al , 2006) Cycle duration has also been used to calculate the time (in seconds) between subsequent positive peaks (Serrien et al , 2000, Swinnen et al , 1997) However, most bimanual coordination studies have calculated the frequency of movement in hertz (Hz) This is measured by determining the amount of cycles (positive to positive peaks) within a given time (Almeida et al , 2002, 2003, Byblow et al , 2002, Serrien et al , 2000, Swinnen et al , 2000, Swinnen et al , 1997) Typically, a mean value over a given amount of time is determined as a measure of frequency for each limb Within-trial and between-trial variability have also been calculated by measuring the standard deviation of frequency but it is less favorable due to the inconsistent results (Almeida et al , 2002, 2003, Byblow et al , 2002, Johnson et al , 1998, Swinnen et al , 2000) Measuring the mean movement frequency produced by each limb can provide information about the temporal aspect of coordination In combination with dopaminergic modulation, movement frequency is an important measure as it can be used to determine the relationship between clinical symptoms such as bradykinesia during continuous coordination and voluntary phase transitions

Movement amplitude of each limb is often determined to measure the spatial aspect of coordination Mean squared amplitude of X and Y direction has been used during bimanual circle drawing (Ponsen et al , 2006) Typically, the absolute distance between positive and negative peaks has been used to measure amplitude (Ponsen et al , 2006, Serrien et al , 2000, Swinnen et al , 2000, Swinnen et al , 1997, Verschueren et al , 1997) Standard deviation of amplitude has also been used to measure spatial variability

but have inconsistent results compared to spatial accuracy (Serrien et al , 2000, Swinnen et al , 1997) The mean amplitude of movement over a given trial is the most common method to determine the amplitude In addition, it can be used with dopaminergic modulation to examine the relationship between hypometria in PD during bimanual coordination and switching performance

Pattern Switching

Original experiments that examined intentional switching behaviour in healthy adults used switching time (the time it takes to switch between patterns) and first exit time as the primary outcome measures (Schoner & Kelso, 1988b) This was calculated by determining the time at which the new pattern is entered *first entry time* compared to *first exit time* as a measure of when the original pattern leaves its stable level, A more recent study calculated switching time by taking the time between the deviating from the mean of the original relative phase to maintenance within 20° of the intended relative phase for 2 consecutive movement cycles (Serrien & Swinnen, 1999)

Visual identification of relative phase data has been used to determine the duration of phase transitions in individuals with PD (Byblow et al , 2002) They examined when the relative phase quickly changed by 180° (or 360°) Markers were placed at the pre and post transition regions A linear regression line was calculated in the midpoint of the transition and when this line intersected the pre and post transitions it classified the start and finish time of transitions The onset of transition was determined from the beginning of the trial to pre-transition time Different measures were used to examine intentional switches using an interactive window in individuals with PD (Almeida et al , 2003) Successful switches were determined by maintenance of the

intended coordination pattern within 45° of goal for at least 2 consecutive seconds

Voluntary switch time was calculated from the time of the auditory cue until the beginning time of a successful switch. They also examined delayed responses to the auditory cue if voluntary switch time was longer than 2 seconds (Almeida et al , 2003)

However, the visual determination of different variables such as time to switch and successful switches allows for subjective interpretations in analyzing the data. In addition, the visual determination may be different between experimenters and have low inter-rater reliability.

A more objective approach was used for the current study to eliminate subjectivity of the experimenter. Voluntary switch time, successful switches and delayed responses were all calculated using a script created in MatLab using previous definitions (Almeida et al , 2003). However, data was automatically calculated and stored rather than extracted from an interactive window by the experimenter. This was suggested to increase the accuracy and eliminate subjectivity by the investigator.

Upper limb freezing

A few definitions and classification methods have been used to document movement interruptions in the upper limbs. Manual motor blocks (MMBs) were documented when the time between sequential taps exceeded 2 standard deviations of the mean inter-tap interval (Ziv et al , 1999). This method used the computer generated values (inter-tap interval) to calculate the amount of motor blocks. Alternatively, other researchers have used computer algorithms using the definition of at least 1 second of no change in movement amplitude to detect upper limb freezing episodes (Almeida et al , 2002, 2003).

Another method used visual determination of displacement profiles by 2 qualified examiners due the possible limitations of computer algorithms in differentiating between voluntary pattern corrections, fatigue and actual freezing (Nieuwboer et al , 2009) They classified upper limb freezing episodes (FO-UL) based on the definition of one or both limbs displayed no change in movement for at least 1 second preceded by reductions in either amplitude or irregular cyclic frequency These authours have attempted to expand the definition of upper limb freezing by incorporating 4 possible scenarios involuntary stop of movement that lasts at least 75% of the mean cycle duration, absence of clear oscillating movement with abnormal form (width and duration) of the cycles for at least 75% of the mean cycle duration, high frequency oscillation without a stop in movement for at least 75% of the mean cycle duration or less than 50% of the mean average normal amplitude (Nieuwboer, unpublished, see Appendix B) However, this approach may also be too subjective and may not be reliable between examiners

Although visual determination can be effective, the exclusive use of visual determination warrants concern about subjectivity and the possibility of experimenter bias in the determination of freezing episodes Thus, the current study attempted to incorporate the objectivity of a computer algorithm in combination with visual inspection after an already defined freezing episode A computer algorithm was used for the current study that used a definition of a 75% reduction in amplitude (25% of the mean reference amplitude) that was maintained for at least 1 second After freezing episodes were identified using this algorithm, visual determination was performed on the displacement to check for any discrepancies This approach has been recommended when using

computer algorithms for electromyography burst onset detection as well (Hodges & Bui, 1996, Nieuwboer et al , 2004)

1.8 References

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Chapter 2 – Study #1: The influence of dopamine replacement on hypokinesia during bimanual coordination in Parkinson’s disease (PD)

2.1 Abstract

The influence of the dopaminergic system on coordinated upper limb movements was examined in Parkinson’s disease (PD) and healthy age-matched participants. Individuals with PD performed two sessions: first session after overnight withdrawal of dopamine replacement (‘off’) than a second session after self-administration of dopamine replacement (‘on’). Three-dimensional wrist flexion-extension coordination was performed in in-phase (simultaneous flexion and extension of wrists) and anti-phase (one wrist flexed while other wrist extended). The frequency of movements was paced with an external metronome and cycle frequency was increased within each trial from 0.75 to 2 Hz by 0.25 Hz. Visual feedback was also manipulated in three sensory conditions: *no vision*, *normal vision* and *augmented vision*. Coordination performance was measured by the mean (accuracy) and standard deviation (stability) in the absolute error of the relative phase. In addition, the mean frequency and amplitude of movement was measured in each limb. Overall, no differences in coordination were observed between PD and healthy participants despite reduced movement amplitude in both limbs of PD participants. Dopamine replacement improved the amplitude in both limbs (hypometria) of PD ‘on’ compared to PD ‘off’ but did not influence coordination. All participants paced the frequency of movements with metronome suggesting that attention was directed at the external cues allowing for preservation of coordinated movements. As a result, the

dopaminergic system does not contribute to overall coordination performance despite improvements in hypometria. It was concluded that dopaminergic system dysfunction and motor symptoms are not directly responsible for coordination deficits in individuals with PD.

2.2 Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder of the dopamine-producing cells of the basal ganglia. Motor symptoms such as bradykinesia (slowness) and hypometria (decreased amplitude) manifest from dopamine loss. These symptoms have been shown to be responsive to dopamine replacement (Espay et al, 2009). Several behavioural studies have identified coordination deficits (e.g. decreased accuracy and/or stability) in individuals with PD during continuous bimanual coordination (inter-limb or inter-manual coordination) (Almeida, Wishart, & Lee, 2002, Byblow, Summers, & Thomas, 2000, Johnson et al, 1998, Serrien, Steyvers, Debaere, Stelmach, & Swinnen, 2000, van den Berg, Beek, Wagenaar, & van Wieringen, 2000). This suggests that basal ganglia dysfunction contributes to poor coordination performance in individuals with PD. In addition, slower (Serrien et al, 2000, Swinnen et al, 1997) and smaller movements (Byblow, Summers, Lewis, & Thomas, 2002, Serrien et al, 2000, Swinnen et al, 1997) have been documented in individuals with PD during bimanual coordination that may be representative of bradykinesia and hypometria. However, it remains unclear if the dopaminergic system influences coordination directly, or if coordination deficits are secondary to the typical hypo and bradykinetic movements in individuals with PD.

Imaging research using fMRI has established that the basal ganglia (e.g. striatum and globus pallidus) are part of a distributed network that are involved in bimanual coordination that includes the supplementary motor area (SMA), cerebellum, primary motor cortex, premotor cortex, cingulate cortex, primary sensorimotor area (Aramaki, Honda, Okada, & Sadato, 2006, Carson, 2005, De Luca, Jantzen, Comani, Bertollo, & Kelso, 2010, Oullier, Jantzen, Steinberg, & Kelso, 2005, Swinnen, 2002). This has important implications for bimanual coordination in PD that associates secondary dysfunction rather than exclusively the dopaminergic system in coordination performance. For example, coordination impairments in PD could be related to sensorimotor integration deficits (Abbruzzese & Berardelli, 2003, Lim, Hamm, Byblow, & Kirk, 2005, Lim, Hamm, Byblow, & Kirk, 2006). Schettino *et al* (2006) manipulated visual feedback and dopamine replacement while coordinating a unimanual reach-to-grasp movement in PD. They demonstrated that PD participants were slower and unable to integrate proprioceptive and visual information for accurate coordination in the task compared to healthy controls participants. Furthermore, dopamine replacement improved the speed of movement but did not influence the ability to integrate visual and proprioceptive information (Schettino *et al*, 2006). Alternatively, increased attentional and cognitive demands may negatively influence coordination performance as suggested by Almeida *et al* (2003). Increased attentional demands may involve performing anti-phase coordination (Johnson *et al*, 1998, Ridderikhoff, Peper, & Beek, 2008) or the combination of anti-phase with the presence of external auditory cueing (Almeida *et al*, 2002). This could be related to difficulties in shifting attention or limited attentional resources that have been proposed for individuals with PD when performing

simultaneous tasks (Brown & Jahanshahi, 1998, Horstink, Berger, van Spaendonck, van den Bercken, & Cools, 1990) It has been argued that executive dysfunction related to attention may be mediated by neural mechanisms that are not responsive to dopamine replacement (Leroi, Collins, & Marsh, 2006, Rodriguez-Oroz, Jahanshahi et al , 2009) Research by Riekkinen *et al* (1998) compared the effects of dopamine replacement and noradrenalin (clonidine) replacement on different attention tasks in individuals with PD It was found that dopamine replacement improved the speed of movement but had no effect on attention itself It was concluded that attentional processes are not influenced by dopamine replacement in PD (Riekkinen, Kejonen, Jakala, Soiminen, & Riekkinen, 1998) Based on these findings, although motor symptoms improve with dopamine replacement, it appears that bimanual coordination may be influenced by dysfunction secondary to dopamine loss that cannot be modulated or corrected by dopamine replacement

The primary objective of the current study was to determine if the dopaminergic system influenced performance alone or in combination with sensory, phase and/or cycle frequency manipulations during continuous bimanual in individuals with PD In addition to coordination performance (accuracy and stability), amplitude and frequency of movements were also examined in order to understand whether dopamine replacement may influence coordination performance through improvements in bradykinesia and hypometria It was hypothesized that if the dopaminergic system influenced coordination performance than deficits would be observed in individuals with PD compared to healthy older participants after withdrawal of dopamine replacement (PD 'off') and dopamine replacement would improve these deficits in individuals with PD Furthermore, if coordination deficits are related to other PD dysfunction (e g executive dysfunction

related to attention or difficulties with sensorimotor integration) than increasing sensory demands, anti-phase coordination and/or increased cycle frequency would result in impairments in coordination performance in individuals with PD regardless of dopamine replacement

2.3 Methods

2.3.1 Participants

Fifteen ($n=15$, mean age= 68 ± 6.3) participants with a confirmed diagnosis of Parkinson's disease (PD) were examined in this study. In addition, fifteen age-matched ($n=15$, mean age= 65.5 ± 7.2) participants without any neurological impairment were investigated as healthy controls. All individuals were right-hand dominant based on responses to the Waterloo Handedness Questionnaire (WHQ) (Steenhuis & Bryden, 1989). To verify that all individuals had the cognitive ability to perform the experiment and free from dementia, they self-reported years of education and were assessed on the Modified Mini Mental State Examination (3-MS) (Teng & Chui, 1987) (see Table 2.1 for demographic information including 3-MS scores). A criterion score of 81 out of 100 was used. This score was the lowest criterion score that had high sensitivity (100%) to correctly identify participants with Alzheimer's disease (AD) and negative predictive power across both groups of education (0-8 and 9+ years) and age (65-79 and 80-89 years) (Tombaugh, McDowell, Kristjansson, & Hubble, 1996). All PD (mean 3-MS= 94.1 ± 5.2) and healthy control participants (mean 3-MS= 96.3 ± 3.8) had scores above the criterion.

PD participants were assessed on the motor subsection of the Unified Parkinson's Disease Rating Scale (UPDRS-III) (Fahn & Elton, 1987) both with ('on') and without

(‘off’) dopamine replacement Assessment ‘off’ (mean UPDRS-III= 30.6 +/- 8.6) occurred after overnight withdrawal from all dopaminergic medications (mean time ‘off’= 14.9 hours +/- 1.8) It is important to note that although the length of withdrawal from dopamine replacement was considerable, it only represented an acute ‘off’ state rather than complete removal of all influences of dopaminergic replacement (true ‘off’ state) After completion of the first session during their ‘off’ state, PD participants self-administered their regular dosage of medications and were re-assessed on the UPDRS-III to represent their ‘on’ state (mean time ‘on’= 76.3 min +/- 8.1) A minimum 5-point difference was utilized as a criterion between ‘off’ and ‘on’ scores on the UPDRS-III to be classified as dopa-responsive for the current study To determine which upper limb was more affected by PD, upper limb laterality scores were calculated and compared for both limbs from items 20-25 on the UPDRS-III that evaluates upper limb motor symptoms similar to what has been performed by previous research (Plotnik, Giladi, Balash, Peretz, & Hausdorff, 2005, Plotnik, Giladi, & Hausdorff, 2008) Based on these laterality scores, individuals with PD were also classified as bilaterally affected if both sides summed to 5 (or above) or were separated by less than 1 point Session two was then completed in their ‘on’ state (mean UPDRS-III= 20.0 +/- 7.9) (see Table 2.2 for clinical characteristics) PD participants maintained their regular schedule and dosage of dopamine replacement after the second session was started Furthermore, to investigate if practice effects were present between the first and second sessions, all of the healthy control participants also performed two sessions (mean time between= 72.6 min +/- 6.5)

Individuals were excluded from the study if they had any recent injury to their upper limbs that would influence their ability to perform the task, uncorrected vision

(including uncorrected macular degeneration, cataracts or glaucoma) or uncorrected hearing. Additionally, participants were excluded if they had previous history of stroke or serious brain trauma. Individuals with PD were included regardless of motor symptoms (e.g. tremor, dyskinesia or freezing). All PD participants were recruited from the patient database at the Sun Life Financial Movement Disorders Research and Rehabilitation Centre (MDRC) at Wilfrid Laurier University. Healthy control participants were recruited from family and friends of the PD participants. Ethics for this study was granted from the Research Ethics Board (REB) at Wilfrid Laurier University.

Table 2 1-Demographic information of healthy control and PD participants

Participant	Group ¹	Age (in years)	Gender ²	3-MS (out of 100) ³	Education (in years)	Time between Session (in minutes) ⁴
1	PD	52	F	100	14	90
2	PD	62	F	96	12	90
3	PD	72	M	96	16	75
4	PD	77	M	98	20	70
5	PD	67	M	91	12	75
6	PD	67	F	92	10	70
7	PD	76	M	93	12	70
8	PD	69	M	88	10	90
9	PD	63	F	100	20	75
10	PD	66	F	98	12	70
11	PD	72	M	100	21	75
12	PD	65	F	98	15	70
13	PD	75	F	83	10	70
14	PD	67	F	91	15	70
15	PD	70	M	88	18	85
16	HC	74	M	100	18	65
17	HC	65	F	99	16	75
18	HC	63	F	100	15 5	70
19	HC	76	F	97	10 5	70
20	HC	75	F	93	16	70
21	HC	67	M	97	14	80
22	HC	66	F	93	9	65
23	HC	58	M	92	15	75
24	HC	62	M	99	18 5	80
25	HC	68	F	89	10	70
26	HC	54	M	98	22	70
27	HC	58	F	100	16	70
28	HC	68	M	100	12	70
29	HC	74	F	92	9	90
30	HC	55	F	95	16	70

¹ PD= Parkinson's disease participants, HC= healthy control participants

² M= male, F= female

³ 3-MS represents the modified Mini-Mental State Examination

⁴ Time between sessions is equivalent to time 'on' medication for PD participants

Table 2 2- Clinical characteristics of PD participants

Participant	Duration since diagnosis (in years) ¹	Duration since 1 st reported symptoms (in years) ¹	Dopamine medications ²	Time 'off' medication (hours)	UPDRS-III 'off' (out of 108) ³	Time 'on' medication (min)	UPDRS-III 'on' (out of 108) ³	Difference in UPDRS 'off' and 'on'	Disease Laterality ³
1	9	10	LD-CD	13 5	27	90	13 5	13 5	R<L
2	5	6	LD-CD,	12	46	90	35 5	10 5	L<R
3	8	10	LD-CD	15 5	30 5	75	22	8 5	L<R
4	4	6	LD-CD	14 5	20	70	12 5	7 5	L<R
5	11	11	LD-CD, ras, pram,	13 5	31	75	22	9	R<L
6	6	6	LD-CD	18	42 5	70	22 5	20	R<L
7	9	9	LD-CD, tri, pram	15	38	70	30 5	7 5	L<R
8	1	3	LD-CD	15	21	90	14 5	6 5	L<R
9	2	6	LD-CD	12 5	32	75	23	9	L<R
10	8	11	LD- CD/entaca pone, ras	16 5	18 5	70	10	8 5	L<R
11	0 5	1	LD-CD	16	21 5	75	12 5	9	L<R
12	4	5	LD-CD, pram	14 5	34	70	23	11	R<L
13	4	5	LD-CD	13 5	41 5	70	30 5	11	R<L
14	4	4	LD-CD	17	26 5	70	10 5	16	L<R
15	5	6	rop, ras	17	29 5	85	17 5	12	R<L

¹ Information obtained from patient history on database. Duration since diagnosis was always reported. Duration since 1st symptoms was reported as duration since diagnosis if not reported differently by patient.

² LD-CD= levodopa-carbidopa (L-dopa/ Dopa decarboxylase inhibitor), ras= rasagiline (MAO-B selective agent), pram=pramipexole (dopamine receptor agonist), ent= entacapone (COMT inhibitors), rop=ropinirole (dopamine receptor agonist), tri= trihexyphenidyl (antimuscarinic).

³ UPDRS-III scores represent clinical evaluation on the motor subsection of the Unified Parkinson's Disease Rating Scale. Disease laterality was based on the sum of scores on the right side compared to the left side.

2.3.2 Apparatus

To perform the bimanual wrist flexion-extension movements, two robotic Phantom Omni haptic devices (SensAble Technologies Inc., Woburn, MA, USA) were placed 28 cm apart on a table (192 by 87 by 66 cm). These devices were synchronized together and used concurrently. The Omni haptic devices were synchronized to a

computer (Dell Computer, with a g-force intel Pentium 4 with SSE2) for data recording using MatLab R2007b (The MathWorks Inc, Natick, MA, USA) Pen-shaped handles (16.5 cm in length) projected from the robotic arms that attached to the base of the device that allowed for three-dimensional (3-D) movements (16 cm in medial-lateral direction, 12 cm in superior-inferior direction and 7 cm in anterior-posterior direction) A device was created (76.5 by 30 by 6 cm) to constrain the forearms to avoid unwanted movements at the elbow and shoulder joints and promote unrestrained 3-D wrist movements (see Figure 2.1) The *forearm constraint* device had the forearms resting on a foam pad and resulted in the hands being elevated above the table 4 cm at rest

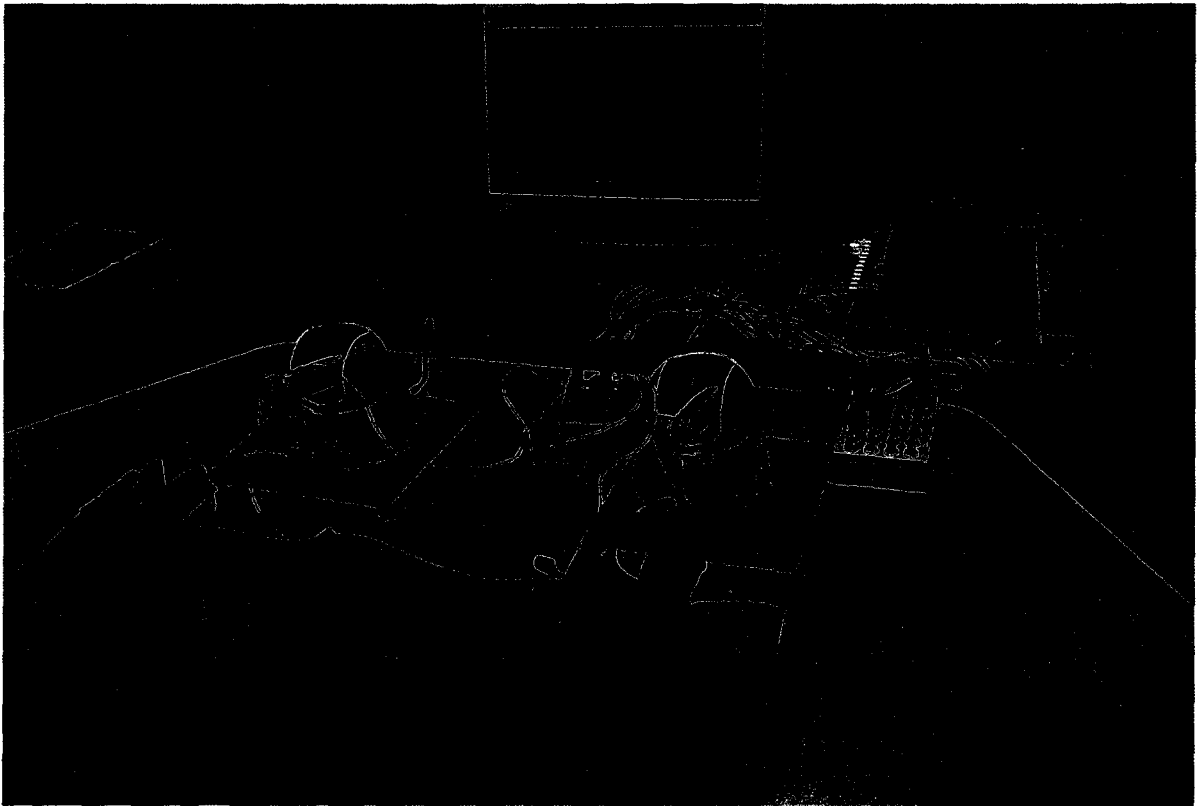


Figure 2.1 – Experimental set-up including Omni Devices, *forearm constraints* and computer monitor with augmented feedback display

A computer program *Free Motion* was created using Simulink in MatLab R2007b to run each trial. An internal computer-generated metronome was synchronized to MatLab using QuaRC (Quanser Inc, Markham, On, Canada) that produced a beat at a pitch of 800 Hz at several different cycle frequencies (see Protocol). *Free Motion* was designed to work with QuaRC to synchronize timing of the metronome beats and record displacement from each of the Omni devices.

A computer monitor (ADI ProVista) was situated 102 cm away from participants at eye level. Online augmented visual feedback was created using Simulink in MatLab R2007b. Augmented visual feedback used the same principles that have been previously applied to create Lissajous plots (Almeida, Wishart, & Lee, 2003, Verschueren, Swinnen, Dom, & De Weerdt, 1997). This form of visual feedback was created by displacement of the right hand that formed the abscissa or vertical line and displacement of the left hand produced the ordinate or horizontal line. The combined movement of both hands produced a single integrated online diagonal or elliptical representation on the computer monitor. The current study presented this form of augmented feedback as a purple ball to represent the displacement of the limbs that did not remain on the computer monitor unlike Lissajous plots. Additionally, two transparent diagonal cylinders with slopes of 1 (for in-phase) and -1 (for anti-phase) were displayed and remained on the blackened computer screen. The length of the diagonal cylinders was equivalent to the maximum movement in the medial-lateral direction (32 cm) and provided the participants with a precise spatial component of the movement (see Figure 4.1). To cover the arms during the trials that used the augmented visual feedback, an *arm-covering* device was created resembling a haircutting apron.

2.3.3 Protocol

Each participant was required to perform the protocol in two sessions within a single day. Participants performed coordinated bimanual wrist flexion-extension movements with their forearms constrained and hands pronated 90° (thumbs facing upwards). Individuals grasped the pen-shaped attachment (16.5 cm) with the whole hand (thumb on-top and facing forwards) to move the robotic arms and rotate the base of the device. Participants were instructed to move primarily in the medial-lateral direction but to not be concerned if they naturally deviated from this path.

Before each trial began, participants were instructed to coordinate their limbs in either in-phase or anti-phase. In-phase and anti-phase have both been shown to be intrinsic, stable coordination patterns that exist in the human motor system and have often been used to evaluate bimanual coordination from the perspective of motor control (Haken, Kelso, & Bunz, 1985; Kelso, 1984; Kelso, Southard, & Goodman, 1979; Schoner, 1990; Yamanishi, Kawato, & Suzuki, 1980). In-phase was performed as a symmetrical pattern that required simultaneous flexion and extension of the wrists. This coordination required the synchronized use of homologous muscles in both limbs and a relative phase goal of 0° or 360° (Schoner & Kelso, 1988b). Anti-phase was performed as an asymmetrical pattern that had participants perform simultaneous flexion with one wrist and extension with the other wrist. This phase pattern required the use of non-homologous musculature in each limb and a relative phase goal of 180° (Schoner & Kelso, 1988b).

Prior to the beginning of each trial, visual feedback was manipulated to permit three sensory feedback conditions: 1) *no vision* eliminated vision by blindfolding

participants, ii) *normal vision* allowed participants to see their wrist movements with the Omni devices, iii) *augmented vision* eliminated vision of the moving limbs and required participants to use the augmented visual feedback on the computer monitor

Before the first session began, participants had a familiarization session of 4 practice trials with the haptic devices and the augmented visual feedback. The investigator instructed participants that the goal of augmented visual feedback was to keep the moving ball in the three-dimensional cylinders since this represented an accurate relative phase and deviations from the required relative phase resulted in the ball going outside the cylinders. The participants were informed that if the ball began to move more horizontally than the left limb was producing inappropriate movements and adjustments were required. Additionally, if the ball moved in a more vertical fashion than the right limb was producing inappropriate movements and corrections were needed. Participants practiced these movements with the augmented visual feedback during the familiarization session.

To begin each trial the investigator manually started *Free Motion Free Motion* automatically produced a warning signal at 5 seconds that indicated to participants to get into a 'ready' position and maintain this position until the metronome began at 12 seconds. The 'ready' position had participants elevate their hands in the superior direction with the Omni devices from 4 to 8.5 cm unless due to rigidity they were already at the desired level. The level of the 'ready' position was marked with a red line on the actual base of each Omni device. After the warning signal, the metronome beats began at 12 seconds at a cycle frequency of 0.75 Hz. Participants were required to move

continuously and rhythmically with the metronome producing a full cycle of wrist flexion and extension with each beat

For the duration of each trial, a dynamic cycle frequency protocol was used to increase the cycle frequency at approximately equal intervals of 7 seconds. *Free Motion* automatically initiated the increases to a specific cycle frequency during each trial at designated time intervals: at 18.64 seconds to 1 Hz, at 24.66 seconds to 1.25 Hz, at 31.06 seconds to 1.5 Hz, at 37.05 seconds to 1.75 and at 43.36 seconds to 2 Hz until 50 seconds. Thus, each trial lasted 50 seconds but coordinated movement was only required for 38 seconds. The use of the dynamic increases in cycle frequency was adapted from studies that have investigated spontaneous phase transitions (Byblow et al., 2002, Byblow et al., 2000, Geuze, 2001). The goal of the cycle frequency manipulations within trials was to promote increases in coordination variability (Kelso, 1984).

Participants were informed that movement characteristics might naturally change especially when cycle frequency is increased resulting in increased variability. Individuals were to preserve the required movement to the best of their ability. If a spontaneous pattern switch occurred, participants were required to maintain continuous movement but switch back to the necessary pattern. Additionally, if a freeze occurred in participants with PD (with one or both limbs) they were to maintain movement in any limb that was not frozen and once they could move the frozen limb to maintain the desired phase relationship and cycle frequency.

The combination of phase and sensory manipulations created 6 conditions. Each condition was performed in a -randomized order 3 times for a total of 18 trials per session. The testing sessions were performed concurrently with other unimanual and

bimanual trials that were concerned with PD tremor (results presented elsewhere) Each testing session lasted approximately one and a half hours including set-up, UPDRS and 3-MS assessments and testing protocol Rest was provided when needed to reduce fatigue

2.3.4 Data Processing and Analysis

Matlab R2007b recorded displacement in all three dimensions at a rate of 1000 Hz per second from each of the Omni devices for a total of 38000 samples per trial Data was recorded and stored in MatLab R2007b Data analysis was performed on medial-lateral displacement using a script created in MatLab R2007b Anterior-posterior and superior-inferior displacement was kept for future analysis

Coordination Accuracy and Stability

A calculation of the relative phase (position of one limb relative to the other) was used to evaluate coordination accuracy and stability The relative phase was determined from the position of one limb relative to the other using the formula

$$\text{Relative phase } (\theta) = \tan^{-1} [(dXR/dt)/XR]$$

Where θ was the relative phase between limbs at each sample, X was the position of each limb within a cycle rescaled to the magnitude $[-1,1]$ and (dXR/dt) referred to the normalized and continuous instantaneous velocity (Haken et al , 1985) Since phase relationships could range from 0 to 360°, a linear transformation was performed on the relative phase to obtain values from 0 to 180° using the formula

$$\text{New Relative Phase } (\theta_n) = 180 - (\text{relative phase } (\theta) - 180)$$

Absolute error (AE) of the relative phase (θ_n) was used to calculate coordination accuracy The mean AE of θ_n was determined for each cycle frequency during every

trial In addition, the standard deviation of AE was determined for each cycle frequency during every trial as a measure of coordination stability

Amplitude

The amplitude of each limb was measured independently to evaluate the spatial component of the movement Specifically, this measure was used to evaluate if any amplitude deficits representative of hypometria existed in individuals with PD The amplitude was determined from each cycle of movement using the formula

$$\text{Amplitude (in cm)} = \text{Amplitude Peakmax (in cm)} - \text{Amplitude Peakmin (in cm)}$$

The mean amplitude of each limb was determined from averaging the amplitude of each peak during each cycle frequency for every trial

Frequency

The frequency of movement of each limb was calculated to evaluate the temporal component of the movement This measure was purposely used to evaluate if any frequency deficits representative of bradykinesia existed in individuals with PD The frequency was calculated using the movement cycles (positive to subsequent positive peak) during a given time using the formula

$$\text{Frequency (in Hz)} = \text{number of cycles} / \text{time (in s)}$$

The mean frequency of each the right and left limb was determined at each cycle frequency for every trial

Statistical Comparison

All of the trials were calculated, coded and organized using MatLab R2007b Each file was then transferred into a Microsoft Excel spreadsheet Statistical analyses were performed using Statistica 8 (StatSoft Inc , Tulsa, Ok, USA) using the general linear

model function T-tests were performed on age, 3-MS scores, education and time between sessions to verify that no differences existed between PD and healthy control participants Additionally, a paired t-test was performed on UPDRS-III scores of PD 'off' and PD 'on'

To analyze coordination accuracy (mean relative phase) and stability (standard deviation of relative phase), a mixed-model (between and within-group) ANOVA was performed session*condition * phase * cycle frequency Planned comparisons were performed between session 1 of PD (PD 'off') and healthy control to determine the effects of basal ganglia dysfunction on coordination performance Additionally, a planned comparison was performed between session 1 (PD 'off') and session 2 (PD 'on') of PD participants to determine the effects of dopamine replacement on coordination performance Finally, a planned comparison was performed on session 1 compared to session 2 of healthy control participants to determine if any practice effects existed (only interactions that included session were reported)

Mean amplitude and frequency were compared in a mixed-model ANOVA session* limb * condition * phase * cycle frequency To determine the effect of basal ganglia dysfunction on amplitude and frequency the more and less affected limbs in PD 'off' (see Table 2 2) were compared to matched hands in healthy controls Hands were matched based on age (and gender when possible) To determine the effect of the dopaminergic system on amplitude and frequency, the more affected limb was compared to the less affected in session 1 (PD 'off') compared to session 2 (PD 'on') of PD participants

An alpha level of 0.05 was used to define statistical significance. Tukey's HSD post hoc analysis was used to investigate any significant interactions.

2.4 Results

2.4.1 Comparison of demographic variables

Student's t-tests were performed on the mean values for each demographic variable. All measures between PD and healthy control participants including age, self-reported education, time between sessions and 3-MS scores were not different (see Table 4.3). The UPDRS-III scores were found to be significantly different (mean difference = 10.6 +/- 3.6) between PD 'off' (mean UPDRS 'off' = 30.6 +/- 8.6) and PD 'on' (mean UPDRS 'on' = 20 +/- 7.9) ($t(14) = 3.5$, $p < 0.01$) (see Table 4.2).

Table 2.3 – Statistical comparisons of age, education, 3-MS and time between sessions of PD and healthy control (HC) participants

	PD	HC	T statistic (df) and p-value
Age (in years)	68 (+/- 6.3)	65.5 (+/- 7.3)	$t(28) = 0.99$, $p = 0.33$
3-MS (out of 100)	94.1 (+/- 5.2)	96.3 (+/- 3.7)	$t(28) = 1.3$, $p = 0.21$
Self-reported education (in years)	14.5 (+/- 3.8)	14.5 (+/- 3.8)	$t(28) = 0.24$, $p = 0.98$
Time between sessions (in minutes)	76.3 (+/- 8.1)	72.7 (+/- 6.5)	$t(28) = 1.4$, $p = 0.18$

2.4.2 PD 'off' vs. healthy control participants

Coordination Accuracy

There were significant main effects of phase ($F(1,28) = 33.47$, $p < 0.01$) and cycle frequency ($F(5,140) = 54.22$, $p < 0.01$) that was superseded by a significant interaction between phase and cycle frequency ($F(5,140) = 18.52$, $p < 0.01$). Tukey's post hoc analysis revealed that there was greater accuracy in coordination during in-phase compared to anti-phase as cycle frequency increased (1.25, 1.5, 1.75 and 2 Hz). Additionally, greater

coordination accuracy was found during in-phase and anti-phase at 0.75 and 1 Hz compared to 1.75 and 2 Hz

No main effect or interactions were revealed between groups for coordination accuracy

Coordination Stability

A significant main effect of phase was found ($F(1,28)=67.31, p<0.001$) that demonstrated that coordination was less variable during in-phase compared to anti-phase. In addition, there was a significant main effect of cycle frequency ($F(5,140)=63.34, p<0.001$). Tukey's post hoc analysis showed that there was less variability at the two slowest cycle frequencies (0.75 and 1 Hz) but coordination became increasingly more variable at each subsequent cycle frequency interval. A significant main effect of condition was also revealed ($F(2,56)=9.96, p<0.001$). Tukey's post hoc analysis found that there was less variable coordination in *no vision* and *normal vision* relative to *augmented vision*.

A difference (main effect or interactions) between groups was not found for coordination stability.

Mean amplitude (affected/less affected limbs PD 'off' compared to matched limbs)

There was a main effect of group on the mean amplitude ($F(1,28)=17.1, p<0.001$). Overall, amplitudes were larger in both limbs in healthy controls (mean=14.6 cm) compared to PD 'off' (mean=8.5 cm). This was succeeded by significant main effects of phase ($F(1,28)=12.2, p<0.01$) and cycle frequency ($F(5,140)=15.9, p<0.001$) and significant interactions between group and cycle frequency ($F(5,140)=12.3, p<0.001$) and group, phase and cycle frequency ($F(5,140)=3.5, p<0.01$). As illustrated in Figure 2.2, Tukey's post hoc analysis showed that healthy controls were performing larger movements with

both limbs compared PD 'off' except comparable amplitudes during anti-phase at 0.75 Hz. Healthy controls increased the amplitude of movements from 0.75 to 1.5 Hz then maintained this amplitude at the faster cycle frequency during in-phase but during anti-phase increased from 0.75 to 1.25, then further from 1.5 to 1.75 Hz and maintained at 2 Hz. PD 'off' did not change amplitude regardless of phase or increasing cycle frequency.

Disease laterality was shown to affect amplitude as revealed by an interaction between limb and cycle frequency ($F(5,140)=3.8, p<.01$). Tukey's post hoc analysis showed that the less affected limb PD (matched limb in healthy controls) had larger movements at 2 Hz compared to the more affected limb. Overall, the more affected and less affected limbs increased amplitude between 0.75 to 1.25 Hz. The more affected limb decreased amplitudes between 1.25 and 1.5 and further between 1.75 and 2 Hz. The less affected limb decreased between 1.25 and 1.5 had an increase in amplitude between 1.5 and 1.75 Hz then decreased between 1.75 and 2 Hz.

There was also a main effect of condition ($F(2,56)=20.4, p<.001$). Tukey's post hoc analysis demonstrated that larger amplitude movements (regardless of group or limb) were produced in *normal vision* compared to *no vision* and *no vision* compared to *augmented vision*.

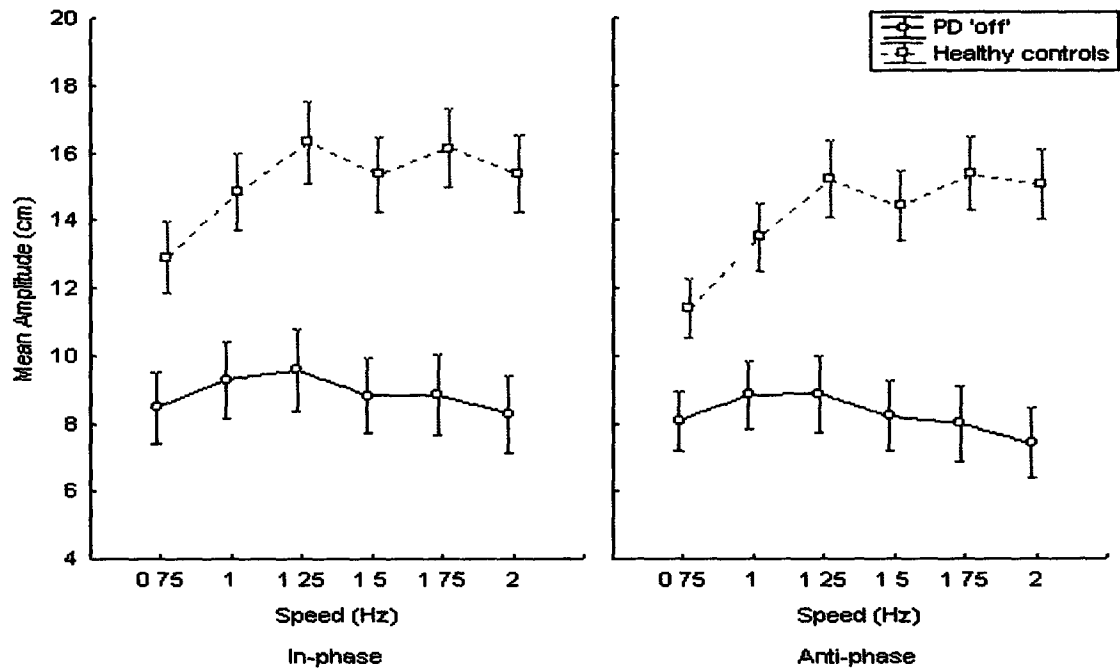


Figure 2.2 –Mean amplitude (cm) of limb movements (including standard error bars) compared between PD 'off' and healthy control participants as a function of phase and cycle frequencies. Results showed that significantly ($p < 0.01$) larger amplitude movements were produced by healthy control participants compared to PD 'off' participants except during anti-phase at 0.75 Hz.

Mean frequency (affected/less affected in PD 'off' compared to matched hands in healthy controls)

There was a significant main effect of cycle frequency ($F(5,140)=394.8, p < 0.001$) that was superseded by a significant interaction between group, limb and cycle frequency ($F(5,140)=3.4, p < 0.01$). Tukey's post hoc analysis indicated that the frequency of both limbs was not directly different at any cycle frequency between PD 'off' and healthy controls. PD 'off' increased the frequency of the both limbs with increasing cycle frequency demand (except a decrease between 1.25 and 1.5 Hz). Healthy control participants also increased the frequency of movements with the both limbs with

increasing cycle frequency (except between 1.25 and 1.5 Hz there was a maintained frequency)

There was also a main effect of phase ($F(1,28)=8.5$, $p<0.01$) that was superseded by a significant interaction between phase and cycle frequency ($F(5,140)=5.5$, $p<0.001$). Tukey's post hoc analysis showed that faster movements were performed during in-phase compared to anti-phase at 1.75 and 2 Hz. Overall, frequency of movements increased with increased cycle frequency demand except maintenance of frequency between 1.25 and 1.5 Hz.

2.4.3 PD 'off' vs. PD 'on'

Coordination Accuracy

Significant main effects were found for cycle frequency ($F(5,70)=29.70$, $p<0.001$) and phase ($F(1,14)=21.23$, $p<0.001$) that was superseded by a significant interaction between phase and cycle frequency ($F(5,70)=11.55$, $p<0.001$). Tukey's post hoc analysis demonstrated that coordination was more accurate during in-phase at 4 cycle frequencies (1.25, 1.5, 1.75 and 2 Hz) compared to anti-phase. Additionally, coordination was more accurate at 3 cycle frequencies (0.75, 1 and 1.25 Hz) relative to 2 Hz during in-phase and more accurate at 0.75 and 1 Hz relative to 1.5, 1.75 and 2 Hz during anti-phase. A main effect of condition was also found ($F(2,28)=4.1$, $p<0.05$) that revealed coordination was more accurate in *no vision* compared to *augmented vision*.

There was no significant influence (main effect or interactions) of dopamine replacement on coordination accuracy.

Coordination Stability

Main effects were found for phase ($F(1,14)=42.5$, $p<0.001$) and cycle frequency ($F(5,70)=32.6$, $p<0.001$) that was succeeded by a significant interaction between phase and cycle frequency ($F(5,70)=13.01$, $p<0.001$). Tukey's post hoc analysis revealed that coordination was less variable during in-phase at all cycle frequencies compared to anti-phase. In addition, less variable coordination was found during in-phase at 0.75, 1 and 1.25 Hz compared to 2 Hz. Furthermore, coordination was less variable at 0.75 and 1 Hz compared to 1.75 and 2 Hz as well at 1.5 Hz compared to 1.75 Hz and 1.75 Hz compared to 2 Hz during anti-phase. A significant main effect of condition was found ($F(2,28)=4.39$, $p<0.05$) that demonstrated coordination was less variable in *normal vision* compared to *augmented vision*.

Similar to coordination accuracy, there was no influence of dopamine replacement (significant main effect or interactions) on coordination variability. *Mean amplitude (More affected compared to less affected)*

The influence of disease laterality and dopamine replacement on amplitude was revealed by a significant main effect of cycle frequency ($F(5,70)=4.5$, $p<0.01$) that was superseded by significant interactions between dopamine replacement and cycle frequency ($F(5,70)=9.0$, $p<0.001$), limb and cycle frequency ($F(5,70)=7.5$, $p<0.001$) and dopamine replacement, limb and cycle frequency ($F(5,70)=4.5$, $p<0.01$). As illustrated in Figure 2.3, Tukey's post hoc analysis indicated that larger amplitude movements were produced with the more affected limb at 3 cycle frequencies (0.75, 1, and 1.25 Hz) in PD 'off' compared to PD 'on'. However, at 1.5 and 2 Hz PD 'on' performed larger movements in their more affected limb compared to PD 'off'. In addition, less affected limb in PD 'off' (compared to PD 'on') performed larger movements only at 1 Hz where

as this limb in PD 'on' (compared to PD 'off') produced larger movements at most cycle frequencies (0.75, 1.5, 1.75 and 2 Hz). Specifically for PD 'off', larger amplitudes were performed with the less affected limb compared to the more affected limb at 1.75 and 2 Hz. PD 'on' performed larger movements in the less affected limb compared to the more affected limb at all cycle frequencies.

There was also a main effect of condition ($F(2,28)=5.5$, $p<0.01$). Tukey's post hoc analysis showed that larger movements were performed in *normal vision* compared to *augmented vision*.

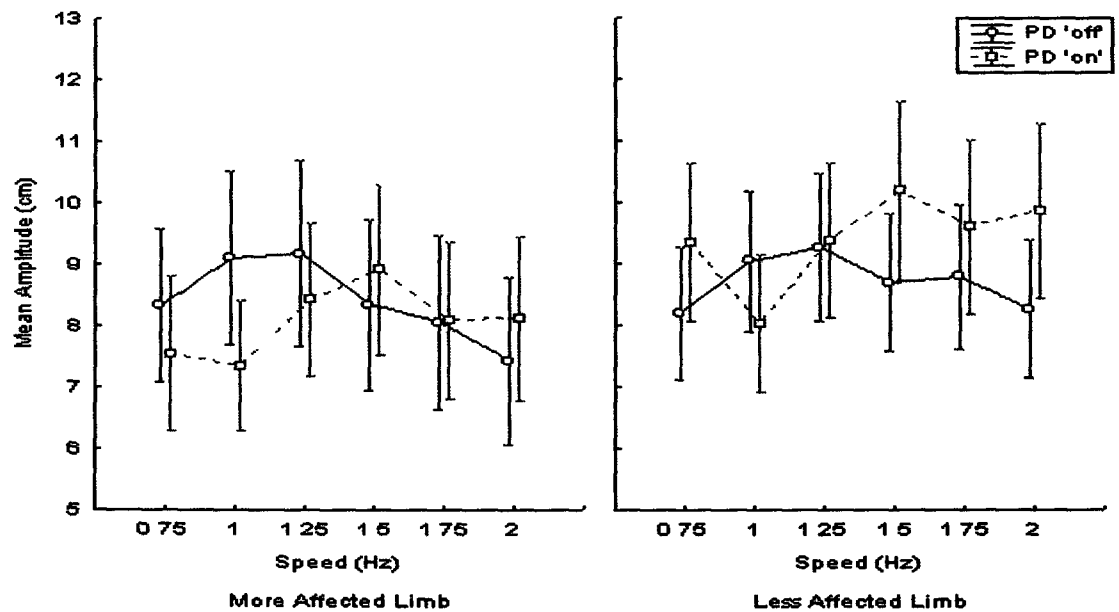


Figure 2.3 – The influence of dopamine replacement on the mean amplitude (cm) of the more and less affected limbs in PD participants across cycle frequencies (including standard error bars). Results demonstrated that PD participants 'on' dopamine replacement produced significantly ($p<0.01$) larger amplitude movements in both limbs predominantly at faster cycle frequencies.

Mean frequency (More affected compared to less affected)

Unlike amplitude, dopamine replacement did not have an influence (significant main effect or interactions) on frequency of either limb. There was a main effect of cycle frequency ($F(5,70)=169.17$, $p<0.001$) that was superseded by a significant interaction

between limb and cycle frequency ($F(5,70)=2.5$, $p < 0.05$) Tukey's post hoc analysis did not demonstrate any direct differences between the more and less affected limbs at any given cycle frequency. The frequency of more affected limbs increased with increasing cycle frequency except maintenance of frequency between 1.25 and 1.5 Hz. In comparison, the frequency of the less affected limbs increased with increasing cycle frequency except a decrease in frequency between 1.25 and 1.5 Hz.

A significant interaction between condition, phase and cycle frequency was found ($F(10,140)=2.4$, $p < 0.05$) Tukey's post hoc analysis showed that during in-phase the frequency of limb movement increased in *no vision*, *normal vision* and *augmented vision* with increased cycle frequency (except stayed same between 1.25 and 1.5). This same effect was seen during anti-phase coordination in *normal vision*. However, during anti-phase in *normal vision*, frequency did not increase between 0.75 and 1 or between 1.25 and 1.5 Hz. During anti-phase in *augmented vision*, frequency of limb movements did not increase between 0.75 and 1 Hz and actually decreased during 1.25 and 1.5 before increasing in subsequent cycle frequencies.

2.4.4 An examination of practice effects in coordination performance (Healthy control's session 1 vs. session 2)

Coordination Accuracy

A significant main effect of session was found ($F(1,14)=15.05$, $p < 0.01$) that indicated healthy control participants' coordination were more accurate in the second session relative to the first session (15.09 vs. 17.06°). There was also a significant main effect of cycle frequency ($F(5,70)=29.83$, $p < 0.001$) that was superseded by a significant interaction between session and cycle frequency ($F(5,70)=2.65$, $p < 0.05$) Tukey's post hoc

analysis revealed that there was more accuracy in coordination at the fastest cycle frequency in session 2 relative to session 1. Additionally, there was more accuracy in coordination at 0.75 and 1 Hz relative to each successive cycle frequency (see Figure 2.4)

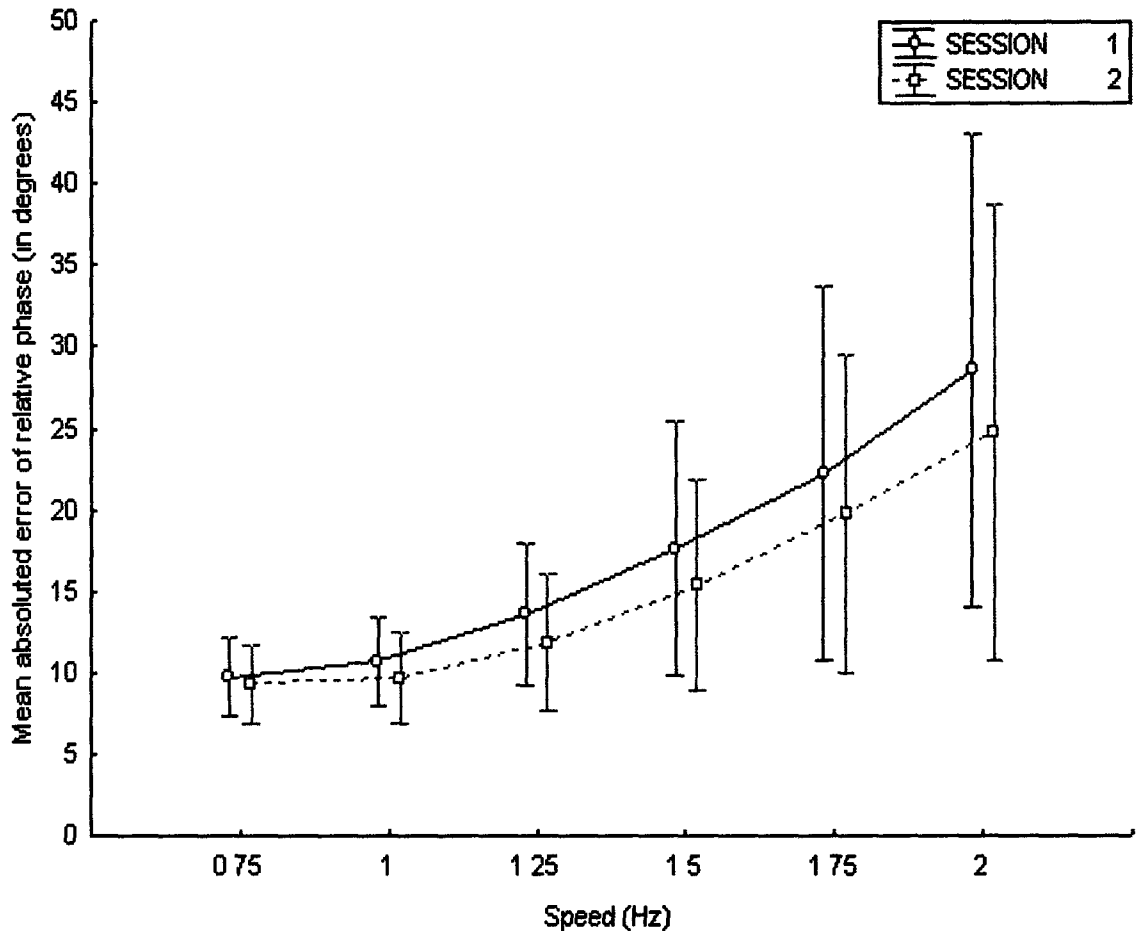


Figure 2.4 – Coordination accuracy as revealed by the mean in absolute error of the relative phase ($^{\circ}$) across two sessions in healthy control participants while coordinating at different cycle frequencies (standard error bars included). Results revealed that healthy control participants were significantly ($p < 0.05$) more accurate at coordinating at 2 Hz during session 2 compared to 1.

Coordination Stability

There was a significant main effect of session ($F(1,14)=31.08, p < 0.001$) that demonstrated healthy controls had less variability in session 2 relative to session 1 (11.77

vs 12.94°) This was further represented by a significant main effect of phase ($F(1,14)=28.86$, $p<0.01$) and a significant interaction between session and phase ($F(1,14)=5.07$, $p<0.05$). Tukey's post hoc analysis revealed that there was less variability during anti-phase in session 2 compared to session 1 (but no difference during in-phase). Additionally, coordination was less variable during in-phase compared to anti-phase (see Figure 2.5).

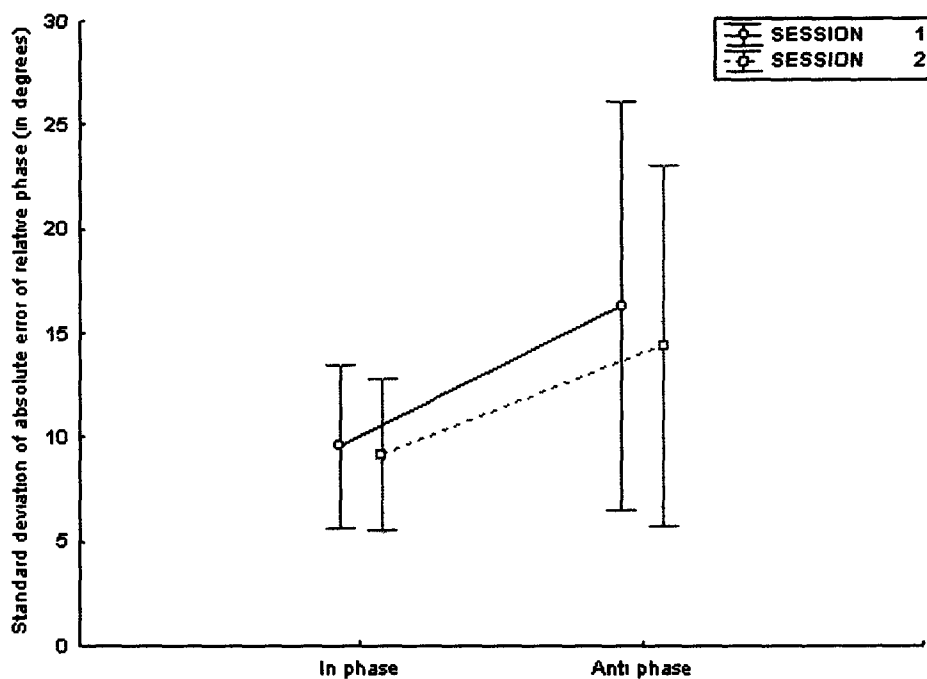


Figure 2.5 – Coordination stability as revealed by the standard deviation of the relative phase in healthy control participants during both in-phase and anti-phase across sessions (standard error bars included). Results revealed that healthy control participants significantly ($p<0.05$) improved their stability during anti-phase coordination.

2.5 Discussion

The primary objective was to determine if the dopaminergic system was associated to performance (coordination, amplitude and frequency) during a continuous bimanual task in individuals with PD. It was hypothesized that regardless of the effects of dopamine replacement on amplitude and frequency of movement, dopamine modulation

would not influence coordination performance in PD. Our results partially supported this hypothesis. The main findings were that dopaminergic modulation increased amplitude of movements in both limbs but did not influence coordination performance in PD. This supports the notion that dopamine replacement improves motor symptoms but not coordination in itself. Although decreased amplitudes were observed in both limbs in PD 'off' (relative to healthy control participants), coordination deficits were not found in PD compared to healthy control participants regardless of manipulations in sensory feedback, phase or cycle frequency. Thus, there was no direct evidence to support that dysfunction outside the dopaminergic system (e.g. sensory and/or attentional deficits) influenced performance during bimanual coordination in individuals with PD.

As expected, anti-phase coordination was performed with greater error and variability at the faster cycle frequencies in all participants (Kelso, 1984). However, no differences in coordination accuracy or stability were found between PD 'off' and healthy control participants. Several studies have found coordination accuracy and stability to be comparable in PD and healthy control participants in rhythmic bimanual coordination during in-phase and anti-phase (Byblow, Lewis, & Stinear, 2003, Byblow et al., 2002), only during in-phase (Almeida et al., 2002, Byblow et al., 2000) and during anti-phase at 2 Hz (Johnson et al., 1998). Johnson *et al.* (1998) suggested that the discrepancy between previous studies was in part due to the relationship between different task demands (e.g. cycle frequency, phase, external cueing, visual feedback, type of movement and amplitude). The current study had participants bimanually coordinate their movements with the presence of an external metronome without any specific amplitude requirements. The current results demonstrated that individuals with PD were able to coordinate with

the appropriate frequency of movements in each limb despite the existence of hypometric deficits. This is in agreement with previous studies that have found that auditory cueing (compared to removal of cues) is useful for maintaining the correct frequency of movements in PD during bimanual coordination (Byblow et al., 2002, Johnson et al., 1998). It has been argued that individuals with PD have an impaired ability to internally regulate timing of repetitive movements especially at fast cycle frequencies (Cunnington, Iansek, Bradshaw, & Phillips, 1995, Freeman, Cody, & Schady, 1993, Georgiou, Bradshaw, Phillips, Iansek, & Mattingley, 1993, Yahalom, Simon, Thorne, Peretz, & Giladi, 2004). In view of the fact that individuals with PD were maintaining the correct frequency of movements with the metronome, it would suggest that attention was directed at synchronizing movements with the external cues to compensate for internal timing deficits. However, these increased attentional demands from external auditory cueing did not negatively influence coordination performance as suggested by Almeida *et al.* (2002).

In addition, the results of the current study do not support the notion that sensorimotor integration deficits can account for coordination performance in individuals with PD. Difficulties in sensorimotor integration in PD are usually observed during slow voluntary movements (Abbruzzese & Berardelli, 2003) such as self-paced reach-to-grasp movements (Mongeon, Blanchet, & Messier, 2009, Schettino et al., 2006) rather than externally cued fast movements like the current study. Furthermore, it has been demonstrated that tactile cues are able to attenuate conflicting proprioceptive information during a 45° horizontal arm matching task (Rabin, Muratori, Svokos, & Gordon, 2010). This would suggest that the fast movements used in the current study and tactile cues

from grasping the stylus on the haptic devices reduced the influence of sensory deficits in PD participants

The current study found that external timing cues were sufficient to remove the effects of bradykinesia (slowness) and dopamine replacement did not influence the frequency of movements during bimanual coordination in individuals with PD. Dopamine replacement was found to improve the amplitude of movement (hypometria) particularly on the more affected limb relative to the less affected limb especially at faster cycle frequencies. This supports previous research that has identified the benefits of dopamine replacement on the amplitude of voluntary limb movements (Espay et al , 2009) and that improvements of amplitude are usually more pronounced on the more affected side relative to the less affected side during bimanual movements (Kishore et al , 2007). However, despite improvements in the amplitude neither coordination accuracy nor stability was influenced by dopaminergic modulation. The lack of contribution of dopamine replacement to coordination was in agreement with the hypothesis that bimanual coordination is influenced by a distributed network (Aramaki et al , 2006, Carson, 2005, De Luca et al , 2010, Oullier et al , 2005, Swinnen, 2002) and not associated directly to dopamine loss or dopa-responsive motor symptoms. However, the current results were not able to attribute this to the proposed sensory and/or attention deficits. One possibility is that the attentional demands of the current task were not sufficient to challenge the attentional resources of individuals with PD. Alternatively, the current results demonstrated that attention was directed at the external auditory cues to coordinate the timing of their movements. It may be possible that individuals with PD directed attention away from visually demanding information and it did not have a major

influence of overall movement performance. This was further supported since no differences were observed in PD and healthy control participants when manipulating visual feedback.

The current study's findings about dopaminergic modulation in PD need to be carefully considered in combination with the improvement in coordination performance observed across sessions in healthy control participants. It was revealed that coordination accuracy (with increased cycle frequency) and stability (during anti-phase) improved from session 1 to 2 in healthy control participants. However, no improvements were seen in PD across sessions (regardless of practice or dopamine replacement). The improvements observed in healthy older adults were surprising given that learning should have been minimal during in-phase and anti-phase coordination since they are considered stable intrinsic coordination patterns (Schoner & Kelso, 1988a). It has previously been suggested that PD are impaired in motor learning (Jahanshahi et al., 2010, Krebs, Hogan, Hening, Adamovich, & Poizner, 2001, Rodriguez-Oroz, Lage et al., 2009). Furthermore, motor learning has been argued to be influenced by dopaminergic modulation (Jahanshahi et al., 2010). Jahanshahi *et al.* (2010) proposed that the tonic release of dopamine as provided by dopamine replacements impairs the phasic release of dopamine that is essential for learning. The lack of learning in individuals with PD could be an alternative explanation for the current results such that motor learning was not able to occur between sessions due to the administration and subsequent influence of dopamine replacement. However, it may be possible that the improvements observed in healthy older adults were in relation to participants becoming more efficient at the movement rather than learning. This needs to be carefully considered in future research.

In conclusion, the current results support that coordination performance is not influenced by dopamine replacement in individuals with PD. In addition, external auditory cueing was beneficial for maintaining the inter-limb timing and frequency of movements of each limb. This resulted in comparable coordination performance in PD and healthy control participants. It is proposed that coordination deficits are not universal in PD but are dependent on the task demands. Collectively, these results could suggest that secondary dysfunction related to attentional demands of the task (rather than dopaminergic system dysfunction) could be responsible for coordination deficits in individuals with PD. Although the current results did not directly support that increased attentional demands result in impairments in coordination performance, this may have been related to the current experimental set-up. Future research should incorporate the use of eye trackers to monitor visual attention. This would be particularly important when examining the attentional demands from different sources of visual feedback. In addition, examining bimanual coordination in individuals with PD during a task that requires increased cognitive and attentional demands could help to reveal the influence of attention on bimanual coordination. This could be done by adding a cued-voluntary switch or dual-task during rhythmic bimanual coordination. Finally, it would be beneficial to examine dopaminergic modulation in PD in studies that limit the possible effects of motor learning.

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Chapter 3- Study #2: The influence of dopamine replacement on cued-intentional pattern switching during bimanual coordination in Parkinson's disease (PD)

3.1 Abstract

Cued-switching during bimanual in-phase (symmetrical, simultaneous movements) and anti-phase (asymmetrical, alternating movements) coordination results in slowed switching, delayed responses and subsequent coordination deficits in individuals with Parkinson's disease (PD). However, due to the known improvements of bradykinesia (slowness) with dopamine replacement, modulation of the dopaminergic system may improve overall performance on such tasks. PD and healthy age-matched control participants were compared on a rhythmic coordination task that required a cued voluntary switch between phases (in-phase and anti-phase) in the middle of trials. PD participants performed two consecutive sessions after overnight withdrawal ('off') then after administration ('on') of dopamine replacement. Coordinated movements were performed at one of two cycle frequencies (1 or 2 Hz) paced by an external auditory metronome and across one of two sensory conditions: *no vision* or *normal vision*. Measures of voluntary switch time and temporally delayed responses revealed that PD 'off' required more time than healthy participants to switch between phases regardless of coordination mode. The deficits in switching resulted in disrupted coordination in PD 'off' participants as revealed by the mean (accuracy) and standard deviation (stability) of absolute error of relative phase. Dopamine replacement decreased the time needed to

switch and amount of delayed responses in PD participants but had no influence on coordination performance. Thus, although modulation of the dopaminergic system could improve slowness during switching that may have been the result of bradykinesia and/or bradyphrenia, impairments in coordinated movements are the result of secondary dysfunction that may be related to attentional demands that cannot be improved with dopamine replacement.

3.2 Introduction

Bradykinesia (slowness in executing voluntary movements) is a cardinal motor symptom of Parkinson's disease (PD) that is caused by a loss of dopamine to the basal ganglia. Clinical assessments have confirmed that bradykinesia can be modulated by dopamine replacement (Espay et al, 2009, Kaufmann, Butz, & Wiesenda M, 1970). Individuals with PD have impairments such as slowness in switching (e.g. sequencing) between different unimanual motor tasks (Benecke, Rothwell, Dick, Day, & Marsden, 1987a, 1987b, Stelmach & Phillips, 1991, Stelmach, Worringham, & Strand, 1987). Research has found that dopamine replacement can improve the speed of executing a switch between different motor programs during a sequential unimanual squeeze and elbow flexion task (Benecke et al, 1987b). Studies that have combined a voluntary cued-switch phase pattern switch during bimanual coordination have identified that individuals with PD initiate switches slower (Byblow, Summers, Lewis, & Thomas, 2002) and perform voluntary switches slower than healthy older adults (Almeida, Wishart, & Lee, 2003, Geuze, 2001). In addition, more delayed responses and inability to execute switches have been identified in PD compared to healthy control participants (Almeida et al, 2003, Byblow et al, 2002, Geuze, 2001). This impaired switching has

been found to contribute to subsequent coordination deficits in both accuracy and stability (Almeida et al , 2003) This might indicate that switching and subsequent coordination performance may be associated with bradykinesia related to dysfunction of the dopaminergic system However, there is no research that has directly manipulated dopamine replacement to examine the contribution of dopaminergic system in intentional switching during continuous bimanual coordination

Almeida *et al* (2003) proposed that increased cognitive and attentional demands required for anti-phase coordination and an externally cued-switch contributed to the slower switching and coordination performance In addition, research on bimanual coordination in healthy adults observed increased attentional demands when initiating anti-phase coordination and when performing a dual-task of verbally responding to a stimulus (Ridderikhoff, Peper, & Beek, 2008) It has also been proposed that external auditory cues provide an additional attentional challenge for individuals with PD (Almeida, Wishart, & Lee, 2002) However, this could be related to difficulties in sensorimotor integration that have also been observed in PD (Abbruzzese & Berardelli, 2003, Lim, Hamm, Byblow, & Kirk, 2005) Previous research has demonstrated that neither attention (Riekkinen, Kejonen, Jakala, Soininen, & Riekkinen, 1998) nor sensorimotor integration during voluntary movements (Mongeon, Blanchet, & Messier, 2009, Schettino et al , 2006) are improved with dopamine replacement Thus, executing a cued-voluntary switch and resulting coordination deficits in individuals with PD may be influenced by attention demands or sensorimotor integration that is secondary to dopaminergic system dysfunction and improvements in bradykinesia

To examine the ability to execute a change during continuous coordination in individuals with PD, the current study used a cued intentional pattern switching task. The goal of the current study was to determine whether the dopaminergic system influenced the execution (speed and completion) of a cued switch during coordinated movement and coordination performance (accuracy and stability). It was hypothesized that if the dopaminergic system was involved in executing a switch and/or coordination performance, then switching and coordination deficits would be observed in individuals with PD after withdrawal from dopamine replacement (PD 'off') compared to healthy older adults. Furthermore, dopamine replacement would improve these impairments in individuals with PD. However, if executing a switch and/or coordination performance was related to other basal ganglia related dysfunction (e.g. attentional or sensorimotor integration deficits) in individuals with PD, then more difficulty in switching and coordination performance would be found when increasing sensory information, anti-phase coordination and/or cycle frequency regardless of manipulations in dopamine replacement.

3.3 Methods

3.3.1 Participants

Fifteen (n=15) individuals with a confirmed diagnosis of PD (mean age=67 +/- 7.5) and fifteen (n=15) healthy older adults (control participants) (mean age=67.8 +/- 8.7) participated in this study (see Table 3.1 for demographic information of PD and healthy control participants). All participants were assessed on the Modified Mini Mental State Examination (3-MS) to examine for signs of dementia and ensure they were cognitively intact to perform the experiment (Teng & Chui, 1987). A criterion score of 81 out of 100

was used as the cut-off based on previous recommendations (Tombaugh, McDowell, Kristjansson, & Hubley, 1996) All PD (mean 3-MS=95.5 +/-4.5) and healthy control participants (mean 3-MS=95.9 +/-3.0) had scores above this criteria. In addition, all participants were right-hand dominant based on responses to the Waterloo Handedness Questionnaire (WHQ) (Steenhuis & Bryden, 1989)

Motor symptoms of PD participants were evaluated on the motor subsection of the Unified Parkinson's Disease Rating Scale (UPDRS-III) (Fahn & Elton, 1987). The first evaluation was performed after overnight withdrawal of all dopamine replacements (mean time 'off'= 14.7 hrs +/- 2.8) and was used as a representation of PD 'off' state (mean UPDRS 'off'= 32.5 +/-8.8). The second evaluation (mean UPDRS 'on'= 24.2 +/-7.8) occurred after completion of the first session and participants self-administered their regular dosage of dopamine replacement (mean time= 74.7 min +/- 6.4). For the current study, a minimum difference of 5 points was used as a criterion between 'off' and 'on' scores to be classified as dopa-responsive (mean difference= 8.2 +/-2.6) for the current study (see Table 3.2 for clinical variables of PD participants)

Participants were excluded from the study if they had uncorrected vision, uncorrected hearing and any upper limb impairments that would not allow them to perform the required task. In addition, participants were excluded if they had previously had a stroke or any serious brain trauma. PD participants included regardless of motor symptoms such as tremor, freezing or rigidity. All PD participants were recruited from the patient database at the Sun Life Financial Movement Disorders Research and Rehabilitation Centre (MDRC) at Wilfrid Laurier University. Healthy control participants were recruited from family and friends of the PD participants. Ethics approval for this

study was granted by the Human Research Ethics Board (REB) at Wilfrid Laurier University

Table 3 1 – Demographic variables of healthy control and PD participants

Participant	Group ¹	Gender ²	Age (years)	3-MS (out of 100) ³	Education (years)
1	PD	F	63	99	18
2	PD	F	75	87	10
3	PD	M	69	93	14
4	PD	M	77	86	11
5	PD	M	58	94	17
6	PD	F	66	99	12
7	PD	F	53	99	17
8	PD	M	76	97	14
9	PD	F	68	97	10
10	PD	M	72	99	20
11	PD	M	74	91	12
12	PD	F	57	99	13
13	PD	M	60	94	14
14	PD	M	72	100	20
15	PD	F	65	98	16
16	HC	F	75	91	15
17	HC	M	68	95	17
18	HC	F	63	100	14
19	HC	F	75	98	16
20	HC	F	54	98	14
21	HC	F	79	94	12
22	HC	F	77	98	11
23	HC	M	58	96	13
24	HC	F	78	95	11
25	HC	F	66	97	12
26	HC	M	54	99	21
27	HC	F	69	91	10
28	HC	M	75	100	18
29	HC	F	59	94	14
30	HC	M	67	92	8

¹ PD= Parkinson's disease participants, HC= healthy control participants

² M= male, F= female

³ 3-MS represents the modified Mini-Mental State Examination

Table 3 2 – Clinical Characteristics of PD participants

Participant	Duration since diagnosis (in years) ¹	Duration since 1 st self-reported symptom (in years) ¹	Dopamine medication	Time 'off' medication (in hours)	UPDRS-III 'off' (score out of 108) ³	Time 'on' medication	UPDRS-III 'on' (score out of 108) ²	Difference between 'off' and 'on'	Disease Laterality ³
1	3	7	LD-CD	12	34	85	25	9	R<L
2	5	6	LD-CD	14.5	38.5	65	31.5	7	L<R
3	3	4	LD-CD	15	35.5	70	29	6.5	L<R
4	1	1	LD-CD	12.5	47.5	90	37.5	10	R<L
5	1	3	Pram	17.5	28.5	70	18.5	10	L<R
6	9	12	LD-CD/ent, ras	16	16	70	9	7	L<R
7	8	11	LD-CD/ent	12.5	42.5	75	32	10.5	L<R
8	2	6	LD-CD	15	32.5	70	23.5	9	R<L
9	7	7	LD-CD	14	26	70	19	7	R<L
10	9	11	LD-CD	12.5	38	75	31	7	L<R
11	3	10	Rop	12	32	75	23.5	8.5	R<L
12	2	2	LD-CD	19	30	80	24.5	5.5	L<R
13	12	12	LD-CD, rop, sel	12	39.5	75	24	15.5	R<L
14	1	2	LD-CD	21.5	15.5	75	10	5.5	R<L
15	5	6	LD-CD, pram	14	31	75	25.5	5.5	R<L

¹ Information obtained from patient history on database. Duration since diagnosis was always reported. Duration since 1st symptoms was reported as duration since diagnosis if not reported differently by patient.

² LD-CD= levodopa-carbidopa (L-dopa/ Dopa decarboxylase inhibitor), ras= rasagiline (MAO-B selective agent), pram=pramipexole (dopamine receptor agonist), ent= entacapone (COMT inhibitors), rop=ropinirole (dopamine receptor agonist), tri= trihexyphenidyl (antimuscarinic).

³ UPDRS-III scores represent clinical evaluation on the motor subsection of the Unified Parkinson's Disease Rating Scale. Disease laterality was based on the sum of scores on the right side compared to the left side.

3.3.2 Apparatus

Individuals were comfortably seated in front of a table with a height-adjustable chair. Two Phantom Omni haptic robotic devices (SensAble Technologies Inc, Woburn, MA, USA) were placed on the table 28 cm apart and synchronized to allow for 3-dimensional bimanual wrist-flexion movements (16 cm in medial-lateral direction, 12 cm in superior-inferior direction and 7 cm in the anterior-posterior direction). To limit unwanted movements at the elbow joint, the forearms were pronated 90 degrees and constrained using an apparatus (see Figure 3.1).

Displacement data was recorded using MatLab R2007b (The MathWorks Inc, Natick, MA, USA) from the Omni devices by synchronizing to a computer (Dell

Computer, with a g-force intel Pentium 4 with SSE2) Computer programs

(*Free_Motion_1Hz* and *Free_Motion_2H*) were created in Simulink in MatLab R2007b

to run each trial To pace each trial, an internal metronome (pitch level of 600 Hz) was

created using QuaRC (Quanser Inc , Markham, On, Canada) and synchronized with the

computer programs in MatLab R2007b Additionally, to initiate pattern switches, a higher

pitched auditory cue of 800 Hz was generated using QuaRC and synchronized in each

trial using MatLab R2007b

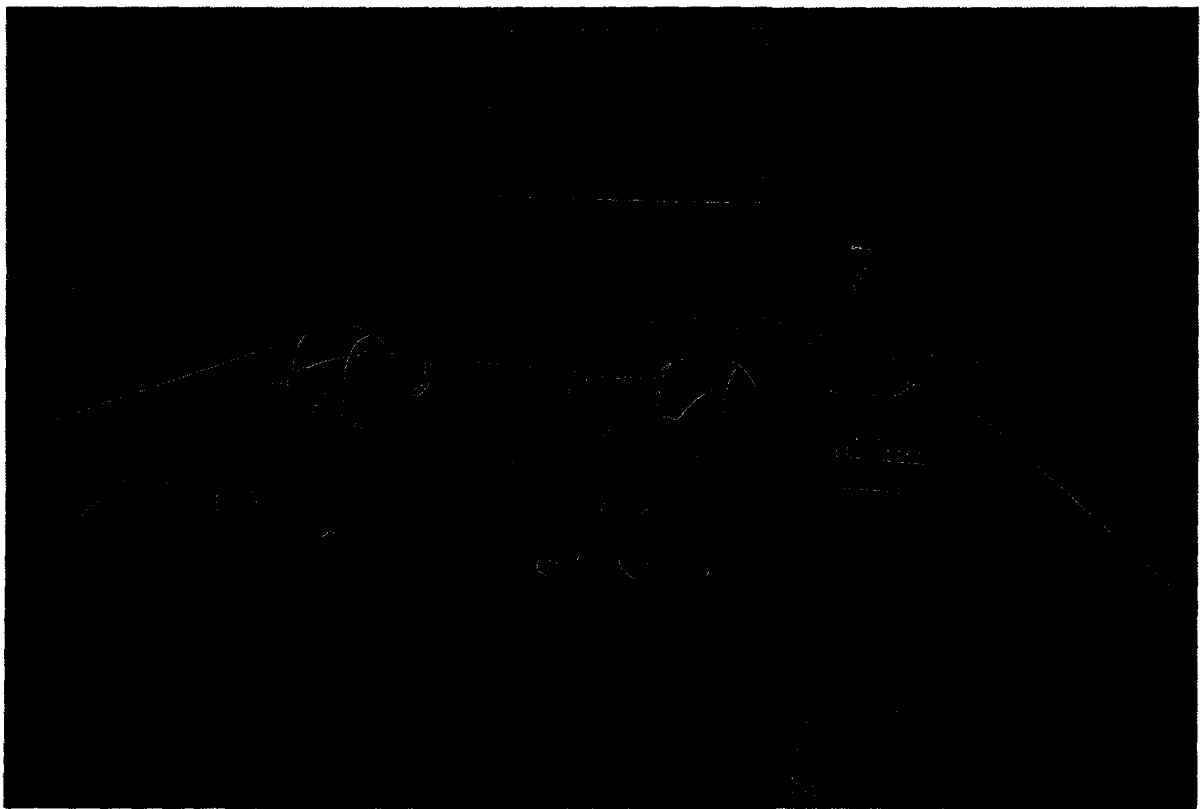


Figure 3 1 – Apparatus used in experiment including Omni Devices, *forearm constraints* and computer monitor

3.3.3 Protocol

All PD participants performed two sessions on the same day. Healthy control participants were only required to perform a single session. Individuals with PD performed the first session after overnight withdrawal from dopamine replacement followed by an approximate 70 min rest after their typical self-administered dopamine replacement (see Table 2 time 'on'). This rest was followed by the second testing session. Participants held the pen-like stylus that attached to the arms of the devices with their thumbs up and facing forward. Wrist flexion-extension was performed primarily in the medial-lateral direction. However, participants were instructed to not be concerned if movements naturally deviated from this movement.

Before trials began, participants were informed which coordination pattern (in-phase or anti-phase) they would be required to perform. The relative phase (see Data Analysis) was a dynamic measurement that measures the phase difference between the two limbs (Haken, Kelso, & Bunz, 1985). Participants heard an auditory cue different from the metronome at the midpoint of a trial (e.g. 12 seconds since movement began at 2 seconds) that signaled that they should attempt to perform a phase transition to the opposite pattern and continue movement in that pattern until the end of the trial. Thus, if participants began in-phase coordination they were required to perform a pattern switch to anti-phase or the reverse if they began in anti-phase. Participants were instructed to perform the transitions as quickly and smoothly as possible without intentionally stopping their movement.

Visual feedback was randomly manipulated to determine the contribution of sensory feedback to the coordinated movement. Half of the trials were performed

blindfolded in a *no vision* condition. The second condition *normal vision* provided participants with the ability to see their moving limbs with the Omni devices.

To initiate each trial, *Free_Motion_1Hz* or *Free_Motion_2Hz* was run in MatLab R2007b. The program produced a warning cue at a pitch of 800Hz and the metronome began at 2 seconds. Two different cycle frequencies were used in this experiment (1 and 2 Hz at a pitch of 600 Hz). To avoid anticipation of the auditory cue, participants were verbally instructed with a “go” signal to begin movement with the metronome, 2 or 4 seconds after the initiation of the metronome. Participants were required to continue wrist flexion-extension movements in rhythm with the metronome beats. After 10 seconds at the midpoint or 12 second time point, the program produced the auditory cue at a pitch of 800 Hz to prompt the phase transitions to the participants. The next beat of the metronome resumed at 13 seconds and participants were required to move in the new phase pattern for the remaining 10 seconds until the end of the trial.

Cycle frequency (1 and 2 Hz) was blocked and the order was counter-balanced across participants. Three trials of each of the four conditions combining phase and condition were randomly performed for a total of twelve trials. This resulted in two blocks of twelve trials for a total of twenty-four trials per session (PD participants performed forty-eight trials). Each testing session lasted approximately 45 minutes including set-up, UPDRS/3-MS assessments and experimental testing.

3.3.4 Data Processing and Analysis

Matlab R2007b recorded 3-D displacement at a rate of 1000 Hz from each of the Omni devices for a total of 23000 samples per trial. Data was stored in MatLab R2007b. Data analysis was performed on medial-lateral displacement using an automated script.

created in MatLab R2007b Superior-inferior and anterior-posterior displacement was kept for future analysis

Coordination Accuracy and Stability

Coordination accuracy and stability were measured by comparing the position of one limb relative to the other, using the formula

$$\text{Relative phase } (\theta) = \tan^{-1} [(dXR/dt)/XR]$$

Where θ was the relative phase between limbs at each sample, X was the position of each limb within a cycle rescaled to the magnitude $[-1,1]$ and (dXR/dt) referred to the normalized and continuous instantaneous velocity (Haken et al , 1985) Since phase relationships could range from 0 to 360°, a linear transformation was performed on the relative phase to obtain values from 0 to 180° using the formula

$$\text{New Relative Phase } (\theta_n) = 180 - (\text{relative phase } (\theta) - 180)$$

Absolute error (AE) of the relative phase (θ_n) was used to calculate coordination accuracy and stability The mean and standard deviation of AE of θ_n was determined for every trial The relative phase accuracy and stability was measured before (4 seconds before the cue) to calculate whether individuals did switch between patterns before and after the cue However, coordination accuracy and stability are only presented for after the auditory cue based on what has previously been reported (Almeida et al , 2003)

Successful switch, delayed responses, unsuccessful switches and voluntary switch time

Voluntary switches were used to measure the planning and execution of a change in movement The criteria for a *successful switch* was similar to what has been previously used (Almeida et al , 2003, Lee, Almeida, & Chua, 2002) A switch was deemed successful when individuals performed a change from the relative phase pattern before

the auditory cue to the new phase after the cue and maintained the error within 45° of the intended phase relationship (e.g. 135° and above for anti-phase or 45° and below for in-phase) for a minimum of 2 seconds. Temporally *delayed responses* were determined if switches took longer than 2 seconds after the auditory cue. Furthermore, trials were classified as *unsuccessful switches* if participants either did not switch patterns or were unable to maintain the intended pattern for at least 2 seconds. *Voluntary switch time* was used to determine the amount of time that was required after the auditory cue to begin a successful switch (maintain 45° of intended pattern for at least 2 seconds) (Almeida et al., 2003)

Statistical Comparison

All of the trials were calculated, coded and organized using MatLab R2007b. Each file was then transferred into a Microsoft Excel spreadsheet. Statistical analyses were performed using Statistica 8 (StatSoft Inc., Tulsa, Ok, USA) using the general linear model function.

A mixed-model (between and within group) ANOVA (session * condition * phase * cycle frequency) was used to calculate the outcome measures (coordination accuracy and stability after the auditory cue, voluntary switch time) in separate analyses. Planned comparisons were performed between session one of healthy control and PD participants (PD 'off') to determine the effects of basal ganglia dysfunction on coordination and switching performance. In addition, a planned comparison was performed between session 1 (PD 'off') and session 2 (PD 'on') of PD participants to determine the influence of dopamine replacement on coordination and switching performance.

Tukey's post hoc analyses were used for any significant interactions. The frequency of successful switches, delayed responses and unsuccessful switches were compared using chi-squared analyses. Additionally, demographic information including age and 3-MS scores was compared using Student's t-tests. UPRDS 'off' and 'on' scores were also compared using a paired student's t-test. An alpha level of 0.05 was used to define statistical significance for all effects.

3.4 Results

3.4.1 Comparison of demographic information

PD and healthy control participants were not found to have any significant difference in age, 3-MS or self-reported years of education (see Table 3.3). UPDRS-III 'off' (mean score= 32.5 +/- 8.8) and 'on' scores (mean score= 24.2 +/- 7.8) were found to be significantly different (mean difference= 8.2 +/- 2.6) ($t(14)= 12.1, p<0.001$).

Table 3.3 – Statistical comparison of demographic variables of PD and healthy control (HC) participants

	PD	HC	T statistic (df) and p-value
Age (in years)	67 (+/- 7.5)	67.8 (+/- 8.7)	$t(28)= 0.27, p= 0.79$
3-MS (out of 100)	95.5 (+/- 4.5)	95.9 (+/- 3.0)	$t(28)= 0.28, p=0.78$
Self-reported education (in years)	14.5 (+/- 3.3)	14.1 (+/- 3.3)	$t(28)= 0.38, p=0.70$

3.4.2 Participants' switching performance

Participants' performance on the switching task was evaluated using a number of dependent measures including the amount of successful switches, unsuccessful switches and delayed responses (see Table 3.4). Chi-squared analysis revealed that PD 'off' had more unsuccessful switches ($\chi^2= 26.3, p<0.001$) and more delayed responses ($\chi^2= 51.9, p<0.001$) than healthy control participants. PD 'off' and 'on' were not different in the

amount of unsuccessful switches ($\chi^2 = 0.45$, $p > .05$). However, PD 'off' did display more delayed responses than PD 'on' ($\chi^2 = 4.77$, $p < .05$).

Table 3.4 – Amount of successful switches, unsuccessful switches and delayed responses for healthy control (HC) and PD participants (both 'off' and 'on')

	Successful Switches	Unsuccessful Switches	Delayed Responses
PD 'off'	327 (91%)	33 (9%) *	65 (18%) ** ***
PD 'on'	332 (92%)	28 (8%)	44 (12%) ***
HC	357 (99%)	3 (1%) *	7 (2%) **
Overall	1016 (94%)	64 (6%)	116 (11%)

* & ** denote significance differences ($p < .001$) *** denotes significant difference ($p < .05$)

3.4.3 PD 'off' vs. healthy control participants

Coordination accuracy

After the auditory cue, healthy control participants (mean error = 29.7°) performed with significantly greater coordination accuracy than PD 'off' (mean error = 40.1°) as revealed by a significant main effect of group ($F(1,28) = 4.9$, $p < .05$). In addition, there were significant main effects for phase ($F(1,28) = 14.3$, $p < .001$) and cycle frequency ($F(1,28) = 16.5$, $p < .001$) as well as a significant interaction between group, phase and cycle frequency ($F(1,28) = 6.1$, $p < .05$). As revealed in Figure 3.2, PD 'off' had less error in coordination after switching to in-phase compared to anti-phase at 1 Hz and during in-phase at 1 Hz compared to 2 Hz. In addition, healthy control participants had less error in coordination when switching to in-phase compared to anti-phase at 2 Hz. There was also a significant main effect of condition ($F(1,28) = 7.3$, $p < .05$) that revealed that less error in coordination was observed in *no vision* compared to *normal vision*.

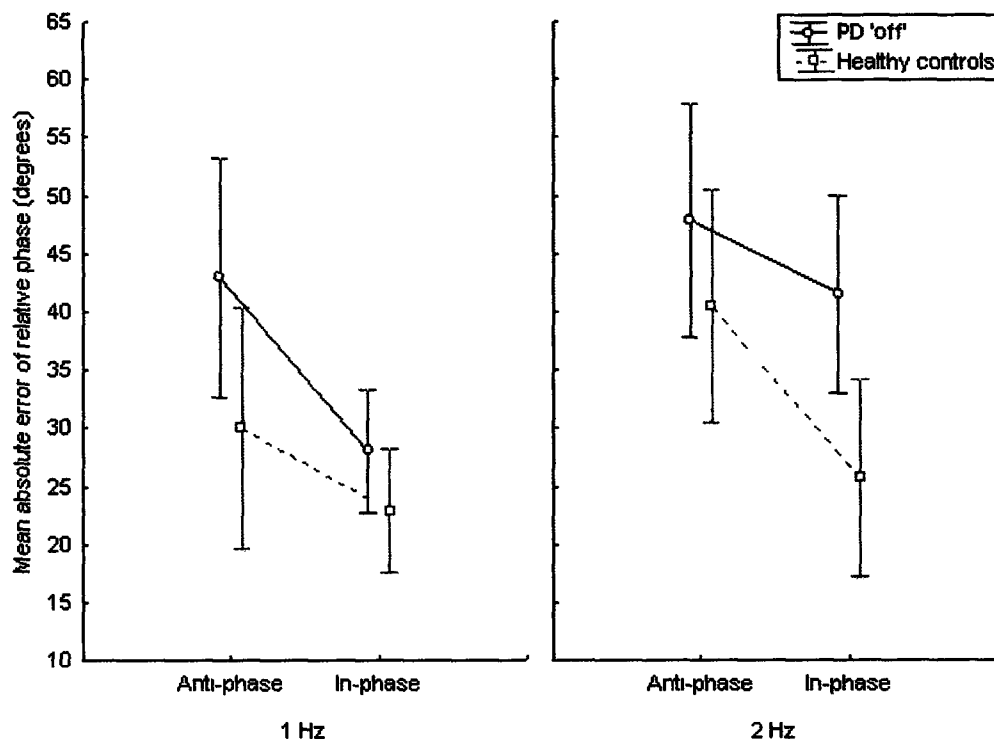


Figure 3 2 – The mean absolute error of the relative phase (coordination accuracy) between PD ‘off’ and healthy control participants with phase and cycle frequency manipulations (standard error bars included) Results demonstrated that overall PD ‘off’ participants produced a significantly ($p < 0.05$) more error in coordination compared to healthy control participants

Coordination stability

A trend was found in the main effect of group for coordination stability after the auditory cue ($F(1,28) = 3.9$, $p = 0.059$) that revealed that healthy control participants (mean variability = 41.8°) had less variability in coordination compared to PD ‘off’ (mean variability = 44.6°). Furthermore, there was a significant main effect for phase ($F(1,28) = 39.1$, $p < 0.001$) and a significant interaction between group, phase and cycle frequency ($F(1,28) = 4.9$, $p < 0.05$). Tukey’s post hoc analysis revealed that PD ‘off’ had more stable coordination when switching and performing in-phase compared to anti-phase at both 1 and 2 Hz while healthy control participants only at 2 Hz (see Figure 3 3)

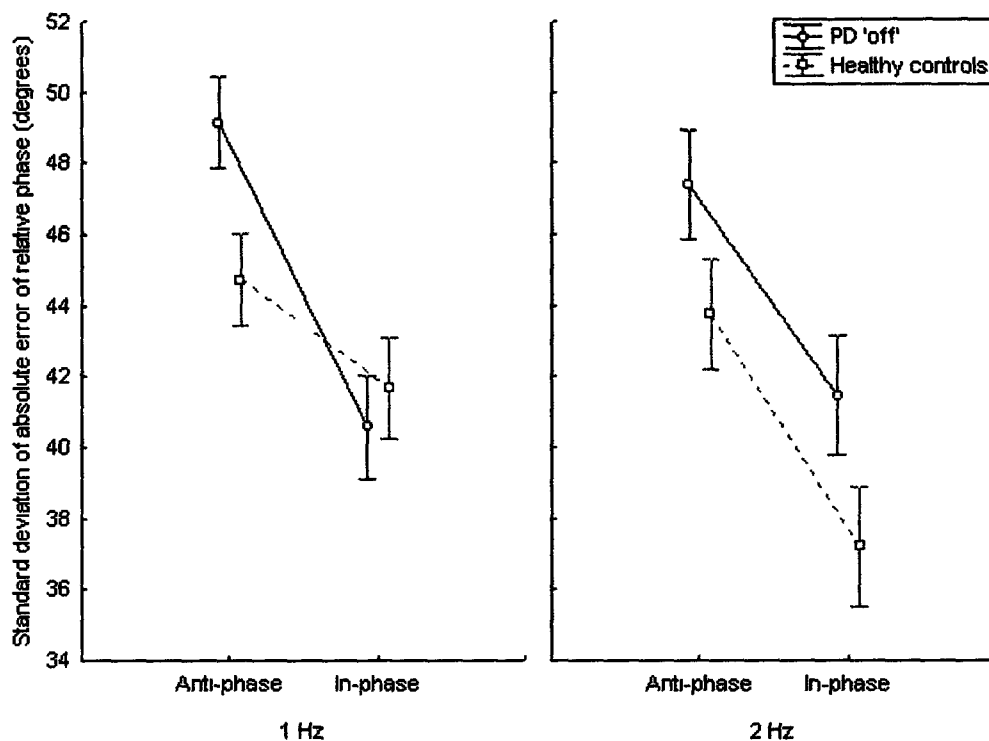


Figure 3.3 – Coordination stability revealed by the standard deviation in absolute error of the relative in PD 'off' and healthy control participants while manipulating both cycle frequency and phase (standard error bars included) Results demonstrated that overall a trend ($p=0.59$) for greater coordination stability in healthy control compared to PD participants

Voluntary switch time

3 PD participants were excluded from these analyses due to the high amount of unsuccessful switches which resulted in insufficient data for these variables. As revealed by Figure 3.4, there was a significant main effect of group on voluntary switch time ($F(1,25)=5.8, p<0.05$) that showed that healthy control participants (mean switch time= 963.04 ms) switched faster than PD 'off' (mean switch time= 1185.68 ms)

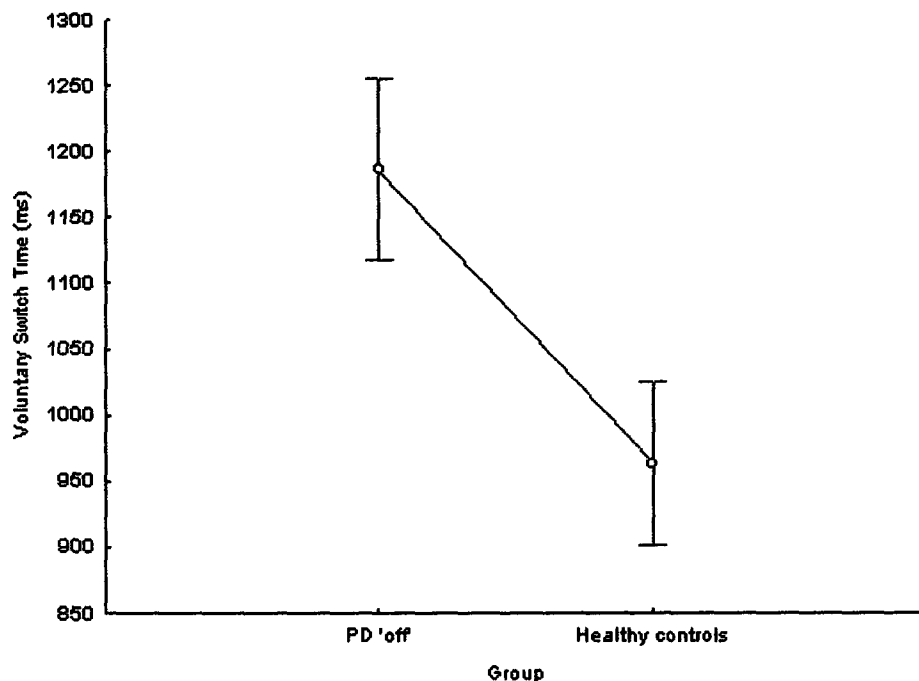


Figure 3 4 – The voluntary switch time (in ms) compared between PD ‘off’ and healthy control participants (standard error bars included) Results revealed that PD participants were significantly ($p < 0.05$) slower than healthy control participants at switching between phase patterns

3.4.4 PD ‘off’ vs. PD ‘on’

Coordination accuracy

A main effect of condition was found ($F(1,14)=7.4, p < 0.05$) that demonstrated that there was less error in coordination in *no vision* compared to *normal vision*. There was also a main effect of phase ($F(1,14)=6.6, p < 0.05$) that showed that coordination was more accurate when switching to and performing in-phase compared to anti-phase. Finally, there was a main effect of cycle frequency ($F(1,14)=9.2, p < 0.01$) that indicated that there was less coordination error at 1 Hz compared to 2 Hz.

No main effect or interactions were found for dopamine replacement on coordination accuracy once prompted to switch.

Coordination stability

A significant main effect of phase was discovered ($F(1,14)=19.3$, $p<0.01$) that revealed that coordination was more stable when switching to and performing in-phase compared to anti-phase after the auditory cue.

Similar to coordination accuracy, dopamine replacement did not influence coordination stability after the auditory cue as revealed by no main effect or significant interactions.

Voluntary switch time

3 participants were excluded from analysis (same as above) due to a large amount of unsuccessful switches that led to insufficient data. Unlike coordination, voluntary switch time was influenced by dopamine replacement as revealed by a significant main effect ($F(1,11)=10.4$, $p<0.01$). As shown in Figure 3.5, PD 'on' (mean time= 1032.26 ms) were able to switch patterns faster than PD 'off' (mean time= 1185.68 ms).

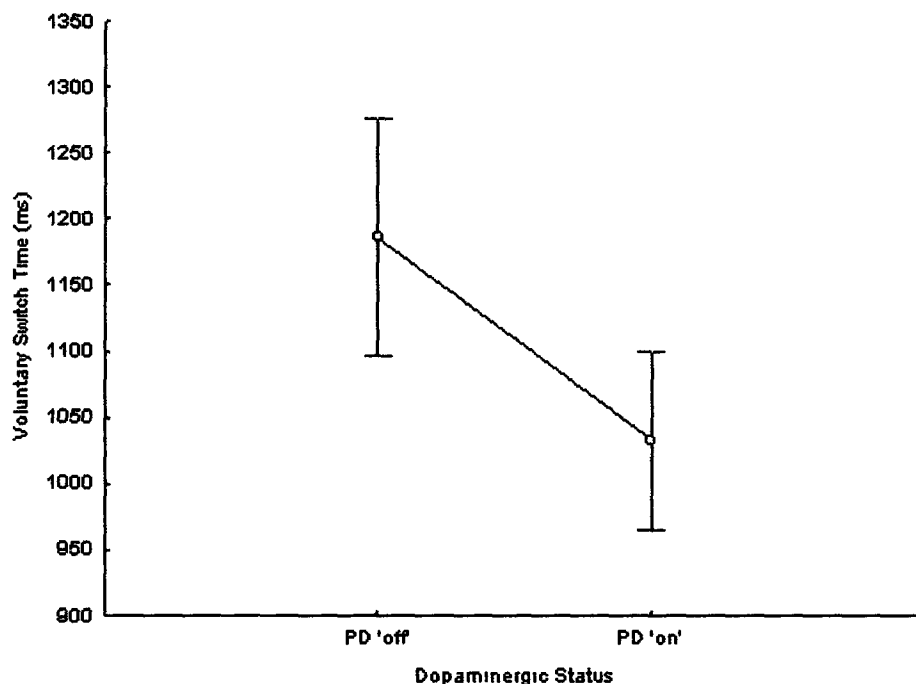


Figure 3.5 – The effect of dopamine replacement on voluntary switch time (ms) in PD participants (standard error bars included). Results revealed that PD participants with dopamine replacement were significantly ($p<0.01$) faster at switching between phase patterns than without dopamine replacement.

3.5 Discussion

The current study aimed to determine whether the dopaminergic system was associated to switching and subsequent coordination performance in individuals with PD. The novel findings of the current study were that impairments in switching performance (voluntary switch time, delayed responses and unsuccessful switches) were observed in PD participants compared to healthy participants. Furthermore, dopamine replacement improved the speed of switches and decreased the amount of delayed responses in individuals with PD. As a consequence, deficits in the execution of an intentional switch may be the result of bradykinesia (slowness in execution of movement) and are influenced by the dopaminergic system during bimanual coordination in individuals with PD. Alternatively, it may be possible that the slowed switching and improvement with dopamine replacement was related to bradyphrenia (cognitive slowing) in individuals with PD. However, dopamine replacement did not influence coordination accuracy or stability in PD 'on' despite coordination impairments in PD 'off' compared to healthy control participants. Thus, coordination performance is not associated to the dopaminergic system and may be related to secondary dysfunction (e.g. attentional or sensorimotor integration deficits) related to PD.

Similar to the current results, individuals with PD (compared to healthy older adults) were slower at sequencing movements (Benecke et al., 1987a, 1987b) and performing cued voluntary switches during continuous bimanual coordination (Almeida et al., 2003, Byblow et al., 2002, Geuze, 2001). Additionally, the current study also observed more delayed responses and unsuccessful switches in PD 'off' (compared to healthy control participants) comparable to what was observed by Almeida *et al.* (2003).

In agreement with previous research in PD, the slowness in switching was regardless of whether the switches occurred from more stable in-phase to less stable anti-phase coordination (Byblow et al , 2002, Geuze, 2001) However, conflicting research on individuals with PD (Almeida et al , 2003) and healthy adults (Carson, Byblow, Abernethy, & Summers, 1996, Schoner & Kelso, 1988) has found that deficits in switching were related to the attraction to in-phase coordination As a consequence, deficits in switching are typically more pronounced when switches occurred from in-phase to anti-phase coordination (Almeida et al , 2003, Carson et al , 1996, Schoner & Kelso, 1988) It is unclear why the current study did not observe the same results

As suggested by Geuze (2001) individuals with PD may not be affected equally by the attraction to in-phase coordination Alternatively, Byblow *et al* (2002) proposed that slowed initiation of switching during bimanual coordination in individuals with PD resulted due to pre-programming deficits when planning sequential movements If pre-programming deficits were responsible for slowness during phase switching, this may point towards a link between bradyphrenia and slowed voluntary pattern switches Bradyphrenia or cognitive slowing has been demonstrated in various cognitive tasks in individuals with PD (Poewe, Berger, Benke, & Schelosky, 1991, Ransmayr et al , 1990, Sawamoto, Honda, Hanakawa, Fukuyama, & Shibasaki, 2002, Tachibana, Aragane, Miyata, & Sugita, 1997) It has previously been argued that it is difficult to separate whether slowness during movement tasks that require planning is caused by bradykinesia and/or bradyphrenia (Marsden, 1982, Sawamoto et al , 2002) Based on the current results, dopamine replacement improved both the speed of switching and decreased the amount of delayed responses It is important to consider that deficits in voluntary

switching during bimanual coordination could be related to dysfunction of the dopaminergic system associated with bradykinesia or pre-programming deficits (bradyphrenia). The contribution of the dopaminergic system, bradykinesia and pre-programming deficits to sequencing movements has been supported by Benecke *et al* (1987b). It was observed that dopaminergic modulation improved the inter-onset latency (onset to onset), pause (termination to onset), movement time for the entire sequence and each individual task in sequential movements that required performing a squeeze then elbow flexion in PD. It was suggested that dopamine replacement improved both the speed of execution and the execution of each component motor program (Benecke *et al*, 1987b). Collectively, these results support that dysfunction related to the dopaminergic system influences switching between coordination patterns rather than the dynamical attraction to in-phase coordination that is observed in healthy adults. Conversely, the subsequent coordination performance was not directly related dysfunction related to the dopaminergic system.

The current study found decreased coordination accuracy and stability in PD 'off' compared to healthy control participants after switching (regardless of phase) that was more pronounced when switching to anti-phase coordination at faster cycle frequencies. This is in agreement with Almeida *et al* (2003) that found after switching from in-phase to anti-phase, coordination was performed with decreased accuracy in individuals with PD. Furthermore, Geuze (2001) also observed decreased coordination stability in individuals with PD compared to healthy control participants after a voluntary switch. The current results also demonstrated that dopamine replacement did not improve coordination performance (accuracy or stability) in individuals with PD. Thus, a

secondary dysfunction related to dopamine loss contributed to coordination performance after an intentional phase switch. Previous research from our lab did not observe deficits in coordination performance in PD 'off' compared to healthy older participants or an influence on coordination accuracy or stability with dopamine replacement in PD (see Chapter 2). These conflicting findings suggest that when greater instability in coordination occurs after switching between phase patterns (compared to when switching is not required) there is an increased reliance on the secondary pathways that are influenced by dopamine loss in PD.

Research by De Luca *et al* (2010) examined neural activity using fMRI during continuous bimanual coordination when an intentional pattern switching was required in healthy adults. Increased activity was observed in the pre-SMA and bilateral putamen during switching that was related to decreased stability of coordination (e.g. switching from a more to less stable pattern or in-phase to anti-phase) and was not correlated with frequency of coordination. Although they did not observe this increased activity post-switch, the increased activity in putamen was observed with decreased stability pre-switch indicative of the phase stability-dependent frontostriatal circuit in switching (De Luca, Jantzen, Comani, Bertollo, & Kelso, 2010). The decreased coordination accuracy and stability observed in individuals with PD 'off' (compared to healthy older adults) in the current study could explain the increased reliance on the dysfunctional frontostriatal pathways to stabilize coordination. However, due to the dysfunction in these pathways caused by PD, efficient switching and subsequent stabilization of coordination could not occur regardless of dopamine replacement. Collectively, these results support that

secondary dysfunction from dopamine loss related to increased attentional demand or sensorimotor integration could have contributed to coordination performance in PD

The current results could have been explained by increased demand of sensorimotor integration since all participants demonstrated more coordination error after switching with normal vision compared to when no vision was provided in our study. However, there was no difference with these sources of feedback between PD 'off' and healthy control participants. Consequently, increased demands of sensorimotor integration were not responsible for the current findings. Alternatively, it is suggested that the increased attentional demands from a cued voluntary switch especially to anti-phase with increased external cueing (at the faster cycle frequencies) contributed to the deficits in coordination performance in individuals with PD as suggested by Almeida *et al* (2003). This has been supported by previous research by Ridderikhoff *et al* (2008) that has observed that there are increased attentional demands when initiating anti-phase coordination and when performing a dual-task of verbally responding to a stimulus during bimanual coordination in healthy adults (Ridderikhoff *et al* , 2008). Furthermore, previous research by Riekkinen *et al* (1998) demonstrated that attentional deficits in PD could not be modulated by dopamine replacement. Thus, the current results support that non dopa-responsive frontostriatal dysfunction secondary to dopamine loss related to increased attentional demands particularly after a cued voluntary switch contributes to coordination deficits in PD.

In conclusion, individuals with PD have a decreased ability to switch between coordination patterns based on dysfunction related to the dopaminergic system that may be the result of bradykinesia and/or bradyphrenia that can be modulated with dopamine

replacement. However, it is proposed that the increased attentional demands of a cued voluntary switch during bimanual coordination resulted in decreased stabilization of coordination and increased dependency on dysfunctional frontostriatal pathways between the SMA and putamen that could not be modulated by dopamine replacement. Imaging research is needed to confirm that attentional demands and the frontostriatal pathways may be responsible for coordination deficits in PD. Furthermore, future research should be directed at understanding the degree of attentional demand that results in coordination deficits in PD. This would be important for developing rehabilitative programs for individuals with PD to assist in properly executing complex voluntary movements (e.g. bimanual coordination) in attentionally demanding contexts since dopamine replacement is not sufficient.

3.6 References

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Chapter 4 – The dopaminergic system in upper limb freezing (ULF) during bimanual coordination in Parkinson's disease (PD)

4.1 Abstract

Upper limb freezing (ULF) (inability to initiate or sudden discontinuation in voluntary movements) has been identified in various tasks in individuals with Parkinson's disease (PD). In particular, ULF has been observed during rhythmic bimanual coordination when switching between phase patterns is required (e.g. between in-phase and anti-phase). However, there has been no consensus on the mechanism that evokes ULF or whether freezing responds to dopamine replacement like other motor symptoms of PD. The current chapter investigated the occurrence of ULF in PD participants without ('off') and with ('on') dopamine replacement in two different experiments using bimanual wrist flexion-extension with externally paced movements. In Experiment 1, coordination was performed in either in-phase (simultaneous flexion and extension) or anti-phase (asymmetrical flexion and extension between the limbs) in either one of three sensory conditions: *no vision*, *normal vision* or *augmented vision*. Cycle frequency was increased within each trial across 7 cycle frequencies (0.75 to 2 Hz). In Experiment 2, coordination was initiated in either phase pattern and participants intentionally switched between phases in the middle of trials with an auditory cue. Trials were performed at one of two cycle frequencies (1 or 2 Hz) and one of two sensory conditions: *no vision* or *normal vision*. Healthy age-matched control participants were also investigated in both experiments for the occurrence of freezing that was measured

using automated detection from a computer algorithm. The results from Experiment 1 indicated that only increasing cycle frequency resulted in more ULF in individuals with PD during continuous coordinated movement. It was proposed that ULF may have occurred due to the increased attentional demand of external auditory cueing rather than necessarily the demand of cycle frequency. Experiment 2 further revealed an increased occurrence of ULF with increased external cueing (cycle frequency). Furthermore, a large amount of ULF was observed when initiating anti-phase coordination at 2 Hz, after external cued switches and with distracting auditory cues when no switch was required. Dopamine replacement was not found to influence the frequency of ULF in either experiment suggesting that ULF was not caused by the dysfunctional dopaminergic system. It was concluded that ULF results from increased attentional demands likely associated with secondary impairment of PD related to executive dysfunction and fronto-striatal pathways.

4.2 Introduction

One of the most debilitating motor symptoms of Parkinson's disease (PD) is akinesia (severe or complete absence of movement) because it incorporates hypokinesia (poverty of movement), bradykinesia (slowness of movement) and freezing (Imai, 1996). Freezing (also referred to as motor blocks) has been defined by abrupt cessations or the inability to initiate voluntary movements (Giladi et al, 1992, Imai, 1996, Nakamura, Nagasaki, & Narabayashi, 1978). Freezing is traditionally identified in the lower limbs during various aspects of walking (e.g. initiation, turning) which has been termed freezing of gait (FOG) (Giladi et al, 2001, Lambert et al, 1997). In addition to FOG, various studies have identified movement interruptions during rhythmic unimanual

finger tapping (Nakamura et al , 1978, Ziv et al , 1999) and bimanual coordination (also known as inter-limb or inter-manual coordination) (Almeida, Wishart, & Lee, 2002, 2003, Nieuwboer et al , 2009) Although upper limb freezing (ULF) has been identified in various studies, the mechanism for ULF and its' response to dopamine replacement remains unclear. Additionally, little is known about the individuals who display ULF (*upper limb freezers*) such as the relationship between disease laterality and FOG.

A few mechanisms have been proposed for movement interruptions in the upper limbs. Motor blocks were documented in PD during internally-paced unimanual movements (Ziv et al , 1999). It was proposed that these movement interruptions were caused by a dysfunctional motor pacemaker resulting in disrupted internal timing. However, ULF has been documented in 81% of anti-phase trials even during externally-paced continuous bimanual coordination (Almeida et al , 2002). Almeida *et al* (2002) argued that freezing occurs due to inhibition of limb synchronization (attraction to in-phase coordination). In a subsequent study, Almeida *et al* (2003) found an increased occurrence of ULF during bimanual coordination after a voluntary pattern switch. Freezing was observed in 53.9% of trials when switching from anti-phase to in-phase (compared to 15.5% in the opposite direction). It was suggested that ULF occurs due to increased attentional and cognitive demands placed on a prefrontal-neostriatal network that is required when shifting between motor sets (Almeida et al , 2003).

Similarly, research on FOG in PD has proposed that an increased cognitive demand observed during dual-tasking (Giladi & Hausdorff, 2006) and attentional demands from perceptual information in the environment (Almeida & Lebold, 2010) may contribute to evoking FOG. It is possible that ULF is associated with deficits in

sensorimotor integration that have been identified in individuals with PD (Abbruzzese & Berardelli, 2003, Lim, Hamm, Byblow, & Kirk, 2005, Lim, Hamm, Byblow, & Kirk, 2006) Nieuwboer *et al* (2009) found a trend that more upper limb freezing occurred without target line visual cues compared to with visual cues However, in the freezer subgroup there was decreased coordination stability with visual cueing It was proposed that deficits in sensorimotor integration could contribute to ULF (Nieuwboer *et al* , 2009) Alternatively, ULF may be related to attention and executive dysfunction Executive function refers to several higher-order processes of the frontal cortex including planning, behavioural control such as inhibiting responses, maintaining attention and shifting attention (Rodriguez-Oroz *et al* , 2009) PD have marked deficits in attentional processes such as sharing resources and shifting attention (Brown & Marsden, 1991, Cools, Rogers, Barker, & Robbins, 2010) However, there is little research that has investigated the relationship between different types of attentional demands (executive function) and/or sensorimotor integration and the occurrence of ULF

Although dopamine replacement improves motor symptoms there is little evidence to support that it can modulate executive functions (Cooper, Sagar, Jordan, Harvey, & Sullivan, 1991) or sensorimotor integration during voluntary movements (Mongeon, Blanchet, & Messier, 2009, Schettino *et al* , 2006) Similarly, it remains unclear if ULF is responsive to dopaminergic modulation The amount of motor blocks was not influenced by dopamine replacement during unimanual finger tapping (Ziv *et al* , 1999) However, there has been conflicting evidence for the response of FOG to dopaminergic replacement (Bloem, Hausdorff, Visser, & Giladi, 2004, Imai, Nakamura, Kondo, & Narabayashi, 1993, Nomoto & Nagai, 2006, Schroeteler, Ziegler, Fietzek, &

Ceballos-Baumann, 2009) (Ianssek, Huxham, & McGinley, 2006) (Okuma, 2006, Schaafsma et al , 2003) Thus, it is unclear if ULF during bimanual coordination is influenced by dopaminergic modulation

ULF was recorded in two different experimental studies using bimanual coordination in PD. The primary objective was to determine whether the dopaminergic system alone or in combination with different forms of attention and/or sensorimotor integration influenced the amount of ULF with (PD 'on') or without (PD 'off') dopamine replacement in individuals with PD. This was investigated by manipulating dopamine replacement across two sessions in PD in two experimental studies. In addition, Experiment 1 manipulated visual feedback, cycle frequency (external auditory cueing) and phase (anti-phase and in-phase) during continuous bimanual coordination. Experiment 2 included a cued intentional pattern switch or a distracting external auditory cue during continuous bimanual coordination while manipulating visual feedback, cycle frequency and phase. It was hypothesized that if ULF was related to the dopaminergic system than a greater occurrence of ULF would be documented in individuals with PD after withdrawal from dopamine replacement (PD 'off') and a decreased occurrence after dopamine replacement (PD 'on'). Alternatively, if ULF was related to other dysfunction caused by PD related to sensory and/or attentional demands than an increased occurrence of ULF would be observed in individuals with PD with increasing sensory demands, anti-phase coordination and/or cycle frequency regardless of manipulations in dopamine replacement. A secondary objective was to document the characteristics of the *upper limb freezers* in PD such as the limb that typically freezes and the relationship between disease laterality and FOG.

4.3 General Methods

4.3.1 Apparatus

The apparatus for these experiments has previously been described in detail (see Chapter 2 3 2 and Chapter 3 3 2) Briefly, both experiments had participants seated in a height adjustable chair with their forearms resting on a padded surface and forearms constrained to avoid unwanted movements at the elbow and shoulder joints The forearms were pronated 90° with the palms facing inward and thumbs facing upwards Movements were performed on two separate robotic Phantom Omni haptic devices (SensAble Technologies Inc , Woburn, MA, USA) that were synchronized and linked to a desktop computer (Dell Computer, with a g-force Intel Pentium 4 with SSE2) for data recording using MatLab R2007b (The MathWorks Inc, Nattick, MA, USA) A pen-shaped stylus was attached to a pivoting arm that allowed for three-dimensional (3-D) movements Wrist flexion-extension movements were performed in rhythm with a computer-generated metronome using QuaRC (Quanser Inc , Markham, On, Canada) To run all the different experimental sessions, automated programs were created using Simulink in MatLab R2007b

4.3.2 Procedure

For both experiments, participants performed wrist flexion-extension primarily in the medial-lateral direction with the hands grasping each stylus However, the wrists were not restricted allowing 3-D movements if necessary The goal of both tasks during continuous bimanual coordination was to maintain rhythmic coordination in pace with the metronome Participants were instructed to perform as large movements as possible with both limbs but no specific amplitude requirements were given

In both experiments, in-phase and anti-phase coordination patterns were used (Kelso, Holt, Rubin, & Kugler, 1981) In-phase required the symmetrical movement of both limbs with simultaneous extension and flexion of the wrists using homologous muscles Anti-phase was performed as an asymmetrical pattern requiring flexion of one wrist and extension of the opposite wrist using non-homologous muscles

Two sensory feedback conditions were used in both experiments In the *normal vision* condition participants were able to see their moving limbs The *no vision* condition involved the removal of vision by blindfolding participants

4.3.3 Data Processing and Analysis

For both experiments, displacement data was collected at a rate 1000 Hz and stored from each Omni device using MatLab Displacement data was used to calculate coordination accuracy, coordination stability, limb frequencies and limb amplitudes (see Chapter 2 and Chapter 3) The movement amplitude of each limb were used for freezing analysis

Voluntary stops were analyzed and documented given that freezing episodes can be falsely identified as intentional arrests in movement (and vice-versa) A voluntary stop was defined as any discontinued movement that was not preceded by a reduction in amplitude (Nieuwboer *et al* , 2009) These could occur in re-establishing coordination after a transition, early termination of movement at the end of a trial or during trials due to equipment restrictions During the testing sessions, two investigators recorded any time distinct voluntary stops occurred due to participants stopping or equipment issues If clear voluntary stops occurred, participants were asked to re-perform the trial However, it was possible that voluntary stops still occurred during trials

The current study classified freezing episodes using criteria that combined previous definitions. Freezing episodes in the upper limbs have previously been classified based on at least 1 second of no change in movement amplitude (Almeida et al, 2002, 2003). However, recent research in freezing of gait has indicated that total cessation in movement does not always occur with a freeze (Giladi & Nieuwboer, 2008). Thus, the definition for upper limb freezing episodes was recently modified to incorporate either a reduction in amplitude (less than 50% of regular amplitude) prior to a freeze or irregular cyclic movement (Nieuwboer et al, 2009) (see Appendix B). For the current study, upper limb freezing episodes were defined as a 75% reduction of amplitude for at least 1 second. The current definition of freezing allowed for classification of ULF that did not produce a total arrest in movement.

4.4 Experiment 1

4.4.1 Methods

Participants

Fifteen (n=15) individuals with Parkinson's disease and fifteen (n=15) healthy age-matched healthy controls participated in the current experiment. These participants have been described in detail elsewhere (see Chapter 2.3.1). Briefly, all participants were right-hand dominant. All participants were evaluated on the Modified Mini-Mental State Examination (3-MS) for signs of dementia and to ensure all individuals had the mental capacity to perform the experiment. All participants performed two experimental sessions separated by approximately 70 minutes study (see Table 2.1 for demographic information of participants).

For individuals with PD, the first session was performed after overnight withdrawal from dopaminergic medication. Individuals were evaluated on the motor subsection of the Unified Parkinson's Disease Rating Scale (UPDRS-III) to document motor symptoms after withdrawal from dopamine replacement (PD 'off'). After completion of the first session, medication was self-administered. Re-evaluation of motor symptoms occurred after the 70 minute waiting period to document the response to dopamine replacement (PD 'on') (see Table 2.2 for clinical characteristics of PD participants). Upper limb laterality scores were calculated and compared for both limbs from items 20-25 on the UPDRS-III that examined upper limb motor symptoms to classify the more and less affected limbs and bilaterally affected PD participants (see Chapter 2.3.1). Patient history was reviewed for symptoms of gait freezing. Any individual who had reported FOG was classified as a gait freezer. PD participants were recruited from the patient database at the Sun Life Financial Movement Disorders Research and Rehabilitation Centre (MDRC) at Wilfrid Laurier University. Healthy controls were recruited from family and friends of PD participants. Ethics approval for the current experiment was received from the Human Research Ethics Board (REB) at Wilfrid Laurier University.

Procedure

In addition to *no vision* and *normal vision*, a third sensory feedback condition *augmented vision* was used for Experiment 1. *Augmented vision* covered vision of the moving limbs but provided a modified Lissajous figure on the computer monitor. A purple ball represented the integrated movement of both limbs. The phases (in-phase and anti-phase) were represented by diagonal cylinders that remained on the computer

monitor In-phase was represented by a diagonal cylinder with a slope of 1 Anti-phase was represented by a diagonal cylinder with a slope of -1 The goal was to maintain the purple ball in the cylinders during the given phase pattern Before the first session began, individuals had a familiarization session with the augmented feedback

A dynamic cycle frequency protocol was used to set the cycle frequency for each trial Similar to previous research that has used scaled frequency during trials (Geuze, 2001), the cycle frequency was gradually increased from 0.75 to 2 Hz at set intervals The dynamic increase in cycle frequency was used to attempt to de-stabilize coordination within each trial and increase the probability of freezing to occur

Each trial lasted 50 seconds beginning with a resting period of 5 seconds The resting period was followed by 7 seconds of maintaining a 'ready' position Continuous coordinated movements began at 12 seconds with the metronome at a frequency of 0.75 Hz At approximately every 7 seconds, the cycle frequency automatically increased (by 0.25 Hz) and participants were required to maintain rhythm with the metronome throughout each trial Each phase and sensory feedback manipulations was randomly performed and resulted in a total of 18 trials within each session Each participant performed a total of 36 trials over 2 sessions

Data Processing and Analysis

Detection of freezing episodes was automated using a script created in MatLab R2007b To detect freezes, the peak-to-peak amplitude of each cycle was measured over a trial and compared to the reference amplitude The reference amplitude of movement was obtained from the mean peak-to-peak amplitude within each trial when participants were moving at 1 Hz (between 7 and 12 seconds) Freezing episodes were classified as a

75% reduction in amplitude compared to the reference amplitude for at least 1 second. All freezing episodes that were detected by the computer algorithm were visually inspected on displacement profiles to ensure that ULF were accurately detected with the automated script. Visual inspection was performed to confirm that the automated script did not classify hypometria (decreased movement amplitude over an extended period of time) or voluntary stops as freezing episodes.

Freezing episodes were classified and described based on different clinical characteristics. All freezing episodes were compared using chi-square analyses on the dopaminergic status, sensory condition, phase and cycle frequency. A significance level of 0.05 was used to define statistical significance. In the event of significance between more than 2 variables for either cycle frequency or sensory condition, individual chi-square tests were performed to determine which factors were different.

4.4.2 Results

Qualitative description of freezing episodes during continuous bimanual coordination in PD

An example of a freezing episode is displayed in Figure 6.1. No freezing episodes were identified in healthy controls. At least one ULF was documented in 6 out of 15 PD participants. Of these 6 *upper limb freezers*, half were more affected on the left side while the other half were more affected on the right side based on upper limb laterality scores on UPDRS. In addition, 3 out of the 6 *upper limb freezers* were considered bilaterally affected. Only 2 out of the 6 were classified as gait freezers (compared to 3 out of 9 non-upper limb freezers were known gait freezers).

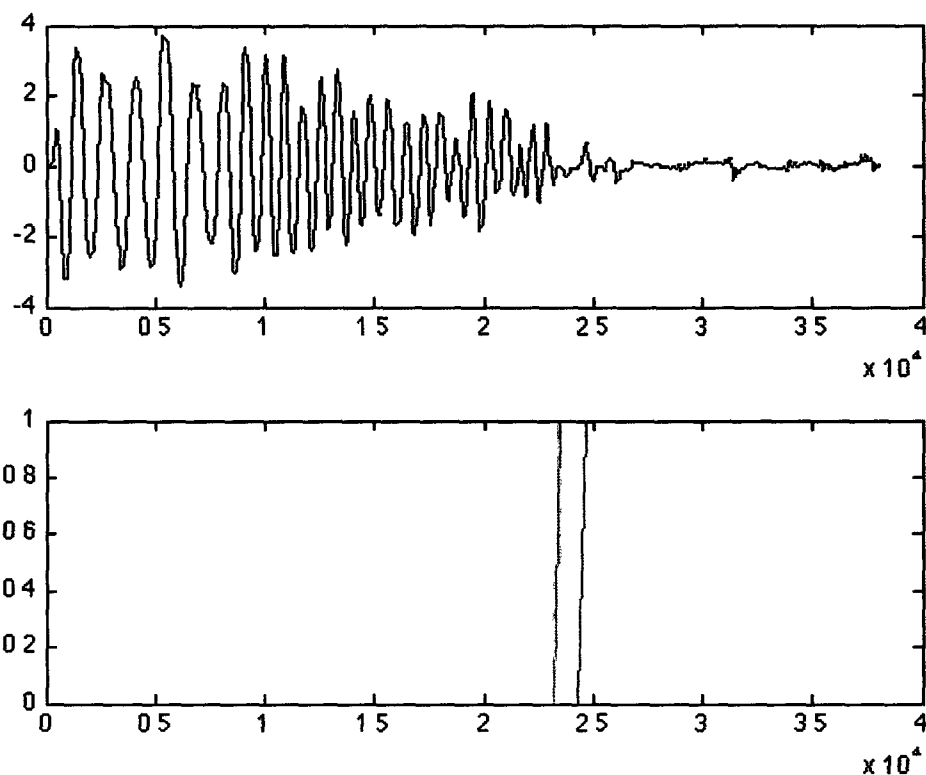


Figure 4.1 – (top) An example of a freezing episode in the more affected left limb of PD non-FOG (below) Red line illustrates the point when all the criteria were met for a ULF by the computer algorithm Green line represents the beginning of the freeze The end of the freeze was represented by the end of the trial

Based on the computer algorithm, freezing episodes were documented in 50 trials. However, 6 trials were excluded after visual inspection (see criteria in Data Processing and Analysis, section 4.3) resulting in 44 out of 50 (88 %) freezing episodes. Multiple freezing episodes occurred within the same trial in 7 of the 44 freezing trials (15.9%). Both limbs froze at the same time in 4 out of 44 freezing trials (9.1%). As a result, freezing episodes were identified in 29 separate trials (in 6 different people). Freezing episodes were documented in 5.4% of all trials (29 out of all 540 trials) of PD participants (see Table 4.1).

Overall, 80.9% of all freezing episodes occurred on the more affected side. The 4 freezing episodes (9.6%) in the less affected limb and 4 (9.6%) that occurred in both limbs (see Table 4.1) were in individuals that were more affected on their right side and were bilaterally affected. The length of freezes ranged from 1.27 to 14.51 seconds with an average length of 2.75 (+/-2.4) seconds.

Table 4.1 – Breakdown of freezing episodes detected using computer-algorithm and visually verified in PD both 'off' and 'off' dopaminergic medication

	PD 'off'				PD 'on'			
	More affected*	Less affected*	Both Limbs*	Total	More affected*	Less affected*	Both Limbs*	Total
Total freezing episodes	18 (13)	1(1)	0	19 (14)	14 (9)	3 (2)	4 (4)	21 (15)
% of total trials **	4.8%	0.04%	0%	5.2%	3.3%	0.07%	1.5%	5.6%
% of total freezes ***	40.9%	2.3%	0%	43.2%	31.8%	6.8%	9.1%	47.7%

* Out of brackets represents all freezing episodes including when multiple freezes occurred in the same trial. In brackets, only represents the first freezing episode and excludes subsequent freezing episodes within the same trial.

** Percentage (%) is calculated by dividing freezing episodes (excluding freezing episodes when multiple freezes occurred) by total trials of each dopaminergic status (=270).

*** Percentage (%) is calculated from all freezing episodes including when multiple freezes occurred (= 44 freezing episodes).

Chi-square analyses of freezing episodes during continuous bimanual coordination in PD

Based on chi-squared analysis, cycle frequency was found to influence the amount of freezing episodes ($\chi^2(5) = 34.6, p < 0.01$). Individual comparisons using chi-square tests revealed that more freezes occurred at 1.75 Hz (n=15) and 2 Hz (n=14) compared to the three slowest cycle frequencies (0.75 Hz (n=0), 1 Hz (n=1) and 1.25 Hz (n=3)). Additionally, more freezes occurred at 1.5 Hz (n= 7) compared to the two slowest cycle frequencies (0.75 and 1 Hz). However, dopamine replacement, condition and phase were not found to influence the amount of freezing episodes ($p > 0.05$).

4.4.3 Discussion

ULF were only identified in PD participants and predominantly in the more affected limb (80.9%). Freezes on the less affected side were demonstrated in PD participants that were more affected on their right side. Individuals that displayed ULF in both limbs at the same time were all bilaterally affected. In addition, *upper limb freezers* were not exclusively gait freezers suggesting that different mechanisms could exist for upper and lower limb freezing. Alternatively, upper limb freezing may precede FOG in individuals with PD or freezing may be influenced differently by walking. *Nieuwboer et al (2009)* found that upper limb freezing episodes were correlated with scores on a freezing of gait questionnaire in individuals with PD suggesting freezing shares a common mechanism (Nieuwboer et al, 2009). Due to the conflicting results of the current experiment, it is unclear whether a similar mechanism is responsible for both upper and lower limb freezing.

Although there has been conflicting results, research has found some evidence that the dopaminergic system can contribute to FOG (Iansek et al, 2006, Okuma, 2006, Schaafsma et al, 2003). Investigations of FOG in PD observed that dopamine replacement could modulate the precursors for FOG (Iansek et al, 2006) and decrease the amount of FOG during turning, walking through narrow spaces and gait initiation (Schaafsma et al, 2003). Based on the current results, dopamine replacement did not influence the occurrence of ULF. *Ziv et al (1999)* also did not find an influence of dopamine replacement on motor blocks during unimanual finger tapping in individuals with PD (Ziv et al, 1999). If the dopaminergic system can contribute to FOG but not ULF, upper and lower limb freezing would likely be influenced by different mechanisms in PD.

The current results did not find any evidence for the influence of sensorimotor integration on ULF as revealed by no influence of sensory conditions on the occurrence of ULF. Ridderikhoff *et al* (2008) have previously suggested that bimanual coordination was not affected specifically by the processing of sensory signals. It was proposed that open-loop control high-order cognitive processes compared to closed-loop control low-order sensorimotor contribute to coordination performance (Ridderikhoff, Peper, & Beek, 2008). Previous research has demonstrated that anti-phase requires greater attentional resources during continuous bimanual coordination in healthy adults (Stinear & Byblow, 2001). Additionally, Almeida *et al* (2002) demonstrated that upper limb freezing only occurred during anti-phase coordination. It was suggested that movement interruptions during anti-phase occur to inhibit limb synchronization (attraction to synergy of in-phase). However, the current results demonstrated that anti-phase coordination did not influence the occurrence of ULF. It is unclear why the increased attention of anti-phase did not increase the amount of ULF. It may be possible that the attentional demands of anti-phase in the current task were not sufficient to evoke ULF. Ridderikhoff *et al* (2008) observed that only initiation of anti-phase (compared to in-phase) required greater attentional demands.

The current results did find some evidence for attentional demand and the occurrence of ULF as more freezing episodes were observed with increased cycle frequency demand that may have been related to external cueing. Alternatively, it may be possible that the increased occurrence of ULF with increased cycle frequency was related to the duration of movement (fatigue) or the frequency of movements. It is important to take into consideration that Almeida *et al* (2002) did not examine the cycle frequency at

which freezing occurred Nieuwboer *et al* (2009) did not find any difference between the amount of freezing during normal and fast-paced coordination This would suggest that ULF is not related to the frequency of movement However, previous research has observed movement interruptions during rhythmic movements with increasing cycle frequency demand due to internal timing deficits in individuals with PD (Freeman, Cody, & Schady, 1993, Nakamura *et al* , 1978, Pastor, Jahanshahi, Artieda, & Obeso, 1992, Yahalom, Simon, Thorne, Peretz, & Giladi, 2004) However, internal timing deficits could not explain the current results as overall individuals were able to perform the movements at the appropriate frequency (see Chapter 2) Johnson *et al* (1998) found that external cueing during anti-phase coordination resulted in decreased coordination performance in individuals with PD It was suggested that external cueing during anti-phase coordination increased the complexity of the task (Johnson *et al* , 1998) These results would suggest that executive dysfunction related to attentional demands may contribute to movement interruptions rather than issues with internal timing, frequency of movements, or sensorimotor integration However, it may be possible that the increased occurrence of ULF was related to the duration of movement (fatigue) rather than the cycle frequency

Experiment 2 further examined the relationship between sensorimotor integration and attentional demands on ULF A cued voluntary pattern switch between phases (e.g. in-phase to anti-phase) during continuous bimanual coordination was added to increase the attentional demands of the task as suggested by Almeida *et al* (2003) while manipulating visual feedback Catch trials were also performed with the presence of the auditory cue without switching required In addition, a portion of the trials were initiated

with external cueing at faster cycle frequencies (2 Hz) compared to initiation only during slow cycle frequencies (0.75 Hz). This was performed to determine if the attentional demands related to initiating anti-phase coordination as suggested by Ridderikhoff *et al* (2008) would increase the amount of ULF. In addition, this would help to determine if the duration of movement was related to the occurrence of ULF. It was hypothesized that if ULF was related to increasing attentional demands than an increased occurrence of ULF would be observed during pattern switching, with a distracting auditory cue (catch trials) and when initiating anti-phase coordination in individuals with PD.

4.5 Experiment 2

4.5.1 Methods

Participants

Fifteen (n=15) individuals with PD and fifteen (n=15) age-matched healthy controls were included in Experiment 2. These participants have been described in detail elsewhere (see Chapter 4.3.1). Similar to Experiment 1, all individuals were right-hand dominant and evaluated on the 3-MS (see Table 3.1 for demographic information of participants). PD participants performed one session after overnight withdrawal of dopamine replacement (PD 'off') and another session following administration of dopamine replacement (PD 'on'). These sessions were separated by approximately 70 minutes. Healthy control participants were only required to perform 1 session. Classification of PD participants followed the same procedure as Experiment 1. Participant recruiting and ethics were also the same as Experiment 1.

Procedure

Unlike Experiment 1, *augmented vision* was not used. In addition, cycle frequencies (1 and 2 Hz) were used in blocks rather than a dynamic cycle frequency protocol. Blocks were randomized across participants.

The experimental procedure had participants begin each trial by performing continuous coordination in either in-phase or anti-phase. At the midpoint of each trial, a high-pitched auditory cue signaled individuals to perform a rapid and smooth transition (intentional switch) to the opposite phase pattern without stopping. Each trial lasted 23 seconds. To avoid anticipation of the voluntary switch, the experimenter randomly initiated trials with a verbal 'go' signal 2, 4 or 6 seconds after the beginning of each trial resulting in a rest period. The auditory cue to switch was maintained at 12 seconds for each trial. The combination of switch, cycle frequency and sensory condition resulted in 24 trials each session. PD participants performed a total of 48 trials across two sessions and healthy controls performed 24 trials in one session.

In addition, to begin each experimental session participants performed 6 *catch trials* (3 at 1 Hz and 3 at 2 Hz). These trials had participants perform continuous coordination in anti-phase for 23 seconds (2 second rest period at the start). At the midpoint a high-pitched auditory cue would be automated but without instructions to voluntarily switch between patterns.

Data Processing and Analysis

Detection and verification of freezing episodes was performed the same as Experiment 1. The reference amplitude for Experiment 2 was different from Experiment 1 for two reasons. Freezing was extremely prominent at 2 Hz as observed in Experiment 1 and not all trials had movements at 1 Hz like Experiment 1. Furthermore, the

investigators noted observationally that some trials participants were frozen for nearly the whole duration of a trial which limited the ability to use the reference amplitude similar to Experiment 1. As a consequence, the mean amplitude was calculated over 4 seconds within each trial before the cue to switch (from 6 to 10 seconds). The trial with the largest maximum amplitude (over these 4 seconds) in each limb for each dopaminergic status was used as the reference amplitude.

The amount of freezing episodes was evaluated before and after a voluntary transition. The freezing episodes were classified and described by different clinical characteristics. Chi-square analyses compared the amount of upper limb freezing episodes based on dopaminergic status, condition, phase and cycle frequency. An alpha level of 0.05 was used to define statistical significance. In addition, the amount of freezes was documented in catch trials after the auditory cue.

4.5.2 Results

Qualitative description of freezing episodes before pattern switching in PD

No freezing episodes were detected in healthy control participants. Freezing episodes were identified in 5 out of 15 PD participants. Only 1 out of the 5 *upper limb freezers* was classified as a gait freezer. All 5 *upper limb freezers* were more affected on the left side. 3 out of the 5 were considered bilaterally affected.

A total of 73 ULF were identified in PD participants using the automated computer algorithm. 53 out of the 73 (72.6%) were visually verified as freezing episodes. Multiple freezes occurred in 9 out of 53 (17%) and 1 out of 53 (1.9%) occurred in both limbs at the same time. Overall, ULF was identified in 43 trials out of 720 (6.0%) total

trials of PD participants. In addition, 96.2% (51 out of 53) occurred in the more affected limb.

Furthermore, 31 out of the 53 (58.5%) freezing episodes that occurred before the cue lasted until after the cue to voluntarily switch patterns. The length of freezes ranged from 1.2 to 5.2 seconds (mean = 2.6 +/- 1.2 s) (see Table 4.2).

Table 4.2 – The amount of ULF before pattern switching in PD participants

	PD 'off'				PD 'on'			
	More affected*	Less affected*	Both Limbs*	Total	More affected*	Less affected*	Both Limbs*	Total
Total freezing episodes	24 (20)	0 (0)	1 (1)	25 (21)	27 (22)	0 (0)	0 (0)	27 (22)
% of total trials **	5.6%	0%	0.28%	5.88%	6.1%	0%	0%	6.1%
% of total freezes ***	45.3%	0%	1.9%	47.2%	50.9%	0%	0%	50.9%

* Out of brackets represents all freezing episodes including when multiple freezes occurred in the same trial. In brackets, only represents the first freezing episode and excludes subsequent freezing episodes within the same trial.

** Percentage (%) is calculated by dividing freezing episodes (excluding freezing episodes when multiple freezes occurred) by total trials of each dopaminergic status (=360).

*** Percentage (%) is calculated from dividing freezing episodes by all freezing episodes (= 53 freezing episodes) including when multiple freezes occurred in same trial and both limbs freezing at same time.

Chi-square analyses of freezing episode before pattern switching

Chi-square analysis revealed that cycle frequency significantly influenced the amount of ULF ($\chi^2(1) = 19.6, p < 0.01$) as more freezes were identified in trials at 2 Hz compared to 1 Hz. In addition, phase significantly influenced the amount of ULF ($\chi^2(1) = 14.8, p < 0.01$) since more freezes were identified during anti-phase compared to in-phase. Dopamine replacement and condition did not influence the amount of freezing ($p > 0.05$) (see Table 4.3).

The four combinations of cycle frequency and phase were also compared. Chi-square analysis found a significant effect ($\chi^2(3) = 32.4, p < .001$). Overall, 29 (54.7%)

ULF occurred during anti-phase at 2 Hz, 11 ULF (20.8%) during anti-phase coordination at 1 Hz and 13 ULF (24.5%) during in-phase coordination at 2 Hz. No ULF were documented during in-phase coordination at 1 Hz.

Table 4.3 – Statistical analysis of ULF before pattern switching in PD participants

	PD 'off'	PD 'on'	
Dopamine replacement	26	27	$\chi^2(1)=0.02, p=0.89$
	No vision	Normal Vision	
Condition	30	23	$\chi^2(1)=1.0, p=0.32$
	In-phase	Anti-phase	
Phase	13	40	$\chi^2(1)=14.8, p<0.001 *$
	1 Hz	2 Hz	
Cycle frequency	11	42	$\chi^2(1)=19.6, p<0.001 *$

Qualitative description of freezing episodes after pattern switching in PD

Three episodes of “freezing” were identified in healthy control participants. Based on visual inspection, these trials represented short voluntary stops due to not being preceded by amplitude reductions (see Figure 4.2). As a consequence, these episodes were not classified as freezing episodes. As well, 41 ULF were identified within the transition period after the cue to switch in PD. 12 out of the 41 episodes (29.3%) had been classified as delayed responses (see Chapter 3). As a consequence, 17 trials remained where transition freezes may have occurred. However, none of these could clearly be identified as freezes based on visual inspection since amplitude reductions would have occurred to perform transitions. In addition, these transition freezing episodes appeared similar in some circumstances to the “freezing” detected in healthy controls (see Figure 4.3).

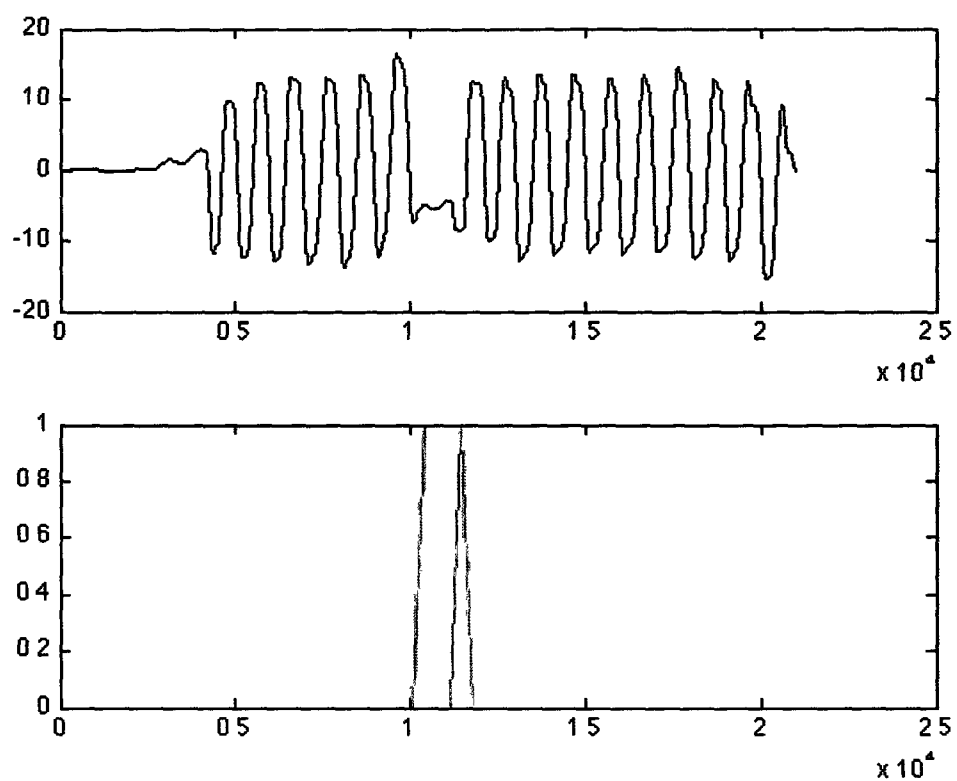


Figure 4 2 – (top) An example of a “freezing episode” detected in the right limb during a transition in a healthy control (below) Red line represents the point when all the criteria were met for a ULF by the computer algorithm Green lines illustrate when the computer algorithm detected the “freezing episode”

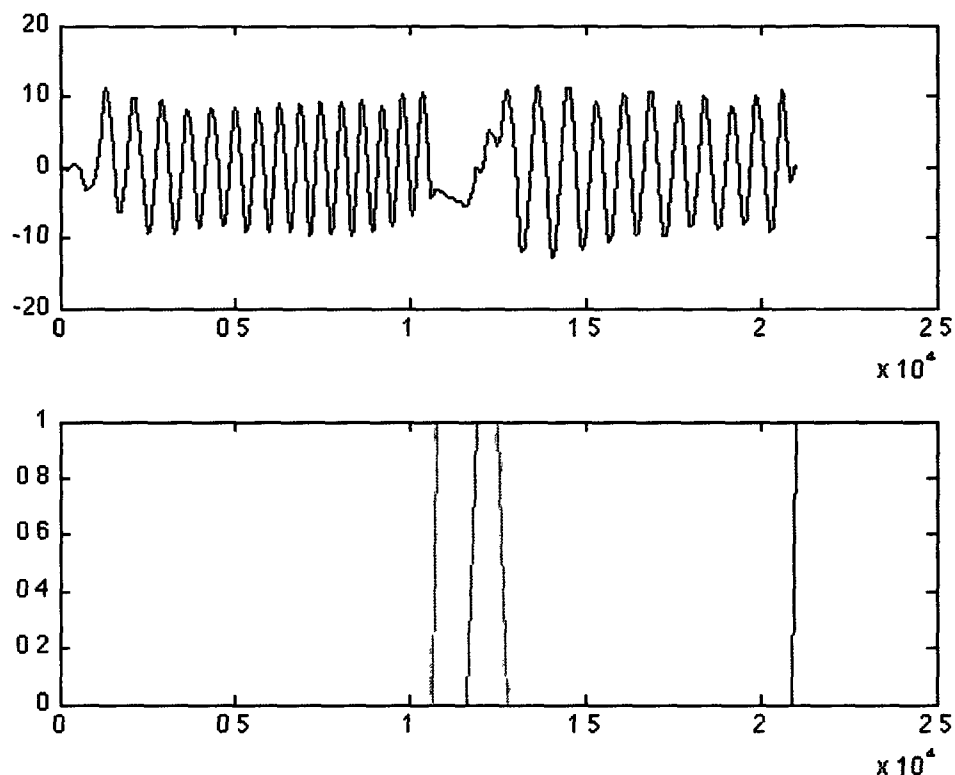


Figure 4.3 – (top) An example of PD “freezing episode” detected in the less affected left limb during the transition period (below) Red line represents the point when all the criteria were met for a ULF by the computer algorithm. Green lines illustrate when the “freezing episode” was detected by the computer algorithm.

Excluding these freezing episodes, an additional 126 ULF were identified after the cue to switch by the computer algorithm. Visual inspection confirmed that 102 out of the 126 (81.7%) were ULF. In addition, 88.8% (90 out of 102) of all freezes occurred in the more affected limb. Multiple freezes occurred in 28 out of the 102 (27.5%) (see Figure 4.4). Freezes in both limbs at the same time were identified in 5 out of 102 (4.9%). Overall, ULF was identified in 66 trials out of 720 (9.2%) total trials of PD participants (see Table 4.4). The duration of freezes ranged from 1.1 to 9.1 seconds (3.02 ± 1.9 s).

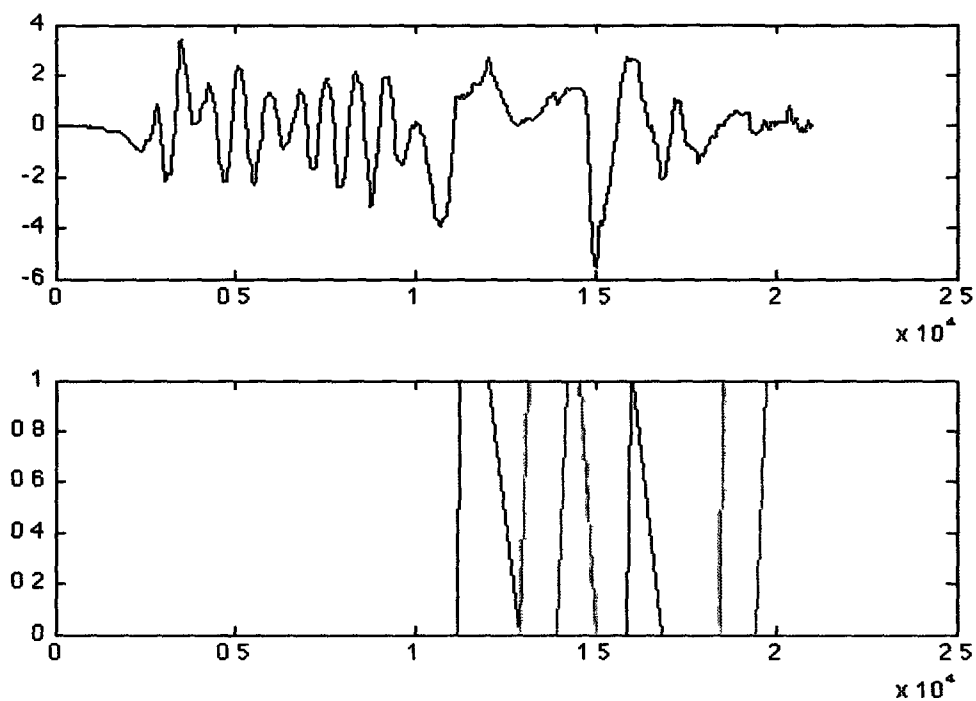


Figure 4.4 – (top) An example of a multiple ULF after a pattern switch from anti-phase to in-phase in the more affected limb of PD (below) Blue lines represent periods of decreased amplitude that did not last 1 second. Red lines illustrate the points when all the criteria were met for a ULF by the computer algorithm. Green lines represent the beginning and end of each freeze. The second freezing episode terminated at the end of the trial.

ULF was identified in 8 out of 15 PD participants. Only 3 out of 8 *upper limb* freezers were freezers of gait (compared to 2 gait freezers out of 7 non-upper limb freezers). In addition, 6 out of the 8 were more affected on the left side and 6 out of the 8 were considered bilaterally affected. Both freezes that occurred in the less affected limb (1.9%) (see Table 4.4) were in individuals that were more affected on their right side. Bilateral freezes (9.3%) occurred in 3 individuals that were more affected on their left side and 1 more affected on their right side. However, all 3 of these participants were considered bilaterally affected.

Table 4 4 – The amount of ULF after pattern switching in PD participants

	PD 'off'				PD 'on'			
	More affected*	Less affected*	Both Limbs*	Total	More affected*	Less affected*	Both Limbs*	Total
Total freezing episodes	41 (31)	1 (1)	5 (5)	47 (37)	49 (28)	1 (1)	0 (0)	50 (29)
% of total trials **	8 6%	0 06%	1 7%	10 6%	7 8%	0 06%	0%	8 3%
% of total freezes ***	40 2%	09%	4 9%	45 2%	48 0%	09%	0%	48 09%

* Out of brackets represents all freezing episodes including when multiple freezes occurred in the same trial. In brackets, only represents the first freezing episode and excludes subsequent freezing episodes within the same trial.

** Percentage (%) is calculated by dividing freezing episodes (excluding freezing episodes when multiple freezes occurred) by total trials of each dopamnergic status (=360).

*** Percentage (%) is calculated from dividing freezing episodes by all freezing episodes (= 102 freezing episodes) including when multiple freezes occurred in same trial and both limbs freezing at same time.

Chi-square analyses of freezing episode after pattern switching during continuous

bimanual coordination in PD

As seen in Table 4 5, chi-square analysis indicated that cycle frequency had a significant influence on the amount of freezes ($\chi^2(1) = 24.2, p < 0.001$) as more freezes were identified at 2 Hz compared to 1 Hz. In addition, a significant influence of phase was seen on the amount of freezes ($\chi^2(1) = 10.3, p < 0.001$) as more freezes were identified after switching to and performing anti-phase compared to in-phase. Dopamine replacement and condition did not influence the occurrence of freezing episodes.

Table 4.5 – Statistical analysis of ULF after pattern switching in PD participants

	PD 'off'	PD 'on'	
Dopamine replacement	52	50	$\chi^2(1)=0.05$, $p=0.83$
	No vision	Normal Vision	
Condition	55	47	$\chi^2(1)=0.7$, $p=0.39$
	In-phase	Anti-phase	
Phase	36	66	$\chi^2(1)=10.3$, $p<0.001$ *
	1 Hz	2 Hz	
Cycle frequency	28	74	$\chi^2(1)=24.2$, $p<0.001$ *

Freezing during catch trials after the auditory cue in PD participants

No freezing episodes were documented in healthy controls. ULF were identified in 64 trials after the auditory cue when no switch occurred in PD participants. Only 41 out of 64 (64.1%) were visually confirmed as freezing episodes. Several of these trials were verified as small voluntary stops with the auditory cue that were noted by the investigators during testing.

Multiple freezes occurred in the same trial in 8 out of 41 (19.5%) freezing episodes. Both limbs froze in 3 out of 41 (7.3%) of freezing episodes. As a result, freezing episodes were identified in 17 separate trials out of 90 (18.9%) total catch trials of PD participants.

4.5.3 Discussion

The primary objectives of Experiment 2 were to verify that increased attentional demands (rather than sensorimotor integration, movement frequency or movement duration) contributed to ULF and dopamine replacement did not influence ULF. The

current findings confirmed the results of Experiment 1 that the dopamine replacement did not influence the amount of upper limb freezing episodes. The current results also verified that *upper limb freezers* were not exclusively freezers of gait. Furthermore, the current results also confirmed that manipulating visual information was not found to influence the amount of ULF.

Similar to Experiment 1, cycle frequency was found to increase the amount of ULF both before and after a pattern switch. The current results also demonstrated that initiating a pattern switch from in-phase to anti-phase and attempted maintenance of anti-phase coordination resulted in a greater amount of ULF. Almeida *et al* (2003) also found that voluntary pattern switching from in-phase to anti-phase (compared to anti-phase to in-phase) resulted in a greater occurrence of upper limb freezing (53.9% compared to 15.5%). It was proposed that phase switching particularly when there was an increased difficulty when attempting to de-stabilize in-phase coordination requires increased cognitive demand resulting in movement interruptions (Almeida *et al*, 2003). The cognitive demands of de-stabilizing in-phase coordination cannot fully explain the current results since the presence of an auditory cue in the middle of anti-phase coordination in catch trials without any switch resulted in a similar amount of freezing to when switching was required. In view with the mechanism proposed in Experiment 1, the auditory cue without a required response would have attracted attention and required a greater cognitive demand to suppress or inhibit any response. Sharing attentional resources and suppressing behaviours are both related to executive function (Rodríguez-Oroz *et al*, 2009). Based on these findings, it would suggest that ULF does not

necessarily occur due to shifting between motor sets but rather due to increased attention demand that can be produced from several attentionally demanding situations

Although Experiment 1 did not find an effect of phase on ULF, Experiment 2 demonstrated that more ULF occurred when initiating coordination in anti-phase (before the cue to switch) Temprado *et al* (1999) and Stinear and Byblow (2001) observed that anti-phase coordination requires greater attentional resources than in-phase. In comparison, Ridderikhoff *et al* (2008) only observed that initiating (rather than maintaining) anti-phase coordination increased attentional demands. The results of Experiment 2 demonstrated that 79.2% of ULF occurred when initiating coordinated movement in either anti-phase or in-phase with increased cycle frequency (2 Hz) confirming that ULF was not related to the duration of movement (fatigue). The main difference between the two studies was that coordination was always self-initiated at slow cycle frequencies and cycle frequency dynamically increased in Experiment 1. In Experiment 2, trials were either initiated at 1 or 2 Hz by a verbal 'go' signal. Thus, it is possible that the discrepancy between Experiment 1 and 2 was that increased attentional demands of the 'go' signal were able to evoke ULF. Alternatively, the difference between Experiment 1 and 2 could be explained by initiating coordinated movements with increased attention to external cueing (e.g. 1 or 2 Hz compared to 0.75 Hz).

Increased attentional demands contributing to ULF was further supported since over half of all ULF (54.7%) before the cue to switch occurred by initiating anti-phase at 2 Hz. These results suggest that the increased attentional demands of external auditory cueing combined with the attentional demands of initiating anti-phase contributed to

ULF The current results provide further support that executive dysfunction related to increased attentional demands may be the primary contributor for evoking ULF in PD

4.6 General Discussion

4.6.1 Attentional demands and sensorimotor integration in ULF

Previous research by Almeida *et al* (2002) has suggested that upper limb freezing during externally-paced bimanual coordination occurs due to difficulties in performing anti-phase coordination. The deficits during anti-phase coordination were proposed to occur due to the inability to divide attention during coordinated movements and decreased ability to inhibit the attraction to in-phase coordination (Almeida *et al* , 2002). In addition, it was subsequently proposed that upper limb freezing resulted due to increased attentional demands required to shift between motor sets (Almeida *et al* , 2003). The main finding from the current studies was that attentional demands appeared to be the primary factor to evoke ULF similar to what was proposed by Almeida *et al* (2003). Increased attentional demands contributing to freezing has also been supported by clinical observations (Giladi & Hausdorff, 2006) and experimental evidence that have found greater cognitive load (Plotnik *et al* , 2010) and dual-tasking (Dagan, Plotnik, Grundlinger, Giladi, & Hansdorff, 2008) exacerbates FOG.

Unlike Almeida *et al* (2003), the current results demonstrated that increased attentional demands could be produced from different sources. It was demonstrated that the cycle frequency rather than anti-phase had an influence on the occurrence of ULF during continuous bimanual coordination (Experiment 1). Participants were able to maintain frequency of movements (see Chapter 2) suggesting that participants focused attention on the external cueing. However, the increased attentional demands of initiating

anti-phase coordination (compared to in-phase) with external cueing at fast cycle frequencies and a verbal 'go' signal resulted in ULF (Experiment 2) Finally, an external auditory cue during continuous anti-phase coordination without switching required and when pattern switching from anti-phase to in-phase coordination resulted in the largest amount of ULF that may have been the result of greater attentional demands for individuals with PD (Experiment 2)

It is important to consider that perceptual demands from different forms of visual feedback were not found to have an influence on the amount of ULF in either of the current studies This confirmed that deficits in sensorimotor integration were not responsible for ULF and higher-order cognitive processes have a greater contribution to bimanual coordination than low-order sensorimotor integration as was proposed by Ridderikhoff *et al* (2009) Previous research in PD proposed that the increased attention to perceptual information required when walking through narrow doorways contributed to an increased occurrence of FOG (Almeida & Lebold, 2010) Thus, it was expected that an increased occurrence of freezing would occur when attentionally demanding visual information was provided (e.g. augmented visual feedback) It may be possible that attentional demands from certain visual sources do not influence the mechanism of ULF

However, the results from the current experiments suggest that attention was focused on external auditory cueing rather than visual feedback Anecdotal evidence documented several cases of participants looking away from the computer monitor or closing their eyes during trials with augmented visual feedback It is possible that visual feedback was ignored when situations became attentionally demanding (e.g. with augmented visual feedback) As a consequence, it remains unclear if the attentional

demands from visual feedback can influence ULF. Based on the proposed mechanism, it would be expected that visual sources that require a great deal of attention resources would increase the amount of ULF.

4.6.2 Dopaminergic modulation and ULF

ULF during bimanual coordination did not respond to dopaminergic modulation, which is consistent with previous research in unimanual finger tapping (Ziv et al , 1999). There has been conflicting evidence for the effect of dopamine replacement on FOG. Several studies have found no effect of dopamine replacement on FOG (Bloem et al , 2004, Imai et al , 1993, Nomoto & Nagai, 2006, Schroeteler et al , 2009). Other studies have found that FOG can be modulated by dopamine replacement (Iansek et al , 2006, Okuma, 2006, Schaafsma et al , 2003). Based on these findings on FOG, *Iansek et al* (2006) has previously suggested that there may be a dual causation for FOG. It was argued that one mechanism involves the reduction in frequency of FOG by improvement in stride length by dopamine replacement eliminating the mismatch between the limbs and the resultant festination. Their alternative mechanism was that dopamine replacement decreases attention or increases mental confusion eliminating the ability to compensate for the internal deficits (Iansek et al , 2006). The alternative mechanism related to attention and mental confusion would support the disrupted executive dysfunction that has been proposed in the current chapter. It can also explain why dopamine replacement was not found to decrease the amount of ULF. Furthermore, it suggests that multiple mechanisms could exist for ULF.

4.6.3 Upper limb freezer vs. FOG

Research has examined the relationship between onset of disease laterality, symptoms and cognitive function in PD (Katzen, Levin, & Weiner, 2006). Individuals with PD who displayed onset of bradykinesia or rigidity had greater cognitive impairments regardless of disease laterality. In addition, PD participants with tremor onset only demonstrated cognitive impairment if tremor symptoms began on the left side (Katzen et al., 2006). As a consequence, ULF may be influenced by disease progression and laterality if the mechanism is related to executive function. Freezes were predominantly in the more affected limb (as revealed by UPDRS laterality scores). There was no trend to suggest that *upper limb freezers* were more affected on the right and left sides. However, bilateral freezes only occurred in individuals that were bilaterally affected. In addition, freezes in the less affected limb were only demonstrated in individuals with PD that had higher UPDRS upper limb laterality scores on their right-side. Stewart (2009) found similar results when examining disease laterality in PD. Individuals with PD who were right-hand dominant (like all participants in the current study) and greater laterality of PD on the right-side demonstrated more symmetry of motor impairments (Stewart et al., 2009). The relationship between disease laterality, motor symptoms and ULF needs to be examined in greater detail.

The current results showed that *upper limb freezers* were not exclusively FOG and not all gait freezers demonstrated ULF. Nieuwboer *et al.* (2009) found conflicting results as a positive correlation between episodes of upper limb freezing and scores on a freezing of gait questionnaire were observed. It was suggested that freezing in the lower and upper limbs shares a common mechanism. The discrepancy between these results could be explained by the type of movements (e.g. externally vs. internally paced).

movements) used in each experiment. Most FOG studies have used self-paced walking similar to the internally-paced bimanual upper limb movements used by Nieuwboer *et al* (2009). However, similar to the current study, movement interruptions in the upper limbs have used externally-paced movements (Almeida *et al* , 2002, 2003, Freeman *et al* , 1993, Nakamura *et al* , 1978, Pastor *et al* , 1992, Yahalom *et al* , 2004). Based on these findings, it may be possible that multiple mechanisms exist for ULF depending on whether the movements are internally or externally paced.

4.6.4 The automatic detection of ULF using a computer algorithm

Recent research has attempted to develop new methods for the automatic detection of freezing (Delval *et al* , 2010) and motor blocks (Popović, Džoljić, & Kostić, 2008). Delval *et al* (2010) suggested that a computerized process is important for detection of subtle and brief freezing that may not be identifiable visually. One of the primary purposes for the use of automated detection of freezing in the current chapter was to eliminate bias and increase efficiency and accuracy of detection. The computer algorithms used in the current studies were able to automatically detect freezing with 72.3%-88% accuracy (based on visual inspection). However, the accuracy after visual inspection was only 64.1% in the trials when no switch occurred. Small voluntary stops after the auditory cue were the primary reason for eliminating trials during visual inspection. The voluntary stops were likely a result of uncertainty related to the distracting auditory cue or inhibiting responses during the second session in each experiment. There were other limiting factors of the computer algorithm since transition periods and hypometria were detected as freezing episodes which reduced the accuracy of the automated detection. The decreased accuracy may have been a consequence of only

using peak-to-peak amplitudes compared to reference amplitudes which also contributed to 3 trials being detected as “freezing episodes” in healthy control participants. Thus, it is necessary to improve the criteria for automatic detection of freezing by computer algorithms possibly using other methods of detection such as time-frequency analysis proposed by Delval *et al* (2010)

4.6.5 Conclusion

In conclusion, increased attentional demands were the primary contributor to evoking ULF. Deficits in executive function such as maintaining, shifting and sharing attentional resources have been identified in individuals with PD (Brown & Marsden, 1991, Cools *et al* , 2010, Rodriguez-Oroz *et al* , 2009). Consequently, the occurrence of ULF with increased attentional demands may have been related to executive dysfunction in individuals with PD. Rodriguez-Oroz *et al* (2009) suggested that deficits in the cortico-basal ganglia pathways could have an essential role in the executive dysfunction that may be regulated by neurotransmitters other than dopamine (e.g. acetylcholine). If ULF involves cortico-basal ganglia pathways that are not regulated by the dopaminergic system than dopaminergic modulation should not influence ULF (comparable to what was observed in the current chapter). Furthermore, Almeida *et al* (2003) also proposed that a network including the prefrontal areas (e.g. dorso-lateral prefrontal cortex and supplementary motor area) and the neostriatum may be responsible for upper limb freezing. It was suggested that movement interruptions occur when there is an increased cognitive demand from shifting between motor sets on the cortico-striatal network resulting in an increased attentional load (Almeida *et al* , 2003). Overall, the current results support that the attentional demands placed by several factors not exclusively

shifting between motor plans can contribute to the breakdown of movement

Conceivably, the cortico-striatal network between the prefrontal areas and basal ganglia could play an essential role in ULF

However, it is possible that multiple mechanisms could exist for ULF, one that may resemble the mechanism of lower limb freezing. Future research should be directed at identifying the neural structures involved in both upper and lower limb freezing. Understanding the activity of neural substrates during freezing may help to clarify the conflicting research and the possibility of different mechanisms. More research is necessary to confirm the effects of different types of attentional load and executive dysfunction on ULF. Dual-tasking during bimanual coordination in PD could provide an important procedure for confirming the effects of attentional load and ULF. Furthermore, more research should be directed at examining whether perceptual demands from different visual sources can evoke ULF by incorporating the use of an eye tracker to monitor visual attention. Finally, research should be directed at developing a more complete definition that could be used for accurate automated detection of ULF.

4.7 References

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Chapter 5 – Epilogue

The primary objective of the current thesis was to determine how the dopaminergic system contributes to bimanual coordination in PD. By manipulating dopamine replacement across consecutive sessions in both experiments and manipulating sensory condition, phases and cycle frequency, it was possible to examine whether the dopaminergic system directly or other secondary dysfunctions (e.g. deficits in attention and/or sensorimotor integration) contributed to movement impairments during bimanual coordination in individuals with PD. Additionally, the influence of dopa-responsive motor symptoms such as hypometria and bradykinesia on the overall movements was examined. Investigation of these factors could help to determine what impairments were associated to the dopaminergic system. Determining the influence of the dopaminergic system on movements would help to direct treatment to circumvent other basal ganglia related dysfunction that is not responsive to traditional dopamine replacement.

In addition, the current thesis secondary objective was to gain a greater understanding of the mechanism that evokes upper limb freezing (ULF) during bimanual coordination in PD. Determining the mechanism for ULF could help to improve methods of diagnosing and treating since there has been a debate about whether freezing responds to dopamine replacement (Iansek, Huxham, & McGinley, 2006, Imai, Nakamura, Kondo, & Narabayashi, 1993, Nomoto & Nagai, 2006, Okuma, 2006, Schaafsma et al., 2003, Schroeteler, Ziegler, Fietzek, & Ceballos-Baumann, 2009, Ziv et al., 1999). The current chapter synthesizes the major themes that were formed from the results. These findings are discussed in relevance to the limitations of the current thesis. Finally, possible

directions of future research will be discussed in relevance to dopaminergic modulation, bimanual coordination and ULF in PD

5.1 Summary of major findings

Four major themes emerged from the current thesis. Firstly, motor symptoms were evident during bimanual coordination that could be modulated by the dopaminergic system. However, these motor symptoms did not have an overall influence on coordination performance. Secondly, movement impairments in individuals with PD compared to healthy older adults were dependent on global impairment related to basal ganglia related dysfunction. Thirdly, attention had a major influence on coordination performance and upper limb freezing (ULF). Finally, ULF is a complex symptom that may involve multiple mechanisms.

5.1.1 The dopaminergic system in bimanual coordination

PD is characterized by cell death to dopamine producing cells within the substantia nigra pars compacta that ultimately leads to dysfunction of the direct and indirect pathways of the basal ganglia system (Alexander & Crutcher, 1990, Crossman, 2000, DeLong, 1990). The decreased dopamine in the basal ganglia results in the cardinal motor symptoms of PD and other secondary complications like gait disturbances (Almeida, Frank, Roy, Patla, & Jog, 2007, Morris, Iansek, Matyas, & Summers, 1994). Clinical assessment on the motor subsection of the Unified Parkinson's Disease Rating Scale (UPDRS-III) has revealed that improvements in motor symptoms such as bradykinesia and hypometria occur after dopamine replacement (Espay et al., 2009, Fahn & Elton, 1987). Improvements in motor symptoms were also verified by the clinical assessments performed in the current thesis (see Table 2.2 and 3.2). It was possible that

improvements in motor symptoms could result in improvements in overall motor function during bimanual coordination

The findings of the current thesis found that movement amplitude could be modulated by dopamine replacement during continuous bimanual coordination (Chapter 2) However, it had no effect on frequency or the overall coordination (accuracy or stability) Overall, these findings would support that the dopaminergic system is involved in certain aspects of coordinated movements but overall motor function during bimanual coordination in PD is regulated by a distributed network Previous research has identified a distributed network involving cortical and sub-cortical structures for bimanual coordination (Carson, 2005, Jantzen, Steinberg, & Kelso, 2009, Kraft et al , 2007, Pollok, Butz, Gross, & Schnitzler, 2007, Swinnen, 2002, Wenderoth, Debaere, Sunaert, & Swinnen, 2005) Furthermore, the current findings of improvements in hypometria but no universal improvement in coordination demonstrates that control of coordinated movements occurs regardless of the dysfunction or improvement of the dopaminergic system

In addition, the dopaminergic system was not found to have an effect on the occurrence of upper limb freezing (ULF) (see Chapter 4) similar to what has been observed by *Ziv et al* (1999) The results from Chapter 4 also demonstrated that increased attentional demands resulted in the greatest occurrence of ULF (see section 4.2.3) These results were indicative that executive dysfunction in the frontal lobes due to PD may have contributed to movement interruptions rather than the dopaminergic system Previous research by *Almeida et al* (2003) proposed that upper limb freezing may be caused by increased attentional demands placed on a prefrontal-neostriatal

network Furthermore, there has been evidence from FOG studies that cognitive demand may be related to the freezing phenomenon (Dagan, Plotnik, Grundlinger, Giladi, & Hausdorff, 2008, Giladi & Hausdorff, 2006, Giladi, Huber-Mahlın, Herman, & Hausdorff, 2007) PD have been shown to have difficulty in executive functions related to the frontal lobe such as shifting, maintaining and sharing attention between resources (R G Brown & Marsden, 1991, Cools, Rogers, Barker, & Robbins, 2010, Horstink, Berger, van Spaendonck, van den Bercken, & Cools, 1990) Overall, these results support that deficits during complex movements in PD are caused by global impairment resulting from PD that cannot merely be circumvented by dopamine replacement It also suggests that brain neural re-organization and compensatory mechanisms may have an important role in complex movements in PD

Neural plasticity has been documented in stroke patients after rehabilitation (Carey & Seitz, 2007, Seitz, Matyas, & Carey, 2008) In addition, positive neural adaptations as revealed by decreased motor symptoms on UPDRS have been observed in individuals with PD after rehabilitation (Farret, Chouza, & Benaiges, 2007, Sage & Almeida, 2009) suggesting a possible role of rehabilitation in treating global impairment in PD No research has documented the amount of cortical dysfunction or subsequent adaptation that results over time from PD However, evidence has supported that cortical adaptation results from dysfunction of the basal ganglia Palmer (2009) used fMRI to examine simultaneous movements of squeezing a rubber ball with one limb while pressing a button with the other limb in PD It was found that PD 'off' and to a lesser extent PD 'on' had a distinct reorganization of connections for bimanual movements compared healthy controls It was argued that these changes were representative of neural

adaptations (Palmer et al , 2009) In support of neural adaptation, Sabatini (2000) used fMRI to investigate a complex sequential motor task in PD It was determined that there was hypoactivation in the rostral part of the SMA and dorso-lateral prefrontal cortex Concurrently, there was increased activity in areas such as the primary sensorimotor cortex It was proposed that these changes in connectivity were an attempt at re-organization to overcome the functional deficits that are characteristic of PD (Sabatini et al , 2000) As a consequence, individuals with PD have the ability to develop compensatory mechanisms to overcome functional deficits outside the dopaminergic system It also proposes that distributed neural function is more important than the dopaminergic system in PD Treatment of PD should focus on rehabilitative methods to compensate for secondary dysfunction rather than exclusively dopamine replacement

5.1.2 PD movement impairments are related to secondary dysfunction not specifically motor symptoms

As previously mentioned, the results from the clinical assessment on the UPDRS-III revealed that individuals with PD have increased motor symptoms including bradykinesia and hypometria without dopamine replacement (see Tables 2.2 and 3.2) It was possible that these motor symptoms could result in coordination and switching deficits in PD compared to healthy control participants Previous research has documented bimanual coordination deficits in PD (Almeida, Wishart, & Lee, 2002, K. A. Johnson et al , 1998) especially when including a change in movement (Almeida, Wishart, & Lee, 2003, Byblow, Summers, Lewis, & Thomas, 2002) In addition, previous research has observed deficits in individuals with PD when changing or sequencing between movements compared to healthy older adults in other upper limb tasks

(Benecke, Rothwell, Dick, Day, & Marsden, 1987a, 1987b, Stelmach, Worringham, & Strand, 1987) It was observed that slowness as revealed by slower voluntary switch time and more delayed responses as well as more unsuccessful switches were evident when changing between phase patterns in PD 'off' compared to healthy control participants (Chapter 3) In addition, the subsequent coordination performance (both accuracy and stability) was impaired in PD 'off' participants compared to healthy older adults (Chapter 3) However, dopamine replacement improved the time to switch and delayed responses but did not influence the subsequent coordination in PD (Chapter 3) It is important to consider that this slowness may have been the result of bradykinesia (slowness in movement execution) and/or bradyphrenia (cognitive slowing) If deficits and improvement with dopamine replacement in intentional pattern switching in individuals with PD were related to bradyphrenia rather than bradykinesia then it would suggest that motor symptoms do not influence performance during bimanual coordination The findings of the Chapter 2 also did not support the hypothesis that motor symptoms contribute to other movement impairments It was found that amplitude deficits (hypometria) were found during continuous bimanual coordination in both limbs in PD 'off' compared to healthy control participants (Chapter 2) However, individuals with PD did not demonstrate impairments in movement frequency (bradykinesia) or coordination performance compared to healthy older adults during continuous bimanual coordination (Chapter 2) Thus, neural damage from PD resulting in motor symptoms such as bradykinesia and hypometria does not inevitably exacerbate other motor impairments such as coordination deficits or freezing

The differences observed with coordination performance without a switch (Chapter 2) and with an intentional switch (Chapter 3) suggests that the basal ganglia are more involved when a change in movement is required in continuous bimanual coordination that may be related to secondary dysfunction from PD. Research by De Luca *et al* (2010) demonstrated that the pre-supplementary motor area (SMA) and bilateral putamen have increased activity during intentional pattern switching from in-phase and anti-phase during bimanual coordination. However, increased activity in the pre-SMA and bilateral putamen was not observed post-switch. Importantly, they observed that increased activity was associated with decreased stabilization of coordination pre-switch indicative of the phase stability-dependent frontal-striatal circuit in switching (De Luca, Jantzen, Comani, Bertollo, & Kelso, 2010). Thus, the decreased stability of coordination when switching is required would partially explain why individuals with PD were more affected with the addition of a change in behaviour during continuous bimanual coordination (Chapter 3 compared to Chapter 2). However, no differences were observed between phase patterns for these slowed and delayed responses (Chapter 3). The results of Chapter 4 did demonstrate that coordinating movements in anti-phase before the cue to switch (compared to in-phase) resulted in a larger amount of ULF in PD. Consequently, the increased amount of freezing would have resulted in decreased stabilization of coordination. In addition, there was a large amount of ULF after the cue to switch (Chapter 4) that may have ultimately contributed to the decreased coordination performance (Chapter 3). Thus, these results emphasize the relationship between fronto-striatal (e.g. SMA, dorso-lateral prefrontal cortex and striatum) pathways and motor impairment during bimanual coordination in PD.

Interestingly, it was suggested that the deficits and improvement in the slowness of switching (voluntary switch time and delayed responses) in individuals with PD might have been related to bradyphrenia rather than bradykinesia (Chapter 3). Although it is difficult to distinguish between these impairments, previous research by Marsden (1982) has suggested that slowness during movement can often be attributed to cognitive slowing during movement planning (bradyphrenia) rather than slowness in movement initiation and execution (bradykinesia) (Marsden, 1982). Sawamoto *et al.* (2002) examined spatial and verbal mental operation tasks in individuals with PD that did not require an explicit voluntary movement. It was found that performance became worse as the frequency of the tasks increased representative of cognitive slowing (bradyphrenia). Regardless of the fact that these tasks did not require a movement, a strong correlation was observed between cognitive slowing (bradyphrenia score) and bradykinesia score based on clinical assessment. It was suggested that both motor and cognitive slowness share common pathways that may be related to dysfunction in the medial prefrontal cortex and/or striatum (Sawamoto, Honda, Hanakawa, Fukuyama, & Shibasaki, 2002). Thus, if the observed improvements in voluntary switch time and delayed responses with dopamine replacement in Chapter 3 were representative of bradykinesia, this might suggest that dopamine replacement can improve function in medial prefrontal-striatal pathways. However, several results in the current thesis such as the unresponsiveness of ULF to dopamine replacement as described in Chapter 4 were linked to prefrontal-striatal pathways. It was proposed that these prefrontal-striatal pathways that were unresponsive to dopamine replacement were linked to the dorso-lateral prefrontal cortex, SMA and striatum (see section 5.2.4). Collectively, the conflict between these results might suggest

that medial prefrontal-striatal pathways are responsive to dopamine replacement where as dorso-lateral prefrontal-SMA-striatal pathways are unresponsive to dopamine replacement This would be in agreement with research by Rodriguez-Oroz *et al* (2009) that argued that although many executive functions related to the frontal cortex can be modulated with dopamine replacement, there are other executive dysfunction that are not improved with dopamine replacement It was argued that this may be in relation to dopamine overdose in frontal-striatal pathways and/or other neurotransmitters such as acetylcholine (Rodriguez-Oroz *et al* , 2009) This would be an important area for future research

5.1.3 Attention has a significant contribution to bimanual coordination and ULF in individuals with PD

In Chapter 2 (and Experiment 1 of Chapter 4), visual feedback was manipulated across 3 different conditions to determine its effects on bimanual coordination These conditions included *no vision*, *normal vision* and *augmented vision* In Chapter 3 (and Experiment 2 of Chapter 4), *no vision* and *normal vision* were compared to determine its' effect on performing a change in movement during bimanual coordination In Chapter 2, it was possible that PD would have difficulty using augmented visual feedback compared to use of visual information since difficulties have been documented in PD (Verschueren, Swinnen, Dom, & De Weerd, 1997) and healthy adults (Puttemans, Vangheluwe, Wenderoth, & Swinnen, 2004) when relying on augmented feedback in non-motor learning situations during bimanual coordination In addition, research has argued that individuals with PD have difficulties with sensorimotor integration (Abbruzzese & Berardelli, 2003, Horne, 1973, Lewis & Byblow, 2002, Lim, Hamm, Byblow, & Kirk,

2005, Lim, Hamm, Byblow, & Kirk, 2006, Moore, 1987) The results of Chapter 2 found no differences in frequency or amplitude between individuals with PD and healthy older adults when relying on augmented visual feedback. In addition, no difference in coordination performance was observed between individuals with PD and healthy older adults when relying on augmented visual feedback (Chapter 2). Alternatively, it was also possible (in Chapters 2, 3 and 4) that PD would have difficulty when blindfolded compared to when they used visual information since research has proposed that PD have difficulties when relying on proprioceptive feedback (Almeida et al., 2005, Mongeon, Blanchet, & Messier, 2009, Rickards & Cody, 1997, Schrader et al., 2008). The results of Chapter 2 found no differences in amplitude, frequency or coordination accuracy or stability when blindfolded between individuals with PD and healthy older adults (Chapter 2). The results of Chapter 3 demonstrated that voluntary switch time and coordination stability and accuracy were no different between PD and healthy control participants with no vision. Furthermore, visual feedback had no influence on the amount of ULF (Chapter 4). These results do not support that deficits in proprioceptive or sensorimotor integration contribute to movement impairments during bimanual coordination in individuals with PD. However, careful consideration needs to be taken to the influence of attentional demands rather than perception or sensorimotor integration on the current bimanual task.

Previous research has suggested that bimanual coordination is regulated by higher-order cognitive (attentional) processes compared to lower-order sensorimotor integration (Ridderikhoff, Peper, & Beek, 2008). Attentional resources are limited particularly in individuals with PD as revealed through difficulty sharing or shifting attentional resources (Cools et al., 2010, Hocherman, Moont, & Schwartz, 2004, Horstink

et al , 1990) It is important to consider that both studies (Chapter 2, 3 and 4) used external auditory cueing Additionally, the goal of the task was to coordinate both limbs in rhythm with the metronome It is possible that the goal of the task and presence of external cueing directed attention to the rhythmic temporal coordination of the limbs The results of Chapter 2 supported that attention was directed at external cueing and maintaining the temporal coordination since individuals with PD were able to maintain the correct frequency of movements and coordination performance The results of Chapter 4 also proposed that increased attentional demands from external auditory cueing at fast cycle frequencies and a distracting external auditory cue during continuous bimanual coordination increased the occurrence of ULF As a consequence, if attention was directed to the external auditory cues and temporal coordination of the limbs there would have been limited attentional resources focused on visual feedback

As described in Chapter 4, anecdotal evidence documented that PD may have focused attention away from visual feedback when it became too attentionally demanding Thus, motor impairments during complex movements may be influenced by attentional demands rather than solely perceptual information or sensorimotor integration Furthermore, research has suggested that impairments during rhythmic movements can be explained by deficits with an internal timekeeper (Freeman, Cody, & Schady, 1993, Konczak, Ackermann, Hertrich, Spieker, & Dichgans, 1997, Nakamura, Nagasaki, & Narabayashi, 1978, Ziv et al , 1999) However, the current results found that directing attention to external cues rather timing contributed to movement impairments in individuals with PD such as freezing (Chapter 4) Thus, it is possible that direction of attentional resources rather than timekeeping mechanisms has a greater contribution to

impairments during rhythmic movements such as bimanual coordination in individuals with PD

5.1.4 Multiple mechanisms could exist for upper limb freezing (ULF) in PD

Freezing has been classified with akinesia as a motor symptom that incorporates exaggerated forms bradykinesia and hypometria (Imai, 1996) Although it has been classified as a motor symptom, there is growing evidence that FOG is more than a simple motor impairment Unlike traditional motor symptoms, there has been conflicting evidence for the response of FOG to dopamine replacement in PD (Ianssek et al , 2006, Imai et al , 1993, Nomoto & Nagai, 2006, Okuma, 2006, Schaafsma et al , 2003, Schroeteler et al , 2009) Research has indicated that cognitive factors such as cognitive demand, stress and anxiety influence FOG in PD (Dagan et al , 2008, Giladi & Hausdorff, 2006, Plotnik et al , 2010) In addition, perceptual demand from visual information may also contribute to the occurrence of FOG (Almeida & Lebold, 2010) Overall, the results from Chapter 4 provided evidence that ULF is a remarkably complex symptom of PD Most of the findings from Chapter 4 supported that increased attentional demands evoked ULF The results of Chapter 4 demonstrated that increased external auditory cueing (Experiments 1 and 2) and initiation of coordinated movements with a verbal cue particularly with increased auditory cueing and anti-phase coordination (Experiment 2) contributed to increased attentional demands and occurrence of ULF Furthermore, a distracting auditory cue in the middle of continuous anti-phase coordination (Experiment 2) and a cued-intentional switch (Experiment 2) also increased attentional demands and increased the occurrence of ULF Based on this evidence, it was

proposed that the primary mechanism for ULF is related to executive dysfunction related to the frontal lobes in connection with the striatum

However, the complexity of ULF was illustrated by the results from Chapter 4 that demonstrated ULF was not exclusively associated to individuals who display FOG in conflict with research by Nieuwboer *et al* (2009) The primary difference between these studies was that bimanual coordination was externally-cued in the current thesis compared to internally-cued in the study by Nieuwboer *et al* (2009) The complexity of ULF was further complicated by the findings that ULF may be related to disease laterality and progression The results showed that most ULF was recorded in the more affected limb (Chapter 4) However, individuals who displayed ULF in the less affected limb were more affected on their right-side (Chapter 4) As well, freezing episodes that were documented in both limbs at the same time were all in individuals that were considered bilaterally affected (Chapter 4) Together, these results suggest that multiple mechanisms could exist for ULF

Plotnik *et al* (2005) have observed that asymmetry in the timing (swing time) of stepping between the left and right limbs was evident in individuals with PD who displayed FOG compared to individuals with PD who do not display FOG The timing asymmetry between the limbs during stepping was proposed to cause deficits in gait coordination and FOG that was independent of motor symptom asymmetry or simple hand timing (Plotnik, Giladi, Balash, Peretz, & Hausdorff, 2005) In a subsequent study, Plotnik *et al* (2008) determined that the asymmetry in the stride durations of each limb during gait as revealed by the phase coordination index (PCI) was greater in individuals with PD who display FOG It was proposed that poor bimanual coordination resulted in

FOG (Plotnik, Giladi, & Hausdorff, 2008) Although timing asymmetry may contribute to FOG, the results from Chapter 2 determined no difference in the frequency of movements between the limbs In addition, the results of Chapter 2 also did not demonstrate coordination deficits suggesting that irregular timing between the limbs is not responsible for deficits in bimanual coordination leading to ULF Almeida (2009) suggested that the asymmetry during bimanual coordination contributing to FOG may be related to amplitude rather than timing (Almeida, 2009) The results from Chapter 2 showed that the amplitude of the more affected limb was smaller than the less affected limb at the fastest cycle frequency (2 Hz) As revealed by the results of Chapter 4, ULF was more evident at faster cycle frequencies Thus, amplitude asymmetry could contribute to ULF

A dual causation mechanism has previously been proposed for FOG in PD (Ianssek et al , 2006) For ULF, the distinction between mechanisms may be related to internally-guided movements (internal timing-deficits) and possibly responsive to dopamine replacement The other mechanism may be related to externally-driven movements with auditory cueing, increased attentional demands and non-responsive to dopamine replacement Dual mechanisms could explain the discrepancy for ULF between the current thesis and the study by Nieuwboer *et al* (2009)

Furthermore, previous research by Katzen *et al* (2006) has indicated that disease laterality at onset and dominant symptoms may contribute to cognitive dysfunction Cognitive impairments were found in individuals with PD with bradykinesia or rigidity onset on both sides but only in individuals that displayed tremor onset on the left side (Katzen, Levin, & Weiner, 2006) Collectively, the results of Chapter 4 proposed that

attention related to frontal lobe function was the primary contributor to ULF which may explain the discrepancies between the presentations of freezing. The results of Chapter 4 demonstrated that freezes were predominantly in the more affected limb, bilateral freezes only occurred in individuals that were bilaterally affected. In addition, the results of Chapter 4 also identified that freezes in the less affected limb were only demonstrated in individuals with PD that were more affected on their right-side. It may be possible that the current mechanism of ULF associated to executive dysfunction is related to individuals with PD that have rigidity or bradykinesia onset on either side or tremor onset on the left side. Alternatively, another mechanism may exist for individuals that have tremor onset on the right side. The side of onset and motor symptom onset could provide an important dissociation between mechanisms of ULF.

5.2 Limitations and Future Directions

Although the current thesis generated many significant findings, there were several limitations that could have influenced the current results. Other methods that could be used to improve these limitations are discussed as future directions for research investigating bimanual coordination and ULF in PD.

The methods used in the current thesis for testing dopaminergic modulation in PD were consistent with previous research (Almeida et al , 2007, Benecke et al , 1987b, A M Johnson et al , 2004, Stegemoller, Allen, Simuni, & MacKinnon, 2010). Individuals with PD performed two consecutive sessions ('off' followed by 'on') within the same day (see 2.3.1 and 3.3.1). However, it was demonstrated that improvements in coordination performance were present as revealed by healthy controls' improved coordination performance between sessions 1 and 2 (Chapter 2). Improvement across sessions suggests

that motor learning may factor into performance between consecutive sessions. Pilot work from our lab found that 48 hours between sessions did not result in practice effects (M J N Brown & Almeida, 2008). Future research that involves testing PD 'off' and 'on' may benefit from testing individuals with PD on separate days and counterbalancing the first sessions. The separation of 'on' and 'off' sessions would be in line with recent research that has adopted this method of testing the dopaminergic system in PD (Jahanshahi et al , 2010, Mongeon et al , 2009).

Fatigue (peripheral, central or cognitive) can have a negative impact on movements in PD (Beiske & Svensson, 2010, Friedman, 2009, Lou, 2009). Participants were allowed to take breaks when needed to reduce the possibility of fatigue in the current thesis. Participants also had a minimum 70 minute break between consecutive sessions. However, the testing procedure may have contributed to fatigue caused by the length of the testing procedure (combined 3 to 5.5 hours). Previous research in rhythmic finger tapping did not find any evidence of a loss of force-generating capacity indicative of peripheral fatigue in PD (Stegemoller et al , 2010). Although there was no evidence that fatigue occurred in the current thesis, research is needed to investigate whether and when fatigue can result from rhythmic bimanual coordination and the consequences of fatigue on the movement outcomes particularly for individuals with PD. Understanding the relationship between repetitive bimanual movements and fatigue would help to set the appropriate testing duration to eliminate the contribution of fatigue in future studies.

Anecdotal evidence was presented (Chapter 4) suggesting that participants did not always rely on the source of visual feedback provided. Situations were documented when individuals closed their eyes during *normal vision* conditions. Additionally, individual

directed vision away from augmented visual feedback. Avoiding attentionally demanding visual information could have influenced certain outcomes in the current study (see 5.2.3). As presented in the current thesis, the direction of attention can have a significant influence on the outcomes of the task since external auditory cueing was beneficial for maintaining the frequency of movements (Chapter 2). Future research that examines the use of visual feedback needs to carefully control for visual attention with the use of an eye tracker. Based on the attentional demand theory proposed in the current thesis, ULF and coordination deficits may occur if attention was focused on visual information that overloaded the attentional resources. The possible influence of increased attentional demands of visual information on ULF would be supported by research that proposed increased attention to perceptual demands of a narrow doorway contributes to FOG in PD (Almeida & Lebold, 2010). Thus, future research is also needed to examine overloaded attentional resources from visual feedback during internally-regulated bimanual coordination in PD. Future research is also needed to examine bimanual coordination in PD that is regulated only by sensory feedback. Manipulating and controlling sensory feedback would help to clarify how sensory impairments such as proprioceptive and/or sensorimotor integration deficits compared to attention related to sensory information contribute to bimanual coordination in individuals with PD.

The current thesis examined bimanual three dimensional (3-D) wrist extension-flexion movements using haptic devices. Previous research that has examined bimanual coordination in PD used movements that are constrained to either one (1-D) or two dimensions (2-D) (Almeida et al., 2002, 2003, K. A. Johnson et al., 1998, Swinnen et al., 1997). Based on the results of the current thesis, there appears to be important differences

when individuals are able to recruit extra degrees of freedom for the movement as suggested by previous research (Buchanan & Kelso, 1993, Buchanan, Kelso, DeGuzman, & Ding, 1997) Future research is necessary to directly compare the differences during bimanual coordination in individuals with PD when movements are constrained to 1D or 2D compared to unconstrained in 3D The available degrees of freedom may have an important contribution to the movement impairments that manifest and will be important to direct rehabilitation aiming to improve upper limb function in PD

Surface electromyography (sEMG) was collected in both studies These results are presented in Appendix A The primary goal of incorporating sEMG in bimanual coordination was to examine the muscle timing before ULF since irregular muscle timing was shown prior to lower limb freezing episodes (Nieuwboer et al , 2004) However, in post-processing the raw sEMG signals it was determined that these signals were too noisy to complete the proposed burst analysis The noise in sEMG signals was hypothesized to result primarily from cross-talk between other small forearm muscles and muscle activity related to PD tremor Research has suggested that isolating forearm muscles is very difficult with surface electrodes (Burne, Blanche, & Morris, 2004) In addition, previous research has demonstrated that PD tremor has distinct and large muscle activity (Caviness et al , 2006) Furthermore, several other factors may have contributed to the noisy signals such as impedance due to fat tissue, electrodes moving on the skin due to the nature of the movement and reduced muscle in elderly participants (Farina, 2006, Farina, Merletti, & Enoka, 2004) It is possible that the noise would have been improved with wireless electrodes and/or fine-wire recording Also, removing participants with tremor or removing tremor in post-processing may have improved collection of sEMG in

individuals with PD Future research is needed to determine the effectiveness of sEMG in detecting muscle timing during bimanual coordination in PD Future research is also needed to determine if muscle activity (timing or amplitude) is irregular for ULF Understanding the muscle timing could be helpful to clarify the relationship between upper and lower limb freezing Additionally, it could be used by clinicians as a diagnostic marker for PD

Finally, the results from Chapter 4 found that the automatic detection using a computer algorithm led to errors in detecting of ULF in 10 to 30% of detected freezes The definition used in the current thesis involved determining 75% reductions in the peak to peak amplitude to reference amplitudes for a minimum of 1 second In comparison, Almeida *et al* (2002, 2003) used no change in movement amplitude for at 1 second However, research has documented that freezing does not always incorporate a complete arrest in movement (Giladi & Nieuwboer, 2008, Nieuwboer et al , 2009) Anecdotal evidence from the current thesis also found that high-frequency oscillations were present during some ULF (Appendix C) Future research is necessary to determine all kinematic variables that are influenced during ULF Incorporating EMG as was discussed in the previous paragraph or time-frequency analysis (Delval et al , 2010) could improve the definition of freezing and allow for accurate automated detection Proper automatic detection of freezing would be important for research that examines the mechanisms of ULF as well as if being used as a diagnostic tool for clinicians

5.3 Conclusion

Overall, the results from Chapters 2, 3 and 4 provided evidence that PD is a complex disorder that cannot be characterized solely by dysfunction of the dopaminergic

system. The traditional model of PD is focused on nigrostriatal dysfunction and dopaminergic modulation of motor symptoms. However, evidence supports that secondary pathways such as the projections between globus pallidus internal and PPN (Nandi, Stein, & Aziz, 2002) and frontostriatal pathways between the motor cortex such as dorso-lateral prefrontal cortex and SMA and basal ganglia (Sabatini et al., 2000) are affected by dopamine loss. As a consequence, research in PD needs to examine motor function from the view of global impairment rather than exclusively the dopaminergic system. The current thesis found that most of the impairments in coordination performance (Chapter 3) and freezing (Chapter 4) were related to secondary dysfunction (e.g. executive dysfunction) resulting from dopamine loss. The results did find some evidence that the dopaminergic system contributes to the amplitude during coordinated movements (Chapter 2) and speed of changing between phase patterns (Chapter 3) since dopamine replacement improved these parameters. However, these improvements did not have an effect on the overall coordination performance or freezing. Furthermore, impairments were observed in the amplitude (Chapter 2) and speed of switching between phase patterns (Chapter 3) in PD 'off' compared to healthy control participants. However, these results could be explained by dysfunction between the SMA and striatum since the results from Chapter 4 demonstrated that attentional demands of external cueing, anti-phase and pattern switching had a major influence on the occurrence of ULF. Overall, research and treatment of PD should be focused on all basal ganglia dysfunction rather than only the dysfunction related to the dopaminergic system. Due to the complex biochemistry and pathways of the brain, it may be a difficult goal for pharmacological treatments to alleviate the influence of executive dysfunction to movement impairments.

in individuals with PD Rehabilitation focused on improving overall neural function including cognitive and motor performance should be the primary focus of treatment in individuals with PD due to the prospect of neural plasticity

5.4 References

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Appendix A - Surface electromyography (sEMG) to detect upper limb freezing during bimanual coordination in Parkinson's disease (PD)

A.1.0 Introduction

Freezing is arguably one of the most debilitating motor symptoms of Parkinson's disease (PD). It is characterized by the inability to initiate movements or sudden arrests in voluntary movement (Giladi et al, 1992, Imai, 1996, Nakamura, Nagasaki, & Narabayashi, 1978). Freezing episodes have been documented by visual detection and using kinematic data in both the upper (Almeida, Wishart, & Lee, 2002, 2003, Nieuwboer et al, 2009) and lower limbs (Almeida & Lebold, 2010, Bloem, Hausdorff, Visser, & Giladi, 2004, Giladi et al, 2001, Iansek, Huxham, & McGinley, 2006, Nieuwboer et al, 2004). Recently, surface electromyography (sEMG) was used to detect a temporal discoordination in muscle activity (i.e. premature activation) in both the gastrocnemius and tibialis anterior muscles prior to freezing of gait (FOG) in PD (Accardo, Mezzarobba, Millevoi, & Monti, 2008, Nieuwboer et al, 2004). They argued that there exists a problem in the central timing mechanism for muscle activation prior to freezing. Furthermore, recent research found a correlation between the occurrence of upper limb freezing and scores on a freezing of gait (FOG) questionnaire (Nieuwboer et al, 2009). It was suggested that freezing in the upper and lower limb share a common mechanism. Since behavioural evidence has been conflicting (see Chapter 6), it is possible that a common mechanism for these types of freezing is an irregular timing of muscle activity. However, no research has examined whether this is also characteristic of upper limb freezing.

Furthermore, sEMG may have additional benefits for detection of upper limb freezing. Traditionally, upper limb freezing has been defined using no change in amplitude over a given amount of time from kinematic data (Almeida et al, 2002, 2003). However, recent research in FOG has suggested that complete arrests in movement do not always occur (Giladi and Nieuwboer, 2008). This has resulted in alternative definitions of freezing that include irregular cyclic frequency (Delval et al, 2010, Nieuwboer et al, 2009)(Appendix B) and significant reductions in amplitude for a given amount of time (Chapter 6). Accordingly, sEMG could also be a useful technique to help detect freezing by quantifying muscle activity before, during and after a freezing episode.

sEMG is used to record the electrical activity of muscles to understand muscle function. In individuals with neurological impairment such as PD, this is often used to understand how dysfunction of particular brain areas (i.e. basal ganglia) can affect control of the muscles. To date, there has been no standardized method developed to analyze sEMG signals particularly for individuals with PD. Due to this factor, there remains uncertainty (i.e. concerns with validity and reliability) about the ability to explain the signal in reference to the neurophysiological processes (Hogrel, 2005). Nieuwboer *et al* (2004) has currently developed the only method to successfully detect muscle burst activity during FOG in individuals with PD. Video assessments were used to verify freezing episodes during gait. The 3 strides before a freezing episode and 2 strides before a voluntary stop were then used to compare muscle burst activity. The raw and processed sEMG activity in both the gastrocnemius and tibialis anterior were normalized as a percentage of the gait cycle. Muscle burst activity was determined by setting a threshold

based on average 3 peaks relative to the background noise. Finally, the normalized for the differences in gait cycles by separating activity during total gait cycle, stride and stance phases as percentages (Nieuwboer et al, 2004). The current study attempted to use similar methods for detecting muscle burst activity during upper limb freezing (ULF) in individuals with PD.

sEMG was recorded during two experiments using bimanual coordination in PD. The current chapter primary objective was to determine if an automated computer-algorithm could be used to detect muscle burst activity during bimanual coordination in PD. In addition, muscle bursts were compared across flexor and extensor muscles to determine whether irregular timing of muscle activity was characteristic of upper limb freezing episodes during bimanual coordination in PD. Finally, the muscle burst activity and amplitude were compared to determine if there was any distinct muscle activity (either in timing or amplitude) prior to, during or after a freezing episode that could aid in the future detection of upper limb freezing.

A.2.0 Methods

A.2.1 Participants

See sections 4.3.1 and 5.3.1

A.2.2 sEMG placement and procedure

The movement used in both the current experimental studies involved bimanual wrist flexion-extension performed on two robotic Phantom Omni haptic devices (SensAble Technologies Inc, Woburn, MA, USA). The forearms were constrained to reduce movements at the elbow and shoulder joints. Arms were pronated 90° degrees (i.e. palms facing inward) for successful grasping of the pen-shaped stylus. Bipolar

surface electromyography (sEMG) was used to examine the rhythmical muscle activity patterns in both forearms. Placement of two Blue Sensor N Ag/AgCl electrodes (Ambu International A/S, Denmark) was on the extensor digitorum and flexor carpi radialis of each forearm muscle. To place these electrodes, the investigators performed two procedures. Firstly, participants performed isometric extension and flexion against the investigators hand to isolate these muscles. Secondly, participants actively performed wrist flexion and extension so investigators could confirm the muscles isolated during isometric resistance. In addition, a ground electrode was placed on the elbow.

The procedure for electrode placement and skin cleaning followed guidelines for sEMG that were previously recommended (Hermens, Freriks, Disselhorst-Klug, & Rau, 2000). Electrodes were placed a minimum of 20 mm away from each other. Placement was the muscle belly, halfway between the most distal motor end plates and distal tendon as well as a transverse location away from the edges to avoid crosstalk. Orientation of the electrode was parallel to the muscle fibers. The skin for all participants was shaved and rubbing alcohol applied to clean the skin for the most reliable results (Hermens, Freriks, Disselhorst-Klug, & Rau, 2000). Electrodes were left on participant's forearms between sessions to avoid any variability.

A.2.3 Apparatus

An Octopus AMT analog electromyography system (Bortec Electronics Inc, Calgary, AB, Canada) was used to collect sEMG from 4 forearm muscles at a rate of 1000 Hz (band-pass filtered between 10-1000 Hz). This sampling rate was above the Nyquist rate ($2 \times$ greater than highest frequency) to avoid aliasing the signal (Ives & Wigglesworth, 2003). Each of the 4 APE 500 electrode-connecting wires had an

amplifiers built in The electrodes were attached to a portable pre-amplifying patient unit that sent the encoded signal to the receiving unit where information was further amplified (Total gain of system=500) Signals were preprocessed from analog to digital BNC cables were connected to a computer receiving unit (National Instruments Corporation, Vaudreuil-Dorion, Quebec, Canada) Digital signals were sent to the computer (Dell Computer, with a g-force intel Pentium 4 with SSE2) and recorded in Matlab R2007b (The MathWorks Inc, Nattick, MA, USA) The raw electromyography signals were available for further offline processing and analysis

A.2.4 Data Processing

Offline processing of raw sEMG signals for muscle activity followed previous recommendations (De Luca, 1997, Difabio, 1987, Hodges & Bui, 1996) This included full-wave rectification and low-pass or band-pass filtering that were done using scripts created in MatLab However, there have been conflicting recommendations for filtering sEMG signals (Hodges & Bui, 1996) so several filtering techniques were attempted in the current study to eliminate high frequency noise These included using low-pass and band-pass filtering and manipulating the cutoff frequencies between 3 – 1000 Hz and using 2nd, 4th, 6th, and 8th order Butterworth filters These methods of filtering were compared to determine at which point there was not enough (high cut-off frequency) vs too much smoothing (low cut-off frequency) (Hodges & Bui, 1996) Based on visual inspection, it was determined that signals were appropriately filtered using a low pass 4th order Butterworth filter with a cutoff frequency of 10 Hz

A.2.5 Data Analysis

Muscle burst detection

Data analyses were performed using scripts created in MatLab. A double threshold technique of detection was used to determine the *onset*, *duration* and *offset* of muscle bursts (Difabio, 1987, Hodges & Bui, 1996, Staude, Flachenecker, Daumer, & Wolf, 2001). This method has been shown to be superior to a single threshold method (i.e. signal goes above a threshold at any point in time) (Reaz, Hussain, & Mohd-Yasin, 2006, Staude et al., 2001). Muscle burst onset involved choosing a threshold (i.e. number of standard deviations above the mean) and a sliding window (i.e. how many ms the signal needed to stay above the threshold). The mean noise of the signal (mV) was calculated for the first 50, 100, 500 or 1000 ms (i.e. data points) within each trial. In addition, several different combinations of standard deviations (SD) above the mean (1, 2, 3 and 5 SD) and sliding windows (25, 50, 100 and 500 ms/data points) were used. This was performed due to the effect that different combinations can have on the accuracy of muscle burst detection (Hodges & Bui, 1996).

Muscle burst *offsets* were calculated in the reverse of the muscle burst *onset* (i.e. below threshold for sliding window duration). Muscle burst *durations* were calculated from the time between *onset* and subsequent *offset* of muscle bursts. In addition, due to the proximity (in time) of detected muscle bursts, bursts were merged if they were 125ms in proximity based on previous recommendations (Merlo, Farina, & Merletti, 2003). The script was also run without burst merging. The script used the same filtering and detection methods for each forearm's flexor and extensor. However, muscle bursts each of the four muscles were detected separately.

Timing of muscle bursts

To analyze the timing of muscle activity before freezing episodes the time of freeze onset was calculated (see Chapter 6) and entered into the script. Each movement cycle was measured (for each limb) from the peak positive to positive amplitude (see Chapter 4 and 5). The 5 movement cycles before each freeze were examined to analyze the time before freezes. This was similar to the 3 step cycles that were used for sEMG before FOG analysis (Nieuwboer et al , 2004). The amount of time in *flexion* and *extension* was calculated for each movement cycle. This was expressed in both time and percentage of overall movement cycle similar to the methods by Nieuwboer *et al* (2004). The *amount of overlap time* for each muscle was calculated between the flexor and extensor within the same limb based on the muscle bursts detected. In addition, the *percentage (%) of overlap* was calculated based on the *amount of overlap time* of each muscle relative to the given burst duration.

sEMG muscle activity related to signal amplitude

In addition to muscle burst activity, the amplitudes of each muscles' sEMG signal was measured over the whole duration of a trial to detect for any *irregular* activity. *Irregular* activity was defined when amplitude was either longer or shorter than the amplitude of the mean muscle burst amplitude. The mean muscle burst amplitude was calculated from averaging each muscle burst for each muscle over a given trial. *Irregular activity* was calculated as either *low- activity* or *high-activity muscle bursts*. *Low activity muscle bursts* were determined when amplitude remained lower than the mean muscle burst amplitude for longer than the average movement cycle duration. *High-activity muscle bursts* were determined when amplitude remained higher than the mean muscle burst amplitude for longer than the average movement cycle duration.

Statistical Analysis

The methods of comparison were adapted from the methods used by Nieuwboer *et al* (2004) This involved comparing all measures in all muscles for trials where upper limb freezing (ULF) occurred to non-ULF trials in PD In addition, ULF, non-ULF in PD were compared to trials of healthy controls The data was averaged across multiple trials An ANOVA was used to calculate the differences between dopaminergic status, conditions, phase and cycle frequency Tukey's post hoc analyses were used on any significant interactions from the ANOVA A separate ANOVA was also performed between the flexor and extensor muscles of each limb Statistical significance was determined with p values < 05

A.3.0 Results

The scripts to analyze muscle burst activity were run on ULF trials first to determine the ability of these to properly detect muscle burst activity Based on observation, it was determined that the computer-algorithm was not properly detecting muscle burst activity during freezing trials Examples are presented below (Figure A 1 and A 2) Several other distinct ULF and non-ULF trials in PD were examined to substantiate this finding An example of a non-ULF trial is presented in Figure A 3 This finding (i e irregular detection of muscle bursts throughout trials) was confirmed by the signals in the majority of ULF (of Experiment 1) and the sample of non-ULF trials that were examined In an attempt to resolve this issue, the parameters of detection (i e filtering, mean noise, threshold and sliding window) were all manipulated in various combinations However, this did not improve the detection method

Based on these findings, statistical analyses were not performed due to a lack of validity in muscle burst detection. A small qualitative description is presented of muscle burst activity in a ULF trial compared to non-ULF (in PD) and healthy control trials.

A.3.1 Qualitative description of muscle burst activity

For the current muscle burst detection the parameters included 500 ms mean noise calculation (during quiet part at beginning of trials), threshold was set at 2 standard deviations above the mean, a sliding window of 50 ms, low-pass 4th order Butterworth with a cutoff frequency of 10 Hz. All graphs compared in each section were controlled for condition, phase and session.

Healthy Control Right Limb

Figure A 1 and A 2 illustrate filtered and rectified extensor and flexor muscle activity, respectively. Despite expected displacement in the right limb, irregularity in muscle burst detection can be seen. This was demonstrated even with manipulations of the detection parameters.

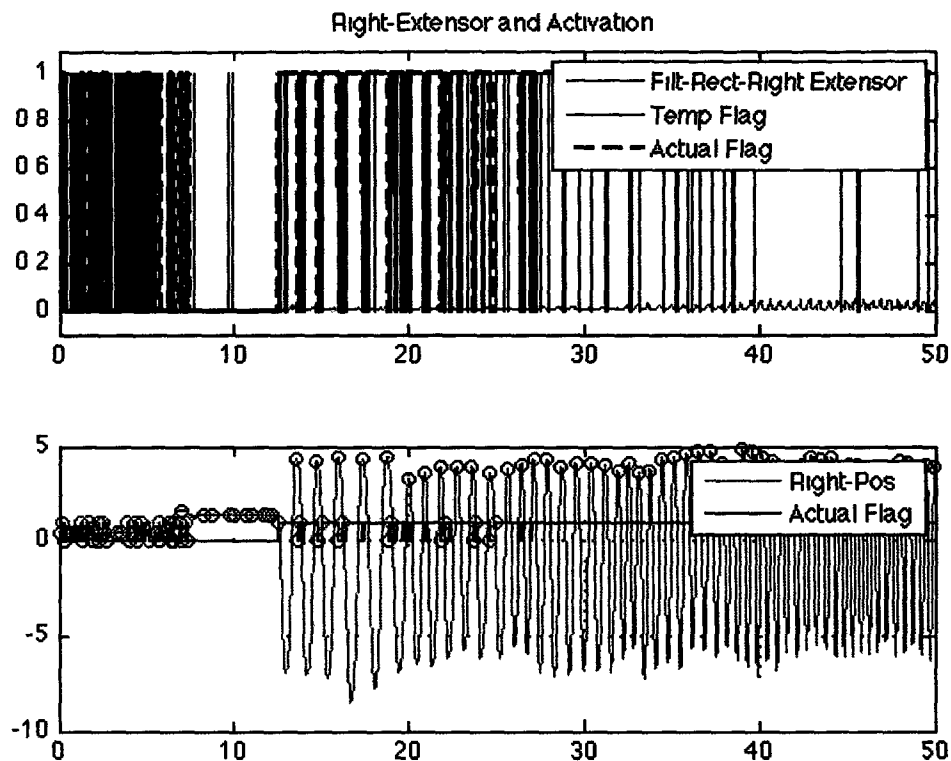


Figure A 1 – Right extensor muscle activity and displacement of a healthy control (*top*) red line represents filtered and rectified right extensor activity, blue lines represent anytime the amplitude exceeded the threshold and black lines represent the actual muscle bursts detected (*bottom*) red line represents the displacement of the right wrist (black circles represent each movement cycle), red circles represent the detected muscle burst *onset* and blue circles represent the subsequent muscle burst *offset*

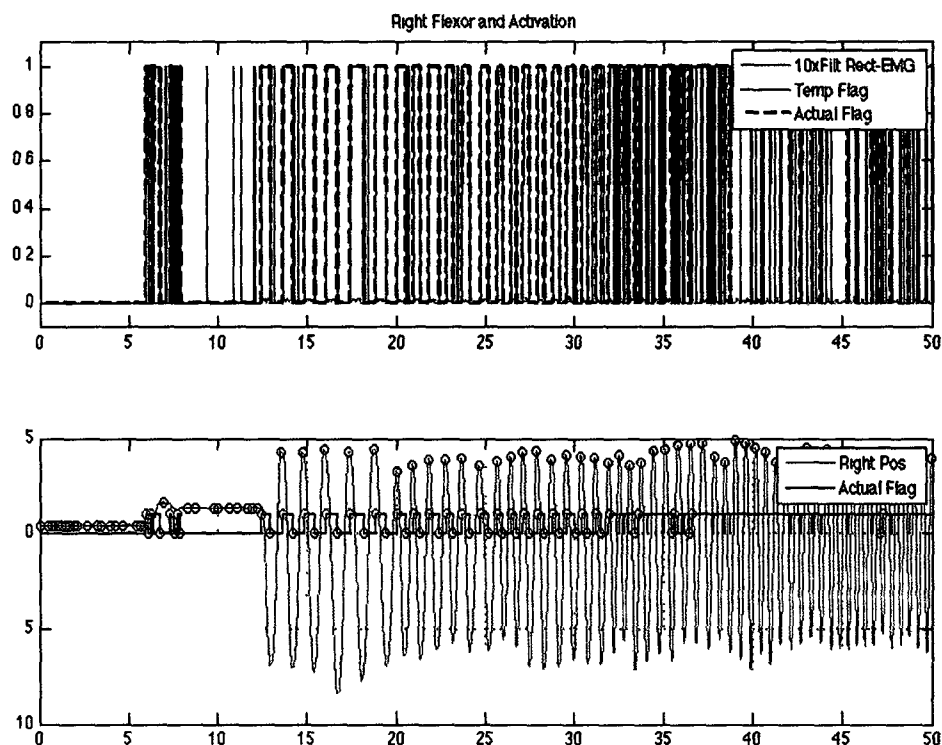


Figure A 2 – Right flexor muscle activity and displacement of a healthy control (*top*) red line represents filtered and rectified right flexor activity, blue lines represent anytime the amplitude exceeded the threshold and black lines represent the actual muscle bursts detected (*bottom*) red line represents the displacement of the right wrist (black circles represent each movement cycle), red circles represent the detected muscle burst *onset* and blue circles represent the subsequent muscle burst *offset*

Healthy Control vs non-ULF PD

Figure A 3 and A 4 present the rectified and filtered left flexor and extensor muscle activity (respectively) of a healthy control. These demonstrated relatively accurate detection of muscles bursts. However, there were still some missing bursts detected (i.e. between 22 and 25 seconds on Figure A 3). Figure A 5 and A 6 depict the rectified and filtered left flexor and extensor muscle activity of a PD non-ULF, respectively. Comparing the activity across participants, there was some indication that PD non-ULF had an increased amount of muscle bursts, particularly in the left flexor.

This is supported by the observation that the detection remained on around 22 seconds until the end of the trial

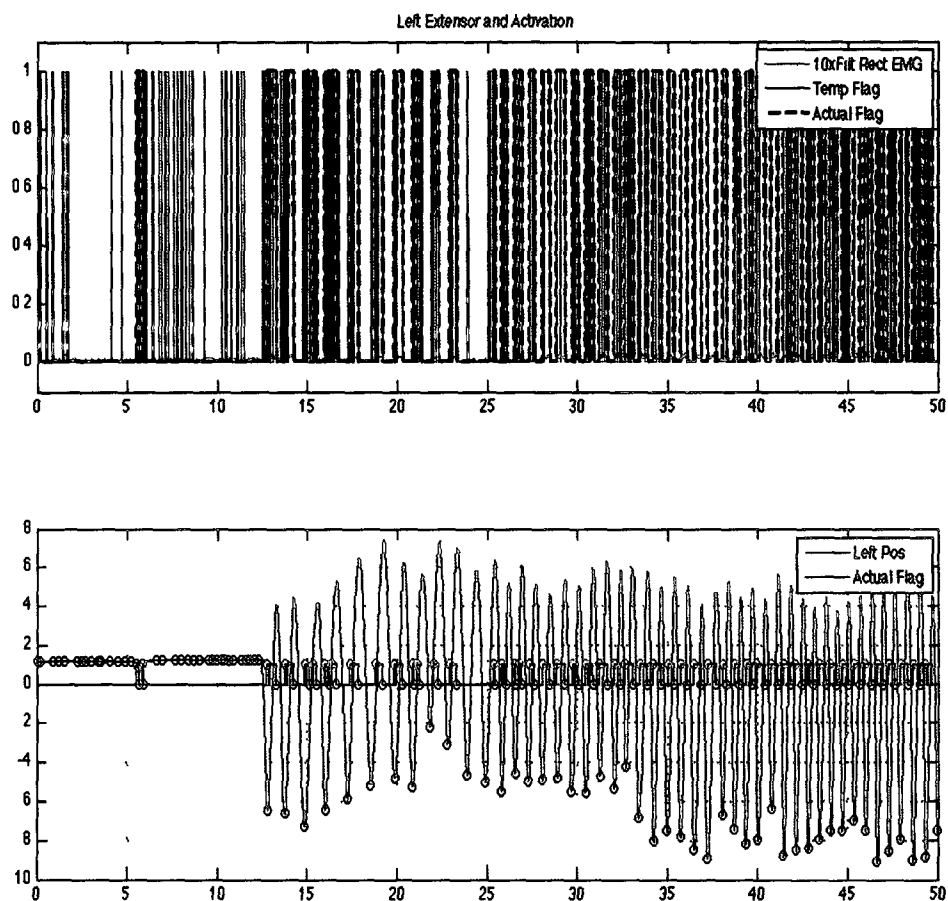


Figure A 3 – Left extensor muscle activity and displacement of a healthy control (*top*) red line represents filtered and rectified right extensor activity, blue lines represent anytime the amplitude exceeded the threshold and black lines represent the actual muscle bursts detected (*bottom*) blue line represents the displacement of the left wrist (black circles represent each movement cycle), red circles represent the detected muscle burst *onset* and blue circles represent the subsequent muscle burst *offset*

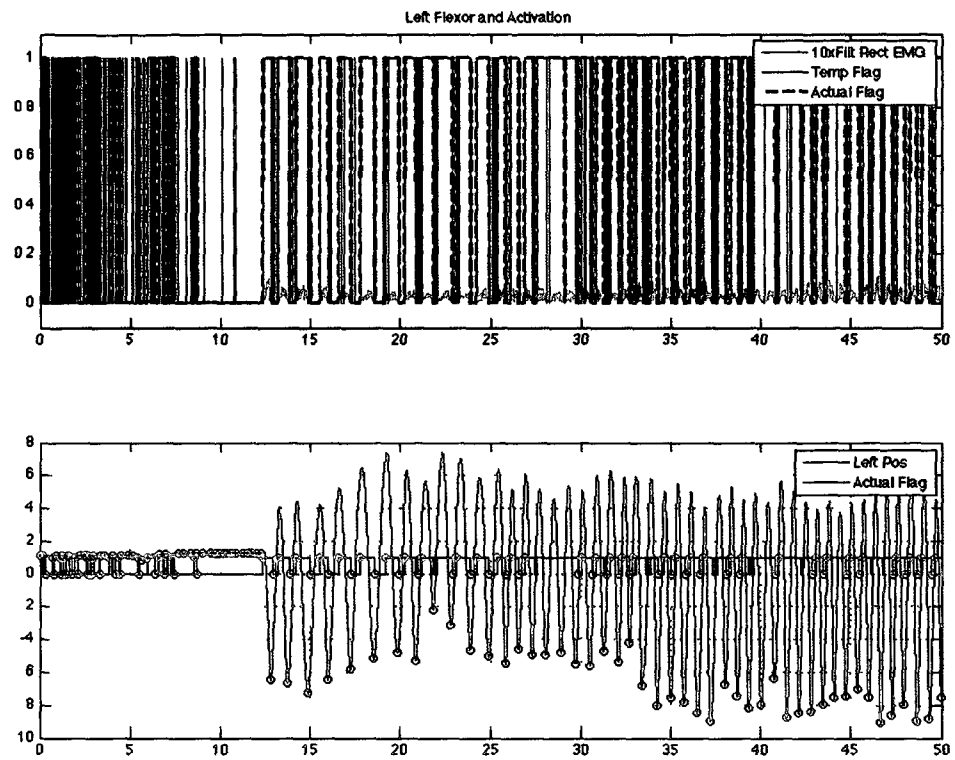


Figure A 4 – Left flexor muscle activity and displacement of a healthy control (*top*) red line represents filtered and rectified left flexor activity, blue lines represent anytime the amplitude exceeded the threshold and black lines represent the actual muscle bursts detected (*bottom*) blue line represents the displacement of the left wrist (black circles represent each movement cycle), red circles represent the detected muscle burst *onset* and blue circles represent the subsequent muscle burst *offset*

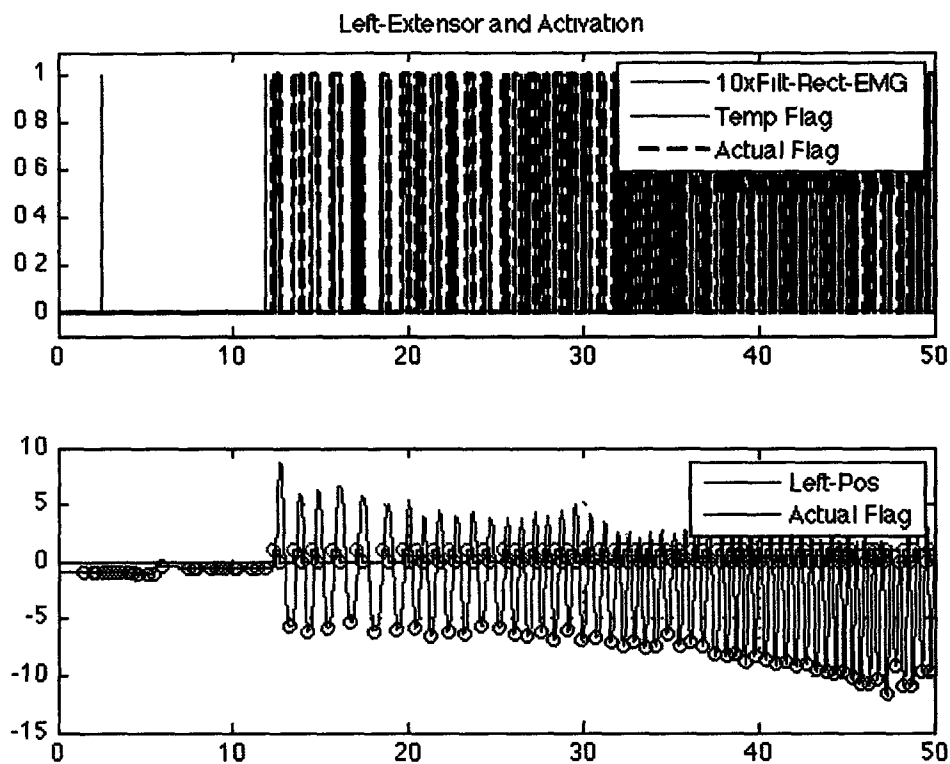


Figure A 5 – Left extensor muscle activity and displacement of a PD non-ULF (*top*) red line represents filtered and rectified left extensor activity, blue lines represent anytime the amplitude exceeded the threshold and black lines represent the actual muscle bursts detected (*bottom*) blue line represents the displacement of the right wrist in cm (black circles represent each movement cycle), red circles represent the detected muscle burst *onset* and blue circles represent the subsequent muscle burst *offset*

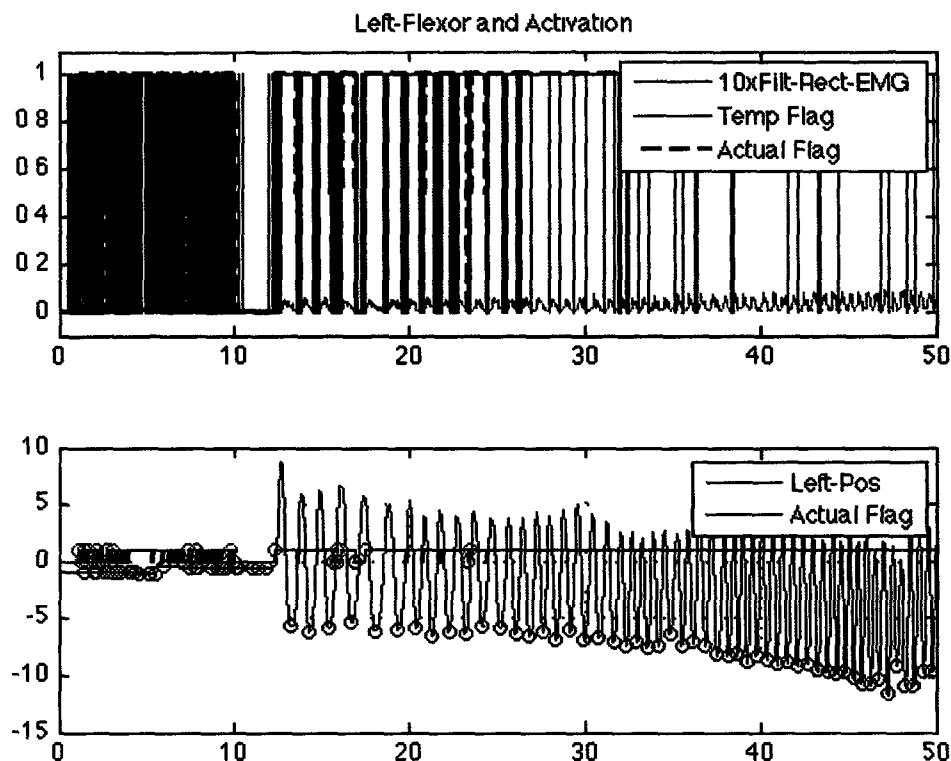


Figure A 6 – Left flexor muscle activity and displacement of a PD non-ULF (*top*) red line represents filtered and rectified left flexor activity, blue lines represent anytime the amplitude exceeded the threshold and black lines represent the actual muscle bursts detected (*bottom*) blue line represents the displacement of the left wrist in cm (black circles represent each movement cycle), red circles represent the detected muscle burst *onset* and blue circles represent the subsequent muscle burst *offset*

ULF vs non-ULF PD

Figure A 7 and A 8 represent filtered and rectified left extensor and flexor muscle activity in a PD non-ULF (different from above), respectively. These figures demonstrated relatively accurate muscle burst detection more so for the left extensor (Figure A 7) compared to the left flexor. Unlike the PD non-ULF, the muscle burst activity appears to be relatively normal when compared to healthy controls (Figures A 3 and A 4). The left extensor activity of a PD ULF is presented in Figure A 9. The onset of the freeze was detected at 35.5 seconds. Despite displacement at the beginning of the

trial, no muscle bursts were detected. This was also found for the left flexors as the activity never even exceeded the threshold or remained active the whole trial. Figure A 10 illustrates the muscle activity in both the left extensors and flexors for this same trial. There were three important observations that can be made from this figure. Firstly, before movement began (i.e. before 5 seconds), there was a substantial amount of noise in both the extensor and flexor. This appeared to be representative PD resting tremor. Secondly, in both muscles the activity (i.e. bursts) appeared to be very irregular, particularly in the flexors. Thirdly, during the freezing episodes there was increased and very irregular activity in both the flexors and extensors. Figure A 11 depicts another ULF in the left limb in a different trial involving 3 different freezes within the same trial. Based on these figures, the muscle activity in the left extensors appears very irregular after 30 seconds. The activity in the left flexors appeared to be normal before 32.5 seconds but two bursts of high activity were observed around the time of the first freeze (34.2 to 35.7s) and for about 2 seconds before the final freeze (45 to 50 s). The same amount of increase and irregular activity was not seen in the flexors and extensors during the final freeze similar to what was observed in Figure A 10.

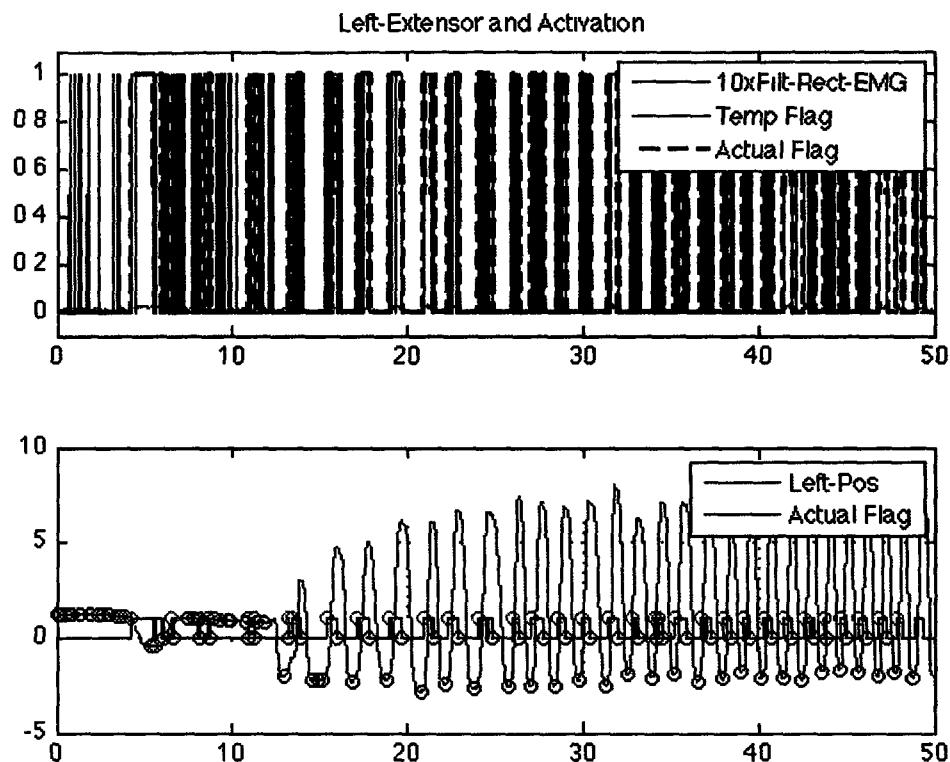


Figure A 7 – Left extensor muscle activity and displacement of a PD non-ULF (*top*) red line represents filtered and rectified left extensor activity, blue lines represent anytime the amplitude exceeded the threshold and black lines represent the actual muscle bursts detected (*bottom*) blue line represents the displacement of the right wrist in cm (black circles represent each movement cycle), red circles represent the detected muscle burst *onset* and blue circles represent the subsequent muscle burst *offset*

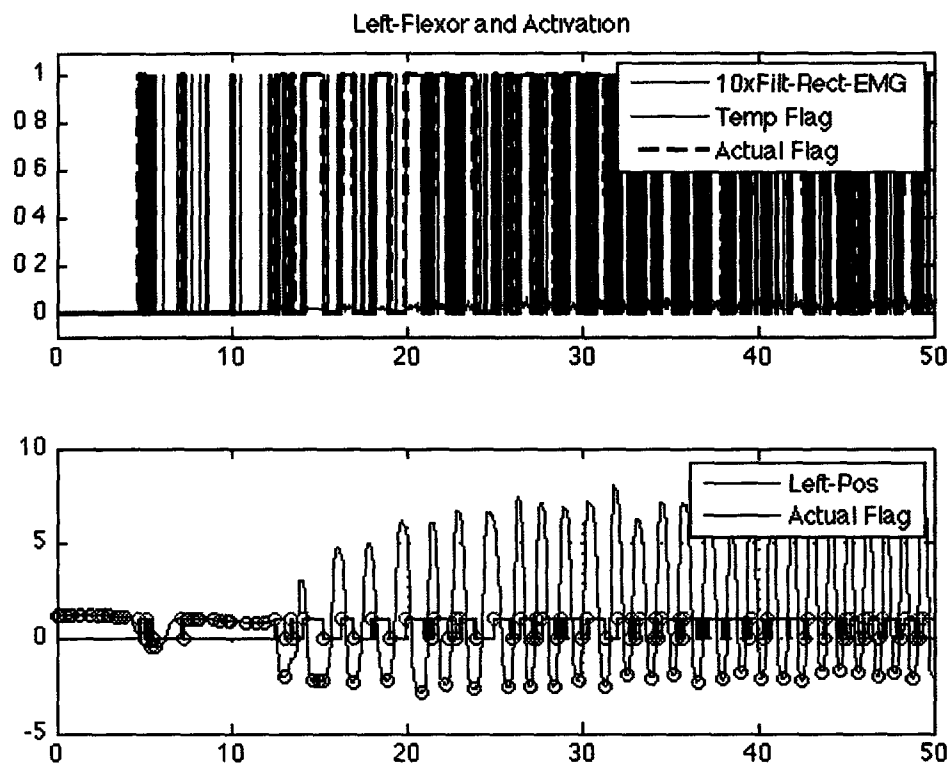


Figure A 8 – Left flexor muscle activity and displacement of a PD non-ULF (*top*) red line represents filtered and rectified left flexor activity, blue lines represent anytime the amplitude exceeded the threshold and black lines represent the actual muscle bursts detected (*bottom*) blue line represents the displacement of the left wrist in cm (black circles represent each movement cycle), red circles represent the detected muscle burst *onset* and blue circles represent the subsequent muscle burst *offset*

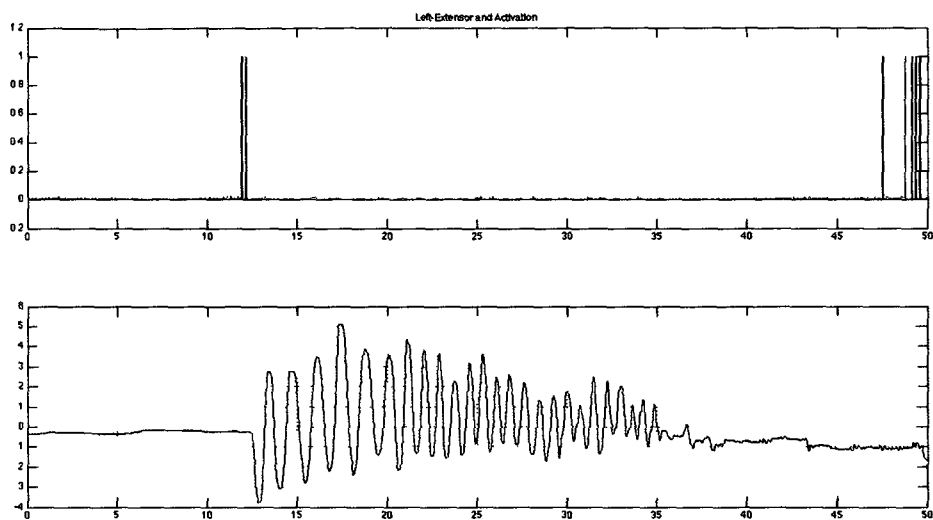


Figure A 9– Left extensor muscle activity and displacement of a PD ULF (*top*) red line represents filtered and rectified left extensor activity, blue lines represent anytime the amplitude exceeded the threshold and black lines represent the actual muscle bursts detected (*bottom*) blue line represents the displacement of the right wrist in cm (black circles represent each movement cycle), red circles represent the detected muscle burst *onset* and blue circles represent the subsequent muscle burst *offset*

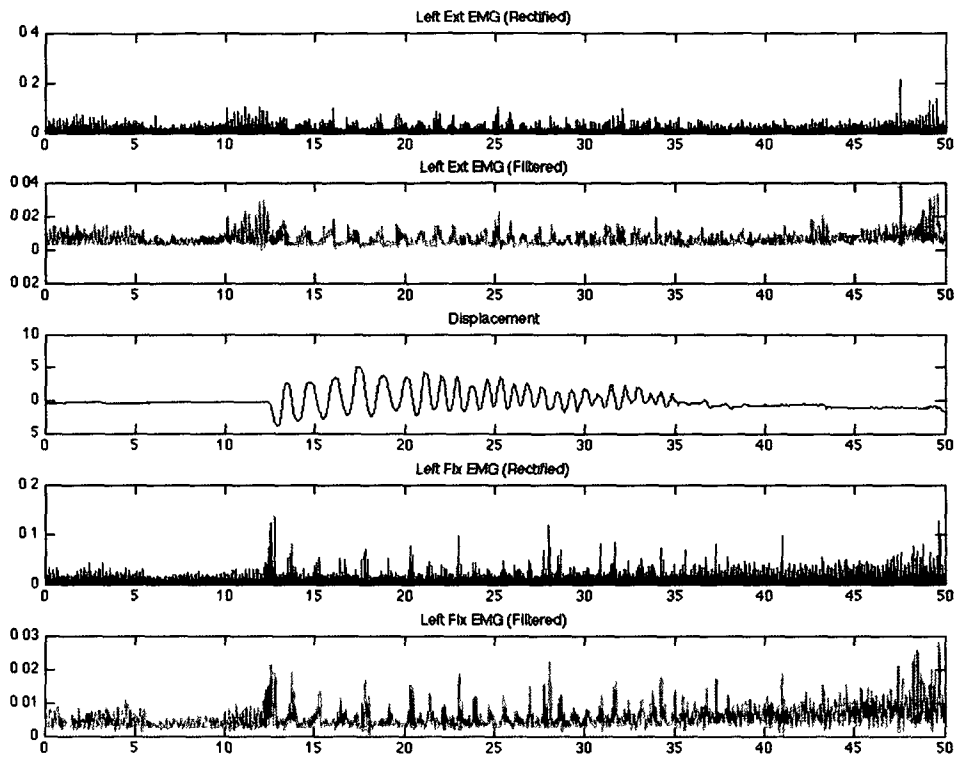


Figure A 10 – The filtered and rectified EMG of the left extensors (top 2 figures) and flexors (bottom 2 figures) of a PD ULF. Displacement of the left limb (in cm) is presented in the middle figure. Freeze onset was detected at 35.5 s until end of trial.

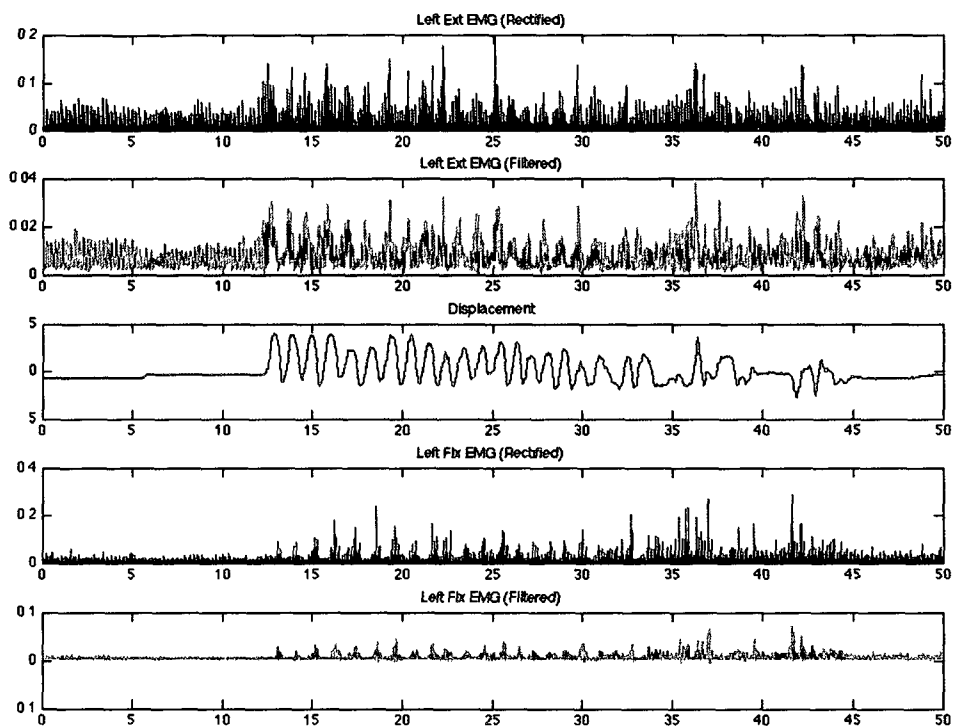


Figure A 11 – The filtered and rectified EMG of the left extensors (top 2 figures) and flexors (bottom 2 figures) of a PD ULF. Displacement of the left limb (in cm) is presented in the middle figure. Freeze onsets were detected at 34.2 s (to 35.7 s), 39.7 s (to 41.8 s) and 44.3 s (until end of trial).

A.4.0 Discussion

The main finding of the current paper was that the current methods of computer-automated detection were not adequate to determine muscle burst activity in PD. Muscle burst activity was examined by a double threshold method that used the criteria of maintaining a level of activity above (or below) a given threshold for a given amount of time (i.e. data points). Despite manipulating all the parameters of detection (i.e. filtering, mean noise, threshold and sliding window) in different combinations, accurate detection of muscle burst activity could not be achieved. Based on qualitative examination, there

was some evidence that muscle activity was irregular in PD. This may be particularly true during trials where ULF was observed.

A.4.1 Evidence for irregular muscle activity in PD during voluntary movements

sEMG has been used to examine various aspects of movement in PD (Hogrel, 2005). The majority of previous research on voluntary upper limb movements in PD has examined sEMG during unimanual movements. These included stereotyped dynamic movements (Hallett, Shahani, & Young, 1977, Rissanen et al., 2009), unimanual aiming and sequential movements (Benecke, Rothwell, Dick, Day, & Marsden, 1987a, 1987b, Pfann et al., 2004), rapid unimanual movements (Berardelli, Dick, Rothwell, Day, & Marsden, 1986, Berardelli et al., 1996), repetitive finger movements (Stegemoller, Allen, Simuni, & MacKinnon, 2010). The majority of research has supported a distinct triphasic pattern of muscle burst activity during discrete voluntary movements. This includes an agonist burst (AG1) followed by an antagonist burst (ANT) concluded by a second agonist burst (AG2) (Berardelli et al., 1996). Only a small amount of unimanual research in PD has focused on the forearm extensor and flexor muscles (Berardelli et al., 1986, Berardelli et al., 1996, Stegemoller et al., 2010). Berardelli *et al.* (1986) examined the muscle activity in the flexor and extensor muscle groups during a rapid wrist flexion movement. They visually determined muscle bursts and integrated the rectified signal for amplitude measurements. They found that PD 'off' demonstrated similar muscle activity and amplitude to healthy controls. In PD 'on' compared to 'off' there was a decreased amount of bursts but bursts were larger in amplitude. Overall, they concluded that muscle activity is not abnormal in PD in this type of movement. Stegemoller *et al.* (2010) examined integrated EMG from the extensor digitorum communis (and first dorsal

interosseous) during repetitive finger movements in PD. They also did not find any significant differences in PD in relation to peak integrated EMG. However, Berardelli *et al* (1996) reviewed previous research and concluded that individuals with PD may not be able to appropriately scale the activation of the first agonist burst to movement parameters. This provided some evidence that muscle burst activity may be irregular in PD.

Only a few studies have previously examined bimanual movements in PD. These included sequential movements (Benecke *et al*, 1987b, Lim, Hamm, Byblow, & Kirk, 2006) and simultaneous movements (Benecke *et al*, 1987b). Lim *et al* (2006) examined self-paced unimanual and bimanual simple finger tapping (i.e. index finger to thumb) and complex finger tapping (i.e. sequential thumb to each finger) for 60s trials. They examined the RMS over a 40 s period in wrist and digit extensors for both limbs but did not find any significant findings related to the sEMG amplitude. Benecke *et al* (1987) examined sEMG (in the biceps and triceps) during a bimanual task that required simultaneously 15° flexion at the elbow and squeezing a strain gauge as rapidly as possible. They qualitatively observed that individuals who preserved the typical triphasic or a multi-burst EMG pattern during individual tasks demonstrated tonic activity in both the biceps and triceps during simultaneous movements. This provided further evidence that there may be irregular muscle burst activity in PD.

Together these results demonstrated that muscle activity amplitude appears to be typical during voluntary movements in PD. However, there may be some difficulties in relation to the muscle burst activity as proposed by Benecke *et al* (1986) and Berardelli *et al* (1996).

A.4.2 Different parameters that may affect sEMG in bimanual coordination in PD

The current paper was the first study to examine rhythmic bimanual coordination of the wrists in PD. Several studies have previously used surface electromyography (sEMG) during wrist bimanual coordination in healthy adults (Peper & Carson, 1999, Ridderikhoff, Peper, & Beek, 2006, Ridderikhoff, Peper, & Beek, 2005, 2007, Ridderikhoff, Peper, Carson, & Beek, 2004, Vardy, Daffertshofer, Ridderikhoff, & Beek, 2007). Only Peper and Carson (1999) examined the EMG muscle burst activity (3 SD above the baseline noise) of the forearm flexor and extensor carpi radialis during bimanual wrist flexion and extension. They found that the timing of EMG onsets was significantly more variable at slower cycle frequencies (1 Hz) compared to faster cycle frequencies (1-4 Hz). These limited results provide some evidence that the parameters related to the task (i.e. cycle frequency) can have an impact on muscle timing.

In addition, there may be PD related factors that may contribute to sEMG. sEMG has been used to examine the effects of dopaminergic modulation on muscle activity in PD (Johnson et al., 1994, Robichaud, Pfann, Comella, & Corcos, 2002, Strambini, Rossi, De Michele, & Sello, 2004). Robichaud *et al.* (2002) used visual inspection to determine muscle burst activity in biceps and triceps during an elbow flexion movement. They determined that dopamine replacement did not affect the timing of muscle activity. However, this has not been examined for bilateral movements.

Muscle activity has been examined in different motor symptoms (other than freezing) in PD such as limb dyskinesia (Silberstein et al., 2005), bradykinesia (Berardelli, Rothwell, Thompson, & Hallett, 2001, Hallett & Khoshbin, 1980), action and

resting tremors (Burne, Blanche, & Morris, 2004, Caviness et al , 2006) and rigidity (Levin et al , 2009, Sepehri, Esteki, Shahidi, & Moinodin, 2009) All of these motor symptoms have been shown to influence the muscle activity observed during sEMG

A.4.3 Limitations and other methods of muscle burst detection in sEMG

Nieuwboer *et al* (2004) used a threshold method to successfully determine muscle burst activity during freezing in the lower limbs in individuals with PD However, the current study was not able to apply all methods for detecting ULF such verifying freezing episodes by video assessment and normalization of the sEMG as a percentage of gait cycles Furthermore, gait cycles were separated based on stride and stances phases of gait (Nieuwboer et al , 2004) The current study defined movement cycles as periods of flexion and extension in the upper limbs rather than swing and stance phases However, clear periods of flexion and extension were not always available particularly during freezing trials (for example see Figure A 11) This provided a major limitation for comparing muscle burst activity across the muscles similar to what was performed by Nieuwboer *et al* (2004) There were several other limitations not related to PD that may have increased noise in the signal and influenced the ability to properly detect muscle burst activity Berardelli *et al* (1996) have suggested that the presence of co-contraction across muscles and co-activation of the different muscle bursts (AG1, ANT, AG2) can affect detection even in rapid, small single limb movements This would be related to the difficulty in isolating the small forearm muscles and the cross-talk that may occur (Farina, 2006, Farina, Merletti, & Enoka, 2004) Previous research has suggested that sEMG examines the forearm flexor and extensor groups rather than individual muscles (Burne et al , 2004)

Other factors may have contributed to the noisy signals such as impedance due to fat tissue, electrodes moving on the skin due to the nature of the movement and reduced muscle in females and elderly participants (Farina, 2006, Farina et al , 2004)

Currently, there are a variety of highly computational methods that have been developed to improve the threshold methods of detecting EMG bursts For wrist bimanual coordination, a method of coherence analysis using weighted coherence and full-wave rectified EMG has been developed to measure the similarity between different muscles activation patterns (Ridderikhoff et al , 2006, Ridderikhoff et al , 2005, 2007) Other automated computer algorithms have been developed for detecting muscle bursts in gait including double thresholds with the inclusion of a whitening filter (Bonato, D'Alessio, & Knaflitz, 1998), continuous wavelet transform (CVT) (Merlo et al , 2003) and advanced methods (i.e. statistical, artificial intelligence) (Reaz et al , 2006, Staude et al , 2001, Vaisman, Zariffa, & Popovic, 2010) However, most of these methods are highly computational and cannot be readily used in clinical research Research by Morey-Klapsing (2004) has suggested that relying only on automatic detection of muscle burst onset times might not adequate in some applications They suggested that incorporating the use of iEMG and onset detection provides more accurate and applicable results

A.4.4 Conclusion

The current paper demonstrated that muscle burst detection is extremely difficult in PD and the current computer-detection methods available to clinicians are inadequate The qualitative examination of muscle activity provided some evidence that there may be irregularities in muscle bursts in PD during bimanual coordination However, no clear conclusions were evident when examining ULF There may have been increased and

irregular activity in one of the two muscles prior to and during ULF. These conclusions need to be further examined. Future research should be focused on developing methods of detecting muscle timing that can be applied in the clinical setting. Future research should also examine the relationship between muscle timing during bimanual coordination and ULF in PD. This could aid in understanding the neural mechanism responsible for ULF. Furthermore, it would help to clarify the relationship between ULF and FOG based on previous observations with sEMG (Nieuwboer et al., 2004). This could also have important applications for diagnosis.

A.5.0 References

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Appendix B - Nieuwboer and colleagues (unpublished) freezing definitions, freezing examples and reliability study

Definition of upper limb freezing

1. We define a freezing episode as:

- involuntary **stop** of ongoing movement with duration > 75% of normal cycle duration*
- OR a clear **absence of effective cyclic movement**
 - 1 clear oscillating movement with abnormal form (width, duration) of the cycle with duration > 75% of normal cycle duration*
 - 2 Uncontrolled festination high frequency oscillation, without real stop of movement with duration > 75% of normal cycle duration
 - 3 Abnormal small movement less than 50% of the normal° amplitude= average amplitude of the first 6 non-cued cycles (cycle 6-12) (compromise for effect of cue and not having enough cycles without freeze)

*Normal cycle duration duration of 3 trials preceding the possible freezing episode (if the 3d is not regular, take the 2nd or 4th)

*A long period of absence of movement without any abnormalities (particularly at the beginning of the trial or at the end), is most likely NOT freezing episodes but a delay due to an attempt to follow the metronome (beginning) or a voluntary stop (end)

2 The beginning of the freeze is

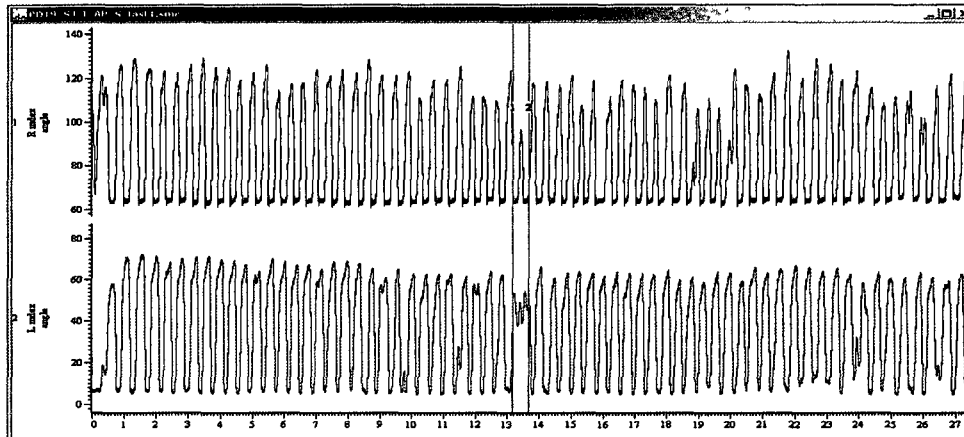
- a Begin of stop
- b Begin of oscillatory movement with abnormal cycle form
- c Begin of high frequency oscillation

3 The end of the freeze is

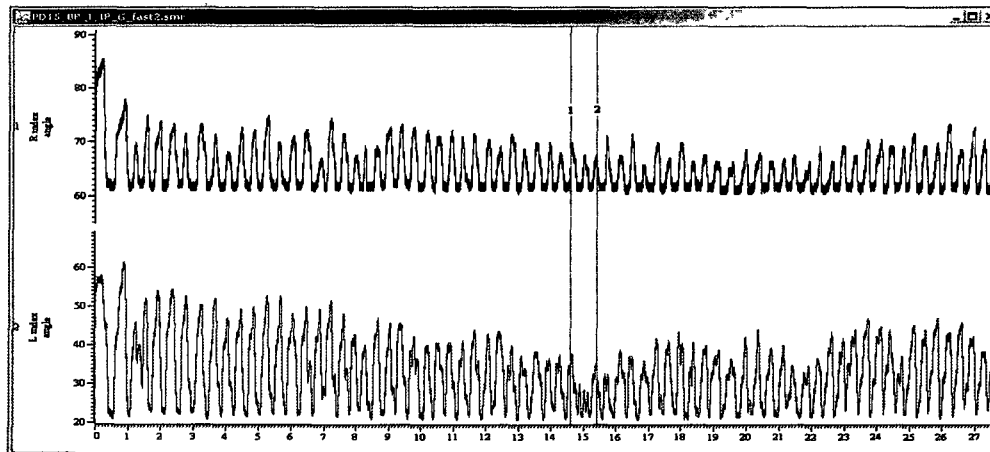
- a The moment after which movement is regular, controlled again for at least one cycle
 - No more stops, festination or interruption
 - One cycle with flexion and extension amplitude >50% of normal° amplitude and no interruption

Freezing episodes (examples)

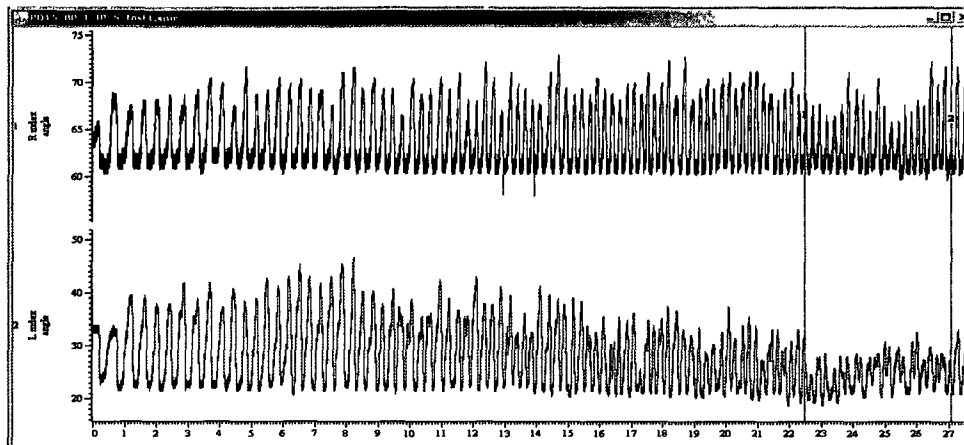
1 shortest freeze (0,59s)



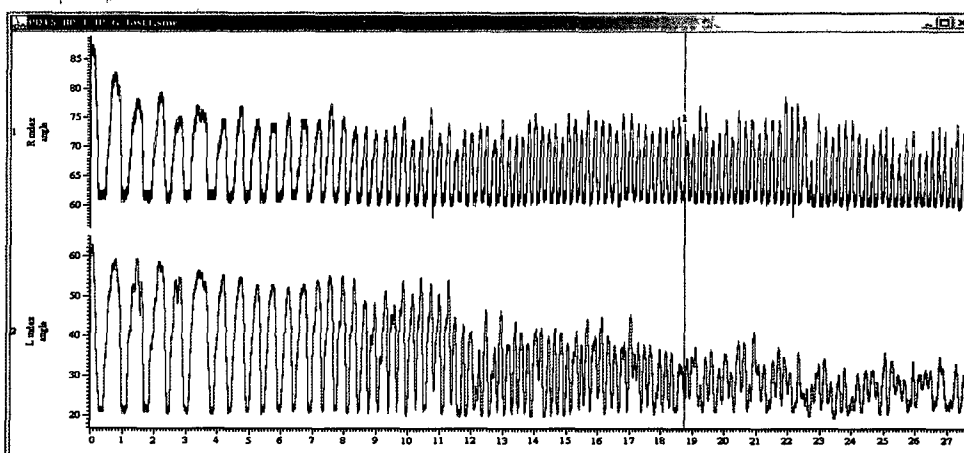
2 Freezing between 0,5 en 1 s



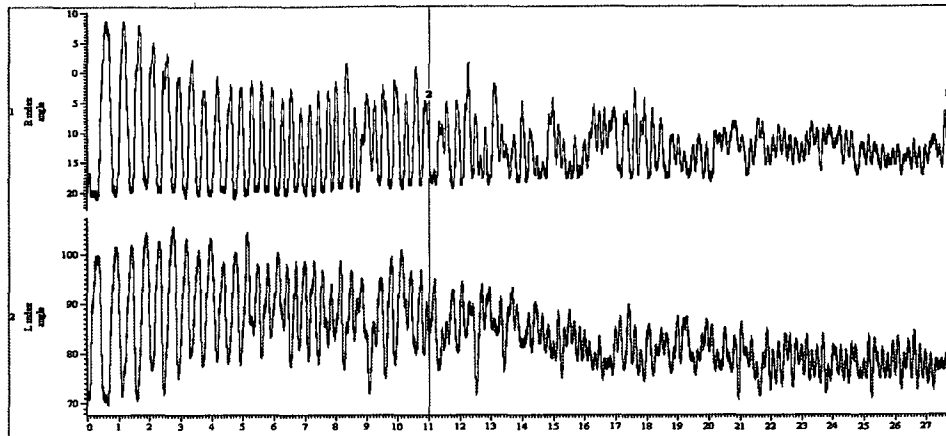
3 Freezing between 1 and 5s



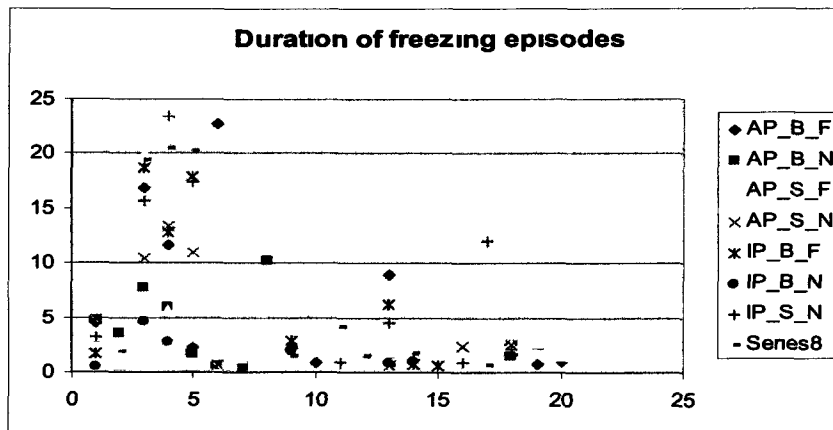
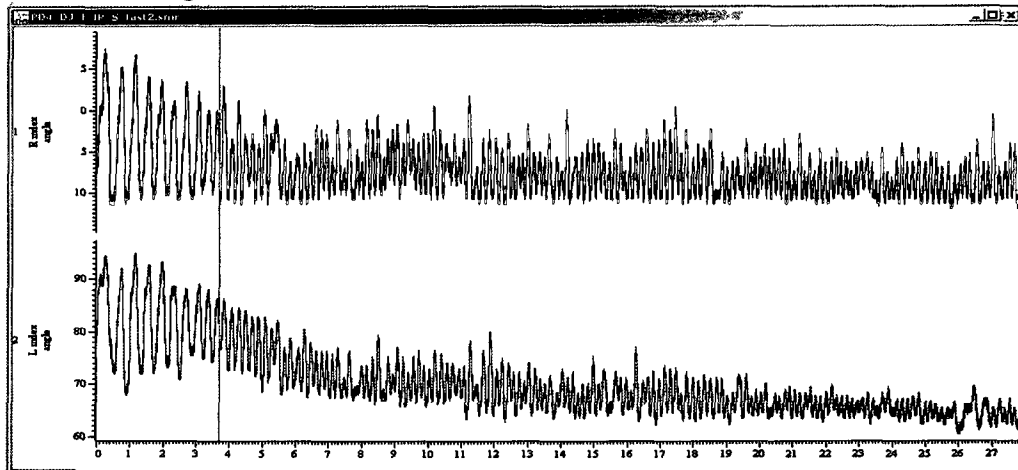
4 Freezing between 5 and 10 s

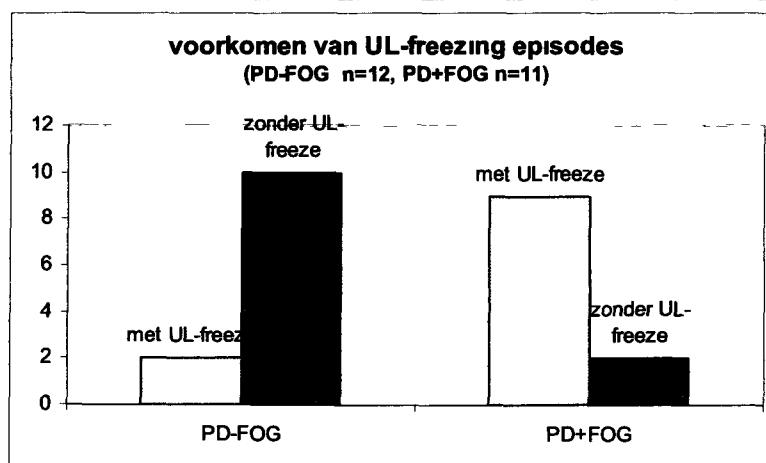
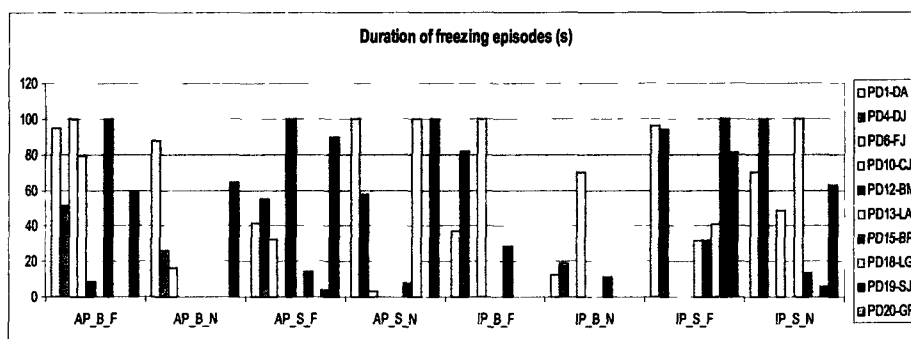
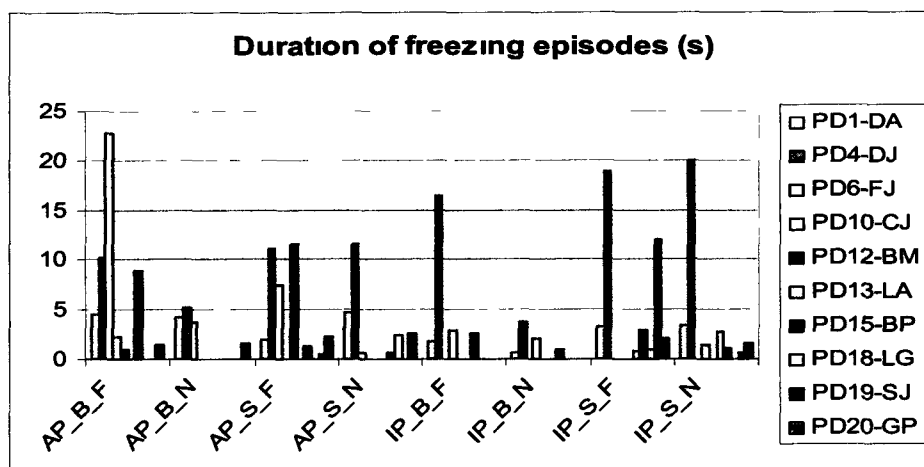


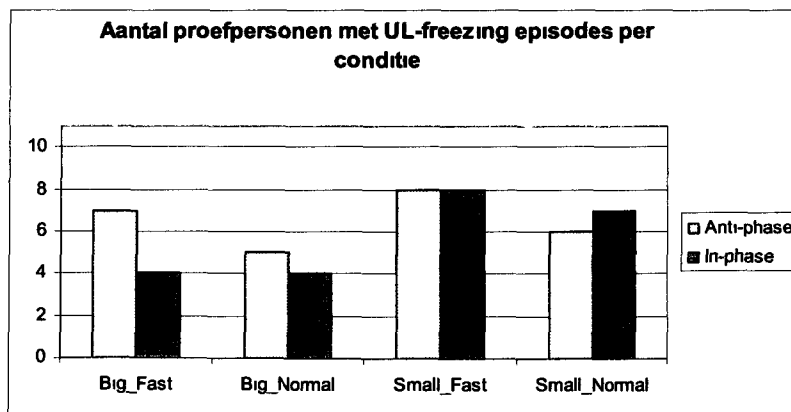
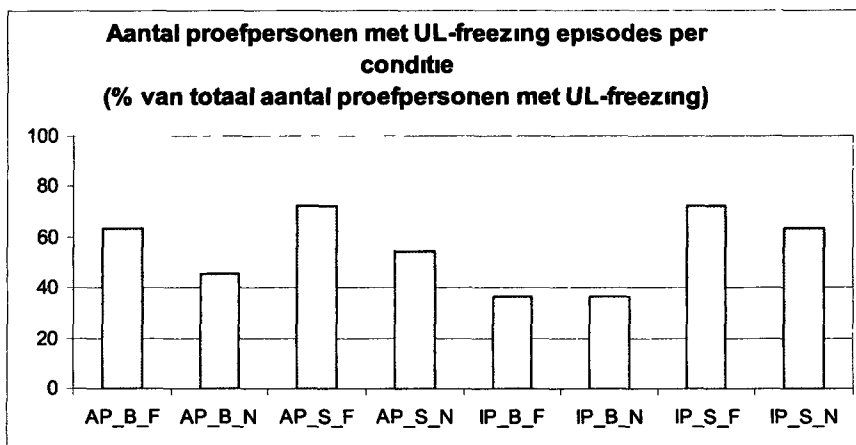
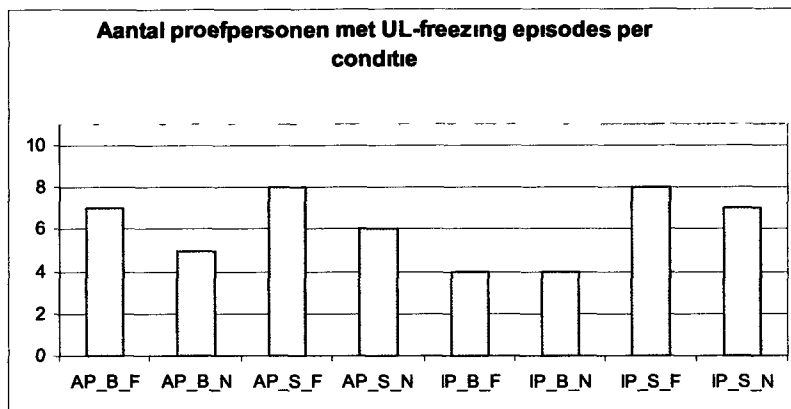
5 Freezing between 10 and 15 s

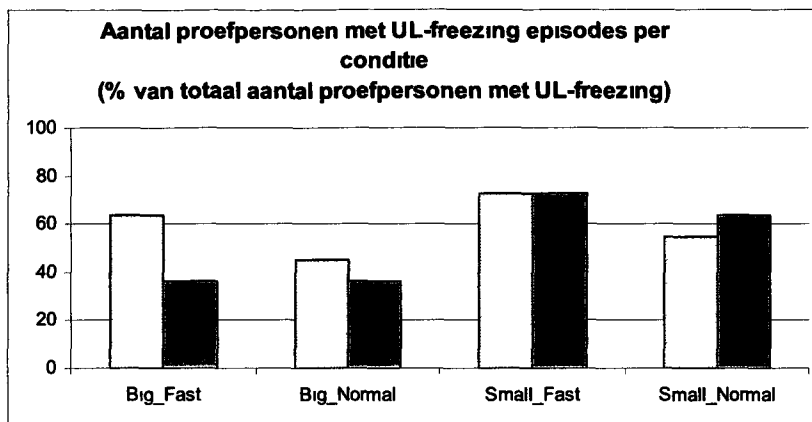


6 Freezing between 15 and 20 s









Reliability study results

12 trials of upper limb movement (bimanual flexion/extension of index finger) were presented to 4 independent raters who were asked to

- 1 Indicate for each trial if they think freezing episodes occurred or not (parameter 'Freeze(1/0)')
- 2 Indicate the beginning and the end of the freezing episodes, allowing to calculate the duration of the freezing episodes in seconds (parameter 'Duration Freeze (s)') and in cycli (parameter 'Duration Freeze(cycle)')

On these three parameters a Intraclass correlation coefficient (ICC) was calculated, showing high correspondence on all raters on all parameters (info and abbreviations + formula below)

							Calculation ICC	(ICC(2 4) (model 2 4 raters)
DURATION FREEZE(cycle)							ICC=	0 982308593
	SS	DF	MS		F	P		
INTERCEPT	233628535	1	233628535		2 664755	0 130864		
ERROR (BS)	964409227	11	87673566	BMS				
RATERS	5198146	3	1732715	RMS	1 128898	0 351587		
ERROR (WS)	50650830	33	1534874	EMS				
DURATION FREEZE(s)							ICC=	0 995140051
	SS	DF	MS		F	P		
INTERCEPT	1561 778	1	1561 778		2 940022	0 114408		
ERROR (BS)	5843 344	11	531 213	BMS				
RATERS	8 345	3	2 782	RMS	1 085012	0 369010		
ERROR (WS)	84 599	33	2 564	EMS				
FREEZE(1/0)							ICC=	0 976034858
	SS	DF	MS		F	P		
INTERCEPT	4 687500	1	4 687500		5 392157	0 040428		
ERROR (BS)	9 562500	11	0 869318	BMS				
RATERS	0 062500	3	0 020833	RMS	1 000000	0 405072		
ERROR (WS)	0 687500	33	0 020833	EMS				

info		
n= number of subjects (12)	Formula used (Portney L G and Watkins M P editors Foundations of clinical research	
k= number of independent raters (4)	Applications to practice New Jersey Upper Saddle River 2000)	(chapter 26 p 564)
ICC= Intraclass correlation coefficient		
BMS= Between subjects Mean Squares	ICC(2 k)=	$\frac{(BMS EMS)}{BMS + (RMS EMS)/n}$
EMS= Error Mean Squares (within subjects)		
RMS= Rater Mean squares (within subjects)		

Appendix C – Videos of upper limb freezing (ULF) during pattern switching (on CD)