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**THE QUANTIFICATION OF L-DOPA INDUCED DYSKINESIA IN
PARKINSON'S DISEASE PATIENTS**

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Thesis submitted to the
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In partial fulfillment of the requirements
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Abstract

Parkinson's disease (PD) patients experience postural instability as a primary motor symptom (Parkinson, 1817). The majority of PD patients use L-dopa to treat motor symptoms associated with the disease; however, extended use of L-dopa can cause involuntary movement production termed L-dopa induced dyskinesia (LID) (Bezard et al., 2001). Recently, researchers have speculated that postural sway variability (CoP variability) is associated with clinically unapparent LID (Rocchi et al., 2004). This experiment sought to determine the relationship between CoP variability and LID in PD patients. Eight PD patients on L-dopa medication and eight age matched neurologically healthy control subjects performed a precision aiming task where we manipulated the orientation, size and distance of the target. We recorded CoP fluctuations using two force plates and kinematics of the head, torso, arm and leg segments using the VICON 3-D motion capture system. The results indicate that decreased joint coordination of the head, arm and torso segments contribute to greater CoP variability in PD patients, particularly in the ML direction. Our results also reveal that increased task difficulty by manipulation of target distance increases movement amplitude, and consequently CoP variability. These findings suggest a causal relationship between LID and CoP variability in PD patients.

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Chapter I

Introduction

The basal ganglia is a group of inter-projecting nuclei in the brain that mediate the production of voluntary movement. Progressive cell death within the substantia nigra of the basal ganglia is the cause of idiopathic Parkinson's disease (PD), a hypokinetic movement disorder affecting 2% of the population over 60 years of age (Mayeux, 2003). PD affects men and women in equal proportion (Parkinson's Society Ottawa, 2007). Although there is no cure for PD, medications such as Levodopa (L-dopa) alleviate the characteristic motor symptoms of the disease (Bezard, Brotchie, & Gross, 2001). Primary motor symptoms include slowness of movement (bradykinesia), tremor, rigidity and postural instability (Parkinson, 1817).

The goal of the human postural system is to maintain the body's centre of mass (CoM) within its base of support (Van Emmerik & Van Wegan, 2002). The resultant of all the forces within the body acting at one point is termed the body's centre of pressure (CoP), and it moves in phase with the CoM to maintain upright stance. The CoP is controlled independently in two directions: anteroposterior (AP) and mediolateral (ML) (Winter, Prince, Frank, Powell, & Zabjek, 1996). CoP variability in healthy populations is typically greater in the AP direction (Collins & DeLuca, 1995), while greater CoP variability in the ML direction is associated with increased risk of falling (Maki, Holliday, & Topper, 1994).

Postural instability is common in PD patients (Parkinson, 1817; Zesiewicz & Hauser, 2007), possibly caused by increased ML CoP variability during quiet standing (Mitchell, Collins, DeLuca, Burrows, & Lipsitz, 1995; Rocchi, Chiari, & Horak, 2002).

PD patients also exhibit altered postural control strategies in comparison to age-matched control subjects while performing precision aiming postural tasks (Lefebvre & Balasubramaniam, 2007). L-dopa medication as treatment for PD patients is generally viewed as an ineffective means of regulating postural responses (Carpenter, Allum, Honeggar, Adkin, & Bloem, 2004) and may play a significant role in the postural control strategies adopted by PD patients (Lefebvre & Balasubramaniam, 2007; Rocchi et al., 2002).

Although L-dopa is effective for the treatment of most primary motor symptoms in PD patients, it often leads to the development of secondary motor symptoms; particularly L-dopa induced dyskinesia (LID) (Bezard et al., 2001). Dyskinesia is a hyperkinetic movement disorder characterized by choreic or tonic muscle activity (Duvoisin, 1974); LID is used as a common reference for all dyskinesia in PD patients (Cenci, 2007). Within 5 years, 50% (Marsden & Parkes, 1977; Marsden, 1982) to 70% (McColl, Reardon, Schiff, & Kempster, 2002) of PD patients will develop LID as a motor complication associated with L-dopa use. LID can occur at peak-dose, low-dose or end of dose/medication onset periods (Durif, 1999).

LIDs predominate in the 1-4 Hz frequency range and are distinct from tremors, which tend to occur at frequencies greater than 4 Hz (Dubinsky, 1995; Hoff, Wagemans, & van Hilten, 2001). Additionally, dyskinetic movements are not well coordinated between body segments, further emphasizing the choreic or 'wobbly' appearance of dyskinesia (Burkhard, Shale, Langston & Tetrud, 1999; Keisjers, Horstink, & Gielen, 2003b). LIDs are exacerbated by the presentation of motor or mental tasks (Durif,

Vidailhet, Debilly, & Agid, 1999) and increase in amplitude in response to visual feedback during target tracking tasks (Liu, Osterbauer, Aziz, Miall, & Stein, 2001).

The use of L-dopa by PD patients can lead to the development of medication-induced dyskinesia (LID), which can proliferate in multiple body segments and consequently result in decreased total body segment coordination. Because LID influences both segmental and whole body CoM, a strong link exists between LID and increased CoP variability in PD patients. Indeed, some researchers have hypothesized that the increased CoP variability may be a reflection of clinically unapparent dyskinesia in these PD patients (Bronte-Stewart, Minn, Rodrigues, Buckley, & Nashner, 2002; Rocchi, Chiari, Cappello, Gross, & Horak, 2004); however, the role of LID in relation to postural control in PD patients has yet to be tested.

This thesis will examine the extent to which LID influences postural control in PD patients on L-dopa medication. We will present literature regarding posture control and balance in healthy and PD populations, the neuropathophysiology of PD, treatments and medication induced motor complications in PD patients. There is a paucity of literature uniting these individual areas of study, and it is imperative that this gap be filled in order to address specific medication and treatment strategies intended for the PD population.

More specifically, this thesis will explore the contribution of LID to postural sway variability in the PD population by employing a precision aiming postural task. This study will also examine the interaction of task difficulty in the prevalence of LID in PD patients by manipulation of target size, orientation and distance for the precision aiming task.

Chapter II

Review of Literature

2.1 Human control of posture

The goal of the human postural system is to maintain the body within the boundaries provided by the base of support afforded to an individual (Van Emmerik & Van Wegan, 2002). The base of support is manipulated by changing the distance and angle between the feet (McIlroy & Maki, 1997). Researchers investigate the dynamics of the centre of pressure (CoP) as a means of quantifying postural sway (Collins & DeLuca, 1993; Winter, Patla, Prince, Ishac, & Gielo-Perczak, 1998). The CoP is the resultant of the normal forces acting at one point, generally within the confines of the support area (Vukobratovic, Borovac, & Potkonjak, 2007). Analysis of the CoP can provide information about the neuromuscular control of posture and balance.

One theory of postural control suggests that the body acts as an inverted pendulum to maintain control of posture and balance, whereby the CoP moves in-phase with the body's centre of mass (CoM) to maintain the CoM within the individual's base of support (Winter et al., 1998). The CoM continually oscillates to integrate visual, vestibular and proprioceptive afferent sensory information (Horak, 1997), while the CoP continually moves to account for changes in the CoM due to sensory integration. Effectively, the CoP acts as the controller of the CoM (Winter, 1995). Morasso and Shieppati (1999) challenged the inverted pendulum hypothesis, arguing that the basis of the relationship between the CoP and the CoM is a simple physical law that is incapable of proving the postural control strategies employed by the central nervous system.

The body is subject to multi-joint coordination synergies in order to maintain the CoM, and consequently the CoP, within a narrowly defined area. Generally, when the torso moves forward, there is an accompanying backward movement of the lower body, which counteracts CoM variability. However, there exists a distinct relationship between upper and lower body segments at varying speeds of movement. For example, if the torso moves forward at a speed of 0.8-1.25 Hz, the upper body leads the compensatory action (hyperextension) of the knees in a sequential (top-down activation) manner. However, if the torso moves forward at a speed of 2-3.3 Hz, the knee flexes in anticipation of torso movement, and eventually compensates by hyper-extending and incorporating hip muscle activity. Fast movements of the torso typically result in simultaneous activation of lower body units (Crenna, Frigo, Massion, & Pedotti, 1987).

Gage and colleagues (2004) related the CoM of body segments to the total body CoM and the net CoP. These researchers showed that displacement of the CoP correlates with whole body CoM, while segmental CoM and whole body CoM are temporally synchronized. Displacement of segmental CoM increases linearly from inferior to superior segments, with greater CoM changes in the anteroposterior (AP) direction than the mediolateral (ML) direction. These findings support the inverted pendulum model of quiet stance, and provide evidence of two distinct control directions (AP/ML) for quiet stance in healthy individuals (Gage, Winter, Frank, & Adkin, 2004).

Although research investigating the relationship between segmental movement and movement of the CoP exists for healthy populations, little is known about these relationships in patients with neural degeneration. For example, there is much literature regarding variance of CoP in PD patients, however, little is known about segmental

involvement in postural control in this population. This thesis will contribute novel information to the scientific community about the relationship between segmental movement and CoP variability in patients with neurodegeneration.

Postural sway is quantifiable in two independently mediated directions: AP and ML (Winter et al., 1996). Activity of the ankle plantiflexors mediates AP sway (ankle strategy), while hip adduction and abduction activity influences ML sway (hip strategy) (Carpenter et al., 2004; Winter et al., 1998). Variability of the CoP and total sway area is larger in the AP direction than in the ML direction (Collins & DeLuca, 1995), regardless of torso orientation (Riley, Balasubramaniam, Mitra, & Turvey, 1998). Recall, Gage et al. (2004) showed greater segmental displacement changes in the AP than in the ML direction.

Balasubramaniam and colleagues (2000) employed a precision aiming task to ascertain the relationship between AP and ML sway. Subjects maintained a laser pointer beam within the confines of a target (32cm^2 or 25cm^2); located in either a parallel or a perpendicular orientation at a distance of 1.1, 2.2 or 3.3 m. Results indicated that a reciprocal relationship exists between AP and ML sway. AP sway variability increases and ML sway variability decreases while in a parallel orientation; while ML sway variability increases and AP sway variability decreases in a perpendicular orientation. This suggests that the postural control system comprises two independent subsystems that maintain a reciprocal relationship to preserve quiet stance (Balasubramaniam, Riley, & Turvey, 2000).

2.2 Neural basis of postural control

The postural system requires input from somatosensory, vestibular and visual systems (Horak, 1997) to anticipate postural perturbations and maintain control of balance. The central nervous system, specifically the cerebellum (Horak & Diener, 1994) and basal ganglia (Horak, Dimitrova, & Nutt, 2005; Visser & Bloem, 2005), integrates the afferent information provided by these systems. Patients with lesions to either of these brain areas often assist as experimental subjects in the research of posture and balance.

2.2.1 Cerebellar contributions. To determine the role of the cerebellum in postural control, examining patients with cerebellar damage is fundamental (Diener, Dichgans, Bacher, & Gompf, 1984). The cerebellum is essential in gauging the magnitude of a postural response in the event of a perturbation (Horak & Diener, 1994). The provision of information from previous experiences is also an important function of the cerebellum. This information is termed 'central set information'. Cerebellar patients show decreased aptitude for relying on this central set information, resulting in hypermetric postural responses that are caused by inaccurately scaled responses (Horak & Diener, 1994).

2.2.2 Basal Ganglia contributions. The role of the basal ganglia in posture and balance is determined by studying PD patients and comparing them to neurologically healthy age matched subjects (Bloem & Bhatia, 2004). The basal ganglia is important in regulating muscle tone, maintaining postural muscle energization, and adopting postural response patterns during specific biomechanical conditions (Horak et al., 2005). Essentially, the basal ganglia optimizes the frequency and amplitude of muscle responses and synergies in the event of a postural perturbation (Henry, Fung, & Horak, 1998).

Sensorimotor integration is another means by which the basal ganglia help to regulate postural control and balance. The basal ganglia organizes afferent information from the visual, vestibular and proprioceptive systems and uses this information to promote motor and mental flexibility. Flexibility in response to an external perturbation is termed set shifting (Visser & Bloem, 2005). PD patients display compromised set shifting in response to postural perturbations, causing increased postural sway variability. This will be elaborated in further sections.

2.3 The basal ganglia and Parkinson's disease

2.3.1 Direct and indirect pathways. The basal ganglia are a group of four inter-projecting nuclei that are located bilaterally in the deep areas of the brain. The striatum (putamen and caudate), the globus pallidus [internus (GPi) and externus (GPe)], the substantia nigra [pars compacta (SNc) and pars reticulata (SNr)], and the subthalamic nucleus form the basal ganglia (Anderson, Costantino, & Stratford, 2004). Grouped projections from these nuclei form a direct and an indirect pathway within the basal ganglia; these pathways work in unison to regulate the production of voluntary movement by reducing the inhibition of thalamocortical neurons. This reduction in inhibition facilitates movement initiation by the cortex (Kandel, Schwartz, & Jessell, 2000) (Figure1).

A stimulatory dopaminergic message from the SNc to the putamen of the striatum initiates the direct pathway. An inhibitory GABAergic projection is then propagated from the striatum to the thalamus, causing a dis-inhibition of the thalamus. The thalamus then

initiates an excitatory glutamatergic projection to the cerebral cortex, which facilitates the production of voluntary movement (Kandel et al., 2000).

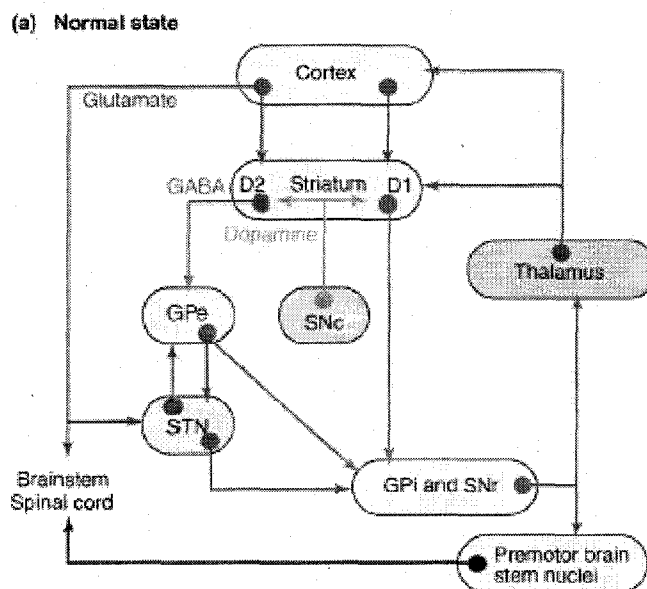


Figure 1. Direct and indirect basal ganglia circuitry in a normal human brain. Yellow arrows correspond to dopaminergic, green arrows correspond to GABAergic and red arrows correspond to glutamatergic projections. Adapted from Cenci, 2007.

The indirect pathway is initiated, however, by an inhibitory dopaminergic projection from the SNc to the striatum. An inhibitory GABAergic projection is propagated from the striatum to the GPe and further to the subthalamic nucleus. At this point, the subthalamic nucleus projects an excitatory glutamatergic signal to either the GPi or the SNr; both of these nuclei project an inhibitory GABAergic signal to the thalamus. The thalamus is then inhibited from sending the excitatory glutamatergic projection to the cortex to promote movement production, resulting in an inhibition of voluntary movement (Kandel et al., 2000).

output. PD patients show diminished voluntary movement production due to the deregulation of the direct and indirect pathways (Hornykiewicz, 2001).

2.3.3 Motor symptoms and their treatment in PD. The primary motor symptoms of PD include resting tremor, bradykinesia (slowness of movement), rigidity (muscle stiffness) and postural instability (Parkinson, 1817; Zesiewicz & Hauser, 2007). Prevalent secondary motor symptoms are akinesia (lack of movement), dystonia (sustained muscle contractions) and dyskinesia (impairment of voluntary movement) (Hoehn & Yahr, 1967). PD patients will often experience symptomatic asymmetries; motor abilities are more greatly impaired on the side of the body contralateral to the majority of neural degeneration (Innis et al., 1993).

Prescription medications provide relief for most primary motor symptoms of PD, the most common being levodopa (L-dopa) (Bezard et al., 2001). L-dopa is the precursor of normal dopamine synthesis and is used because extra-systemic dopamine cannot pass the blood-brain barrier. The appeal of L-dopa was that if the few remaining dopamine producing neurons could be stimulated to produce more dopamine, the motor symptoms of PD would subside. However, because L-dopa fails to stop the further deterioration of dopaminergic cells, the therapeutic effect of the treatment often fades over time, resulting in short and long duration motor fluctuations that occur after prolonged or increased use of the treatment (Nutt, 2001).

It must be clarified that L-dopa is not the only treatment option available to PD patients, and certainly, it is not necessarily the only therapy prescribed for the individual. PD patients work in tandem with their neurologists to find the most effective therapy (medication, rehabilitation or alternative) to address their needs. Often, PD patients will

wait a number of years before beginning medications; however, this is a personal choice. We speak of L-dopa purely because it is the most common form of medicinal treatment for the PD population.

2.4 Postural control in PD

Postural instability is a primary motor symptom of PD, and PD patients typically show greater postural instability to backward perturbations (Carpenter et al., 2004), greater postural sway variability and greater total sway area when compared to neurologically healthy age matched control subjects (Rocchi et al., 2002). Other research shows that patients have increased ML sway in quiet stance (Mitchell et al., 1995). Recall that increased ML sway is associated with increased risk of falling (Maki et al., 1994), which can help explain the postural instabilities experienced in this population.

Some studies show that L-dopa medication increases the amplitude of ML sway, which reverts to greater amplitude of AP sway while not medicated (Rocchi et al., 2002). This medication effect might be due to a decrease in muscle stiffness without a concurrent increase in neuromuscular control of posture. L-dopa therapy in PD patients can also encourage greater sway amplitude and decreases in velocity, frequency and coupling of upper and lower limbs during quiet stance (Maurer et al., 2003). The reduction of coupling between upper and lower limbs correlates with increased sway amplitude, suggesting that decreased axial stiffness while on medication may reveal a deficit of the sensorimotor postural control loop (Maurer et al., 2003). Researchers show that the use of L-dopa is generally ineffective in regulating postural response (Carpenter

et al., 2004), and may contribute to greater sway variability and area than while not medicated (Rocchi et al., 2002).

Work by Lefebvre and Balasubramaniam (2007) shows PD patients on and off medications, as well as neurologically healthy age matched controls who performed a precision aiming postural control task. The participants were to maintain the beam of a laser pointer within a target (36cm^2) located in either a parallel or a perpendicular orientation at a 1m or 2m distance. Overall, sway variability was greater in PD patients off medication than patients on medication, or control subjects. PD patients were unable to modulate AP and ML sway due to task demands, particularly in the ML direction. PD patients on medication showed increased ML sway variability in the parallel orientation while off medication patients showed increased ML variability in the perpendicular orientation. In addition, PD patients on medication showed enhanced and differently organized postural sway patterns, but PD patients off medication did not show these differently organized sway patterns when compared to controls. This suggests that the medication manipulation might affect postural control strategies of PD patients (Lefebvre & Balasubramaniam, 2007).

Unilateral pallidotomy, a surgical intervention for PD patients, often results in improved postural instability scores and sensory equilibrium scores when compared to pre-surgical values (Bronte-Stewart et al., 2002). Bilateral deep brain stimulation of the subthalamic nucleus or the GPi often results in postural sway ranges of similar magnitude to neurologically healthy age matched subjects (Rocchi et al., 2004). This indicates that both the direct and the indirect pathways may play a crucial role in maintaining posture and balance, particularly in the PD population. Comparing all surgical treatments, deep

brain stimulation of the subthalamic nucleus and GPi are more effective than unilateral pallidotomy in improving postural stability and gait disorders in PD patients (Bakker et al., 2004).

Interestingly, re-introduction of L-dopa to patients who have received some form of surgical treatment increases spontaneous postural sway, CoP variability and mean velocity of the CoP (Bronte-Stewart et al., 2002; Rocchi et al., 2004). The greater variability in the CoP of these patients may reflect clinically unapparent increases in dyskinesia, caused by the L-dopa medication (Rocchi et al., 2004). Clinically unapparent refers to the clinicians' inability to detect the presence of dyskinesia, perhaps due to spontaneous or low amplitude fluctuations. We will discuss dyskinesia in further depth.

Increases in the variability and velocity of the CoP can also be caused by increases in tremor; tremor is an excessive amount of rhythmic muscle contraction (Rocchi et al., 2002) (Burleigh, Horak, Nutt, & Frank, 1995). Postural tremor during quiet stance is common in PD patients (Bain, 2002). Prevalence and amplitude of tremors increase when muscle rigidity is decreased (Winogrodzka et al., 2001), and they decrease with the production of voluntary or target directed movement (Smaga, 2003). Greater variability and velocity of the AP CoP signal can be attributed to increased tremor while off medication; incidentally, PD patients tested while on medication and without tremor showed comparable AP CoP velocity profiles as age matched healthy controls.

Researchers have postulated that if tremors can be reflected in the CoP, then so might medication-induced dyskinesia (Rocchi et al., 2002). We will further discuss this possibility in detail.

Recall the Gage et al. study (2004) which investigated the contribution of changes in segmental CoM to greater CoP variability. The results indicated that displacement of segmental CoM increases linearly from the level of the ankle (inferior) to the head (superior). Therefore, superior segmental CoM changes contribute more strongly to CoP variability. Although this relationship has been tested in healthy individuals, this has yet to be tested in individuals with neurodegeneration; this will be a unique contribution of this research project.

2.5 Dyskinesia

2.5.1 Characteristics and prevalence of dyskinesia. Dyskinesia is a hyperkinetic movement disorder characterized by alternating or combined choreic (purposeless movements) or dystonic (sustained, abnormal) muscle activity (Duvoisin, 1974; Fabbrini, Brotchie, Grandas, Nomoto, & Goetz, 2007). Dyskinesia can proliferate in the musculature of the limbs, hands, trunk and feet as well as the thoracic, abdominal and facial areas (Jancovic, Lai, Ben-Arie, Krauss, & Grossman, 1999). Dyskinesia can be spontaneous, or they can be a toxic side effect of medication use (IPCS Intox Database, 2007). Such examples are tardive dyskinesia, which occur after the withdrawal of narcoleptics, or L-dopa induced dyskinesia (LID), which can occur after prolonged L-dopa use (Bezard et al., 2001).

After 28 months of L-dopa treatment, 72% of PD patients develop LID (McColl et al., 2002), with an approximate 50% of patients displaying LID within 5 years of disease progression (Marsden, 1982). The duration of L-dopa treatment (Schrag & Quinn, 2000) and the age at onset of PD are the most significant risk factors for LID. Likewise,

patients treated with medications for a long time (6 years +) and young onset, aggressive diagnoses are more likely to develop LID (Schrag & Schott, 2006).

2.5.2 Neural mechanisms and treatment of dyskinesia. There is increased activation of the supplementary and primary motor areas in LID, as evidenced by single photon emission tomography (SPECT) studies of PD patients (Rascol et al., 1998). Recall that the thalamus projects to both the supplementary and primary motor areas via the direct and indirect basal ganglia loops.

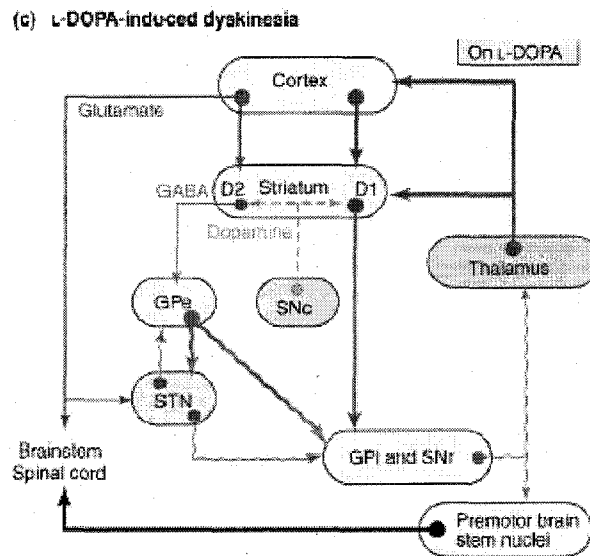


Figure 3. Circuitry of the basal ganglia in a patient with LID. Yellow lines correspond to dopaminergic, green arrows correspond to GABAergic and red arrows correspond to glutamatergic projections. Note the over activation of motor cortical areas as a side effect of dopamine treatment. Adapted from Cenci, 2007.

Currently, researchers believe that LID is caused by reduced activity in the subthalamic nucleus, GPi and SNr, which results in the over-activation seen in the cortical motor areas; this is similar to Huntington's disease, a hyperkinetic movement disorder (Cenci, 2007; Crossman, 1990) (Figure 3). However, this is not the only model

of LID; other theories have yet to be ratified (Fabbrini et al., 2007; Graybiel, Canales & Capper-Loup, 2000).

Few treatment options exist for LID in PD patients, aside from removing L-dopa from the treatment protocol entirely. This is obviously not the preferred solution, because the primary motor symptoms normally assuaged by L-dopa would return; for this reason, many patients choose to continue with the L-dopa therapy and accept LIDs as a side effect. Currently, the only drug clinically shown to reduce dyskinesia without affecting 'on' time is Amantadine (Snow, Macdonald, McAuley & Wallis, 2000), and may be an option for patients who experience disturbing or painful dyskinesia.

Surgical interventions such as deep brain stimulation or ablation have the advantage of reducing the need for L-dopa as a treatment, therefore reducing the prevalence of LID in patients. Unilateral pallidotomy (Verhagen Metman & O'Leary, 2005) and GPi stimulation provide immediate reduction in LID, where STN stimulation provides delayed improvements (Krack et al., 1998). Surgical interventions such as those mentioned are not a common primary treatment for LID, due to their invasive nature (Fabbrini et al., 2007).

2.5.3 Types of LID. Recall that the term LID is used when referring to all types of dyskinesia in PD patients. Primary forms of LID are monophasic, biphasic and off-period dyskinesia (Durif, 1999). Monophasic dyskinesia, also known as peak-dose dyskinesia, is typically choreic movements; they are the most common form of LID and occur when the blood concentration of L-dopa is highest. Biphasic dyskinesia, also known as onset or end-of-dose, are predominantly dystonic or ballistic lower limb movements; they appear when the blood concentration of L-dopa is increasing or decreasing. Off-period

dyskinesia commonly appear as dystonic muscle activity of the feet; they appear when blood concentration of L-dopa approaches zero, such as first thing in the morning (Durif, 1999; Fabbrini et al., 2007). LID severity is subject to diurnal variation, escalating throughout the day and peaking in the late afternoon/evening (Nutt, 2001).

2.6 Quantification of dyskinesia

Initially asymptomatic (McColl et al., 2002), patients with dyskinesia may be unaware of their presence, unless resulting in interference during specific motor tasks (Vitale et al., 2001). Quantifying observed and reported dyskinesia using rating scales can be difficult and subject to inter- and intra-rater reliability (Fabbrini et al., 2007).

The Unified Parkinson's Disease Rating Scale (UPDRS), the Abnormal Involuntary Movement Scale (AIMS) and the Goetz scale are clinical scales used to assess dyskinesia. The UPDRS uses patient recall information, and does not include clinical observation. The AIMS targets tardive dyskinesia patients who display predominance in orofacial involvement. The Goetz scale uses no segmental categories when analyzing secondary disabilities from dyskinesia. Due to reliability issues between the clinical rating scales, quantification of tardive and LID at rest and during movement has historically relied on accelerometry techniques (Manson et al., 2000; Tyron & Pologe, 1987).

In a relatively novel investigation, Burkhard et al. (1999) used a rotation sensitive movement monitor (RoMM) at the wrists to quantify upper body LID in PD patients performing mental tasks. The RoMM was sensitive to changes in frequency, amplitude and the frequency power spectrum (FPS); these factors are reliable in predicting

movement intensity. The experiment investigated the correlation between UPDRS dyskinesia scores and movement outcomes.

The FPS demonstrates that dyskinesia is restricted to frequencies below 5 Hz, with the peak frequency range for dyskinesia being 0.25-3.25 Hz (Figure 4). Choreic dyskinesia predominate at frequencies of 1.5-3.25 Hz, while dystonic dyskinesia predominate in frequencies of 0.25-1.25, when compared to the UPDRS clinical scores (Burkhard et al., 1999).

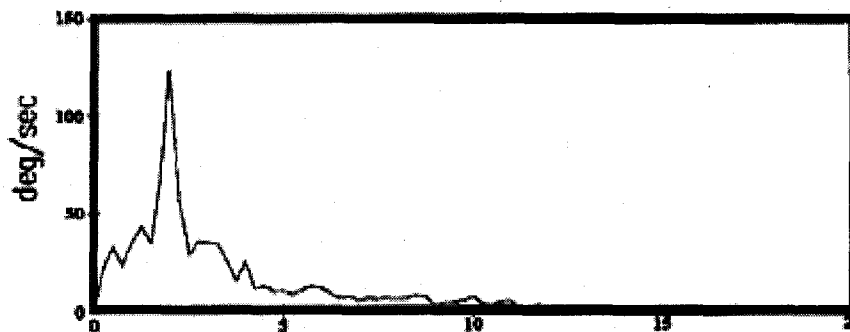


Figure 4. Frequency Power Spectrum of a sample dyskinetic patient. Frequency values (Hz) are presented on the x-axis, while the y-axis shows the amplitude of the frequency peaks (deg/sec.). Adapted from Burkhard et al., 1999.

The FPS can detect 100% of asymmetries in clinically apparent dyskinesia, where a 25% difference between FPS values at the wrist denotes an asymmetry (Figure 5). Previous structural neuroimaging of the patients indicated that advanced degeneration on one particular side of the brain suggested the presence of an asymmetry in dyskinesia. When the neuroimaging results were consulted, all patients whose results suggested an asymmetry demonstrated greater FPS values on the “most affected side”.

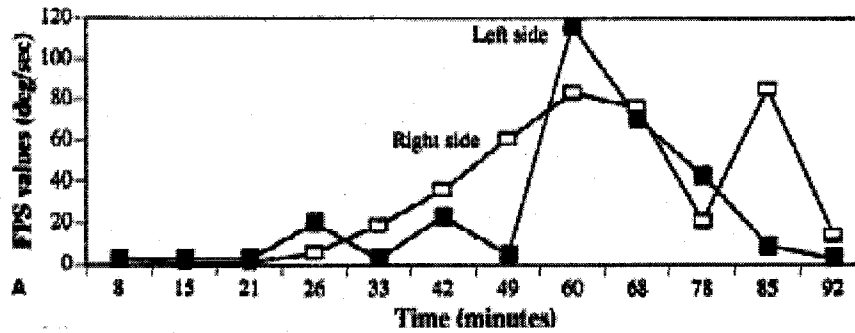


Figure 5. Frequency Power Spectrum of a sample asymmetrical patient. The x-axis represents time (minutes) after ingestion of L-dopa. The y-axis represents FPS values (deg/sec.). Adapted from Burkhard et al., 1999.

Further to the Burkhard et al. study (1999), Manson and colleagues (2000) measured LID in PD patients performing motor tasks by placing three uniaxial accelerometers on the patients' shoulder. Accelerations at the shoulder that correlate with AIMS and Goetz clinical scores offer validity to the statement that patients rarely display dyskinesia in limb segments without co-existent axial (trunk) dyskinesia (Redmond & Hegge, 1985). Preliminary recordings displayed a 1-3 Hz frequency bandwidth for dyskinesia. Patients displayed mild to moderate dyskinesia and minimal segmental variation, as indicated by mean AIMS scores for the neck (1.75), trunk (1.74), upper limbs (1.74) and lower limbs (1.76). The mean acceleration of the shoulder correlated with the AIMS and Goetz scales, concluding that shoulder joint accelerometry is sufficient to predict whole body dyskinesia (Manson et al., 2000).

Using similar methods, Hoff et al. (2001) measured movement frequencies of PD patients' upper leg, wrist, trunk and upper arm using paired accelerometers. Analyses of dyskinesia were divided into frequency bandwidths of 1-4 Hz (slow) and 4-8 Hz (fast). Wrist movements and sitting/standing leg movements of both fast and slow speeds

correlated with UPDRS and AIMS clinical scores. Slow trunk movements showed the strongest correlation with clinical measures. During stressful situations or while the patient was talking, increased dyskinesia were observed by clinicians and were mirrored in the changes of frequency detected by the accelerometers. This provides evidence for a distinct relationship between task demand and LID (Hoff et al., 1999).

These initial studies which quantify dyskinesia provide evidence that dyskinesia predominate in the 1-4 Hz rather than the 4-8Hz range (Hoff et al., 1999). Furthermore, with the implementation of a motor or mental task, dyskinesia amplitude increases (Durif et al., 1999). These primary observations led researchers to examine what happens to dyskinesia amplitudes with the provision of visual feedback of motor goals. Lemieux and colleagues (2007) showed that visual feedback in target tracking increases whole body displacement, velocity and LID amplitude (Lemieux, Ghassemi, Jog, Edwards, & Duval, 2007). Liu and colleagues (2001) hypothesized that voluntary error correction in response to visual error feedback in patients with LID sums with the dyskinesia to create a greater movement response and ultimate movement error. In effect, when the patient is aware of the dyskinesia, the amplitude actually increases, instead of being suppressed by the individual.

In a series of studies, Keisjers and colleagues (Keisjers, Horstink, van Hilten, Hoff, & Gielen, 2000; Keisjers, Horstink, & Gielen, 2003a; Keisjers et al., 2003b) formulated a neural network to assess and monitor LID, using accelerometric measurements from the upper arms, upper legs, sternum and the wrist of the most affected side. The neural networks approach distinguished between voluntary movements and LID, and defined inherent parameters to each; the parameters identified as being the

most important to define LID were segment velocities, percentage of time spent moving and cross correlation. Uncoordinated body movements serve as the basis for dyskinesia, therefore, a high cross correlation value would indicate that the body segments co-vary and are unlikely to be dyskinetic. While a low cross-correlation value indicates a high likelihood that the body segments vary and are dyskinetic.

Initial results from these studies (Keisjers et al., 2003a; Keisjers et al., 2003b) demonstrate that dyskinesia predominate in the lower frequency domain (1-4 Hz), distinct from tremors, which occur at higher (<4 Hz) frequencies (Dubinsky, 1995). As well, low segmental cross correlation values between 0.2 and 0.38 are apparent in dyskinesia, suggesting that dyskinetic movements of body segments are not well coordinated (Keisjers et al., 2000). This supports the hypothesis and observation that dyskinesia are uncoordinated movements of body joints in space.

The neural networks approach of the Keisjers et al. study (2003a) was able to predict dyskinesia of the trunk, arm and leg based on the following parameters. Dyskinesia of the trunk is predicted when trunk movement amplitudes are large relative to the standard deviation (SD) of leg segment velocity. Dyskinesia of the arm is predicted when the most affected leg moves at lower frequencies (<3Hz), and there is a high cross correlation between wrist and trunk. Marconi and colleagues (1994) argue that severe dyskinesia of the leg implies at least a mild dyskinesia of the arm, supporting the findings of Keisjers group. Dyskinesia of the leg is predicted when the SD of velocity for the less dyskinetic leg is low, and the most affected leg moves for a longer fraction of time (Keisjers et al., 2003a). These results might show the existence of an upper and lower body coupling mechanism in patients with dyskinesia.

In summary, LIDs are involuntary movements that are not well coordinated between body segments, predominate in the 1-4 Hz frequency range and are exacerbated with the presentation of motor or mental tasks.

2.7 Statement of the problem

L-dopa use in PD patients, although useful in the relief of most primary motor symptoms, often exacerbates postural instability and balance problems in these patients. Extended use of L-dopa can cause secondary motor symptoms, such as the toxic form of dyskinesia known as L-dopa induced dyskinesia (LID); LID occurs in 50 to 70% of PD patients. Given that LID influences both segmental and whole body CoM, a strong link exists between LID and increased CoP variability in PD patients; indeed, researchers have alluded to a possible causal relationship between the two. However, the exact relationship between LID and CoP variability in PD patients has yet to be tested.

This study investigates the relationship between LID and CoP variability in both AP and ML directions, and the effects of manipulating task difficulty on the amplitude of LID fluctuations. In the present study, we investigate CoP and kinematic variability during the performance of a precision aiming task similar to the Balasubramaniam et al., 2000 and Lefebvre & Balasubramaniam, 2007 studies. Task difficulty in this study was manipulated by altering the following: target size, distance and orientation of the target.

This study helps to bridge the gap between effects of pathology and medication induced motor disorders on postural control in PD patients. The **overall objective** of this experiment is to gain insight to the relationship between LID and postural control (CoP variability) in PD patients on L-dopa medication.

The **Specific objectives** are:

1. To test **hypothesis 1**: That PD patients will display greater AP and ML CoP variability than neurologically healthy control subjects.
2. To test **hypothesis 2**: That PD patients will display greater kinematic variability than neurologically healthy control subjects.
3. To test **hypothesis 3**: That dyskinesia in superior segments (hip level and up) will contribute to greater CoP variability in the ML direction. That dyskinesia in inferior segments (below hip level) will contribute to greater CoP variability in the AP direction.
4. To test **hypothesis 4**: That dyskinesia amplitude will increase with task difficulty. Decreased target size and increased target distance will be the manipulated factors to test task difficulty.

Chapter III

Methods

3.1 Participants

We recruited eight subjects diagnosed with idiopathic Parkinson's disease (PD) and eight neurologically healthy age-matched adults for this study. Recruitment of PD patients was a joint effort between the neurology department of the Ottawa Hospital and the Parkinson's Society of Ottawa. Control subjects were recruited from the community at large. The University of Ottawa health research ethics board (Appendix 1) approved the study.

Control subjects were matched for age and gender as closely as possible (mean age = 63.9 years, four males and four females) with PD patients (mean age = 69.3 years, five males and three females). Control subjects had similar height and weight profiles (mean height = 166.1 cm, mean weight = 77.7 kg) as the PD patients (mean height = 168.3 cm, mean weight = 70.3 kg). Table 1 shows PD patient characteristics.

All participants completed a health questionnaire (Appendix 2) outlining pertinent characteristics (age, sex, weight, and height), current medications and co-morbidities. All PD patients were using L-dopa as a monotherapy or part of a combined medication therapy. PD patients were screened to ensure that they were not using the anti-dyskinetic drug Amantadine. Although history of dyskinesia was not a pre-specified recruitment requirement, all PD patients identified having a history of dyskinesia during the health questionnaire administration.

The Folstein mini-mental state exam (MMSE) (Appendix 3) ensured that cognitive functioning in the patient group was not impaired; the MMSE was an important

tool to ensure comprehension of the experimental task, so that results of the testing session reflected motor aptitude of the individual. The UPDRS (Appendix 4) assessed motor disability, therapy complications and disease severity in PD patients; greater UPDRS scores indicate greater motor impairment.

Table 1.

PD Patient characteristics: Sex, age, height, weight, duration of disease, number of years using L-dopa, medication dosage, UPDRS motor sub-score

Patient	Sex	Age (yrs)	Height (cm)	Weight (kg)	Duration (yrs)	Medications (yrs)	Medications ^a	UPDRS motor ^b
1	M	60	182.9	95.3	13	13	Sinemet CR 200/50 (6x/day)	16
2	F	62	185.4	72.5	7	7	Mirapex 1.325mg (3x/day) Sinemet 100/25 (5x/day)	29
3	M	69	172.7	70.7	12	8	Sinemet CR 200/50 (5x/day) Apo-levocarb 100/25 (5x/day) Tolcapone 100mg (5x/day)	56
4	F	86	149.9	45.3	7	4	Apo-Levocarb 100/25 (3x/day)	29
5	M	68	167.6	75.2	9	9	Apo-Levocarb 100/25 (3x/day) Sinemet CR 200/50 (2.5x/day) Mirapex 1.5mg (3x/day) Azilect 1mg (1x/day)	33
6	M	76	172.7	65.7	13	12	Sinemet CR 200/50 (1.5 3x/day) Comtan 200mg (3x/day)	42
7	F	62	154.9	63.5	5	5	Mirapex 1.25mg (3x/day) Sinemet 100/25 (3x/day)	22
8	M	71	160.0	72.6	8	8	Sinemet CR 200/50 (4x/day) Mirapex 0.5mg (3x/day)	34
Average		69.3	168.3	70.3	9.3	8.3		32.6

^aMedications used for the treatment of PD symptoms

^bUPDRS motor sub-score calculated by addition of sections II and III of full UPDRS

3.2 Procedure

We asked participants to maintain their normal morning routine the day of testing. PD patients attended the testing session 1 hour after taking their L-dopa, within the three-hour period of 8:30 to 11:30am, to negate the effects of diurnal variation in dyskinesia. The testing session began with the administration of the health questionnaire, UPDRS (we did not measure question 42 regarding symptomatic orthostasis) and MMSE.

We recorded the kinematics of movement using non-invasive reflective markers located on the head, base of the neck, the sternum and bilaterally on the shoulder, elbow, wrist, hip, knee and ankle. Participants stood with one foot on each of the two AMTI forceplates located in the middle of the laboratory. We assessed baseline quiet stance of all participants by having the subject stand quietly on the forceplates, breathe normally and look straight ahead.

Two targets (large or small) were placed in front of the individual (parallel orientation) or 90° to the right of the individual (perpendicular orientation) at either a 1m or a 2m distance from the subject. The targets comprised of a white square (large= 36 cm^2 , small= 25 cm^2), each superimposed on a black square of 122 cm^2 . We recorded three 30-second trials of each of the following conditions:

- 1) *Parallel orientation, large target, 2m distance*
- 2) *Parallel orientation, small target, 2m distance*
- 3) *Parallel orientation, large target, 1m distance*
- 4) *Parallel orientation, small target, 1m distance*
- 5) *Perpendicular orientation, large target, 2m distance*
- 6) *Perpendicular orientation, small target, 2m distance*
- 7) *Perpendicular orientation, large target, 1m distance*
- 8) *Perpendicular orientation, small target, 1m distance*

Participants were instructed to maintain the projection of the beam of a laser pointer, affixed to their right hip, within the white square of the target. Direct visual

feedback informed subjects if the laser beam deviated from the target; if the laser point deviated from the target, subjects would recruit the necessary corrective measures to return the laser beam within the white square. We provided multiple breaks between trials to reduce fatigue and a spotter was present at all times while testing PD patients.

3.3 Materials & Apparatus

The experiment was conducted in the Sensorimotor Neuroscience laboratory at the University of Ottawa. Two AMTI force plates recorded 2-dimensional centre of pressure information from beneath each foot and the resultant ground reaction forces. The VICON motion capture system in the lab recorded 3-dimensional kinematics from the reflective body markers placed on the participants. These two systems sampled in synchrony at a rate of 200Hz. Analyses were performed using Matlab software, and statistics were performed using SPSS v 16.0 for Windows.

3.5 Analyses

We limited our analyses to include kinematics from the head, sternum, shoulder, hip, knee and ankle on the right side of the body. All computations were performed in AP and ML directions, and results were averaged between trial types for each subject unless specified otherwise. To filter tremors, we used a bidirectional (to preserve phase) 1024th order Fir1 4 Hz bandpass filter for kinematic data (except movement variability).

We computed the variability of the centre of pressure (CoP) by first finding the CoP_{net} from the two force plates using the Winter et al., 1998 equation, and then by taking the root mean square variability (RMS) of the CoP_{net} values.

We computed movement variability using the standard deviation of movement of each kinematic marker. Separate stepwise multiple regressions for PD patients and control subjects determined the predictive relationship between movement and CoP variability in AP and ML directions during the precision aiming task.

Traditionally, dyskinesia has been quantified using mean acceleration (Manson et al., 2000), predominant frequency (Hoff et al., 2001), frequency amplitude (Burkhard et al., 2000) and neural networks designs (Keisjers et al., 2003a). We used relatively novel means to quantify dyskinesia by computing principal component analysis (PCA), average mutual information (AMI), directional coupling (DC), relative phase (RP) and spectral coherence (SC).

PCA is useful in determining the joint segments (factors) which contribute to the overall spatio-temporal variance of the system, and the strength of their contribution. We computed the PCA using the group mean values of each trial type in the AP and ML directions. No statistics were performed on the PCA.

The following analyses were performed between the joints, which define the head segment (head and base of the neck), arm segment (wrist and shoulder), torso segment (shoulder and hip) and the leg segment (hip and ankle) on the right side of the body. For these computations, we also removed the mean from the recorded time series.

The AMI uses a time series to quantify the amount of information shared between them, yielding a value in bits of the entropic quantity of the joint probability distribution function. More mutual information shared between two joints indicates a greater likelihood of the joints sharing a dependent relationship. Less mutual information shared between the two joints indicates a greater likelihood of independence of the joints.

The DC used an evolution map approach (Rosenblum, Cimponeriu, Bezerianos, Patzak & Mrowka, 2002) to measure the extent that movement at one joint actively drives movement of another joint, yielding a positive or negative value to indicate the strength of the DC. Positive values indicate that the DC between the two joints is driven by the first of the joint pair; negative values indicate that the DC between the two joints is driven by the second of the joint pair.

The RP measures the difference of the phase relationships between two time series, useful in investigating phase relationships within segments. Mean circular relative phase (RP_{mean}) between two joints is most stable in two phase relationships; In-phase 0° phase relationship and anti-phase 180° phase relationship (Haken, Kelso, & Bunz, 1985). The variability (standard deviation) of the relative phase (RP_{var}) provides an indication of the stability of the relationship; greater variability indicates less stability while greater stability is indicated by less variability.

The SC determines the dominant frequency that exists mutually between two oscillators; the frequency of coherence was used as a descriptive measure for the value of coherence between the segments. We computed the minimum value of coherence (Minval) and its frequency (MinF) as well as the maximum value of coherence (Maxval) and its frequency (MaxF). Stronger coherence (approaching 1.0) indicates that movement of the two joints is in tandem while lower values (approaching 0) indicated minimal coherence.

A 5-way ANOVA with one between factor and 4 within factors [2 (group: PD/control) x 2 (orientation: parallel/perpendicular) x 2 (distance: 1m/2m) x 2 (target size: large/small) x 2 (direction: AP/ML)] was performed on mean values of the dependent

measures of CoP variability, movement variability, AMI, DC RPmean, RPvar, Minval and Maxval. Significant main and interaction effects are reported at $\alpha=0.05$. Degrees of freedom were reported using the error degrees of freedom of the 2x2x2x2x2 ANOVA measured with the SPSS program.

Chapter IV

*Results***CoP variability***Quiet standing*

Mean CoP variability was greater in PD patients than in control subjects, as evidenced by the significant main effect of group $F(1, 28) = 4.282, p < 0.05$ (Figure 6). No other significant main or interaction effects were found for CoP variability during quiet standing.

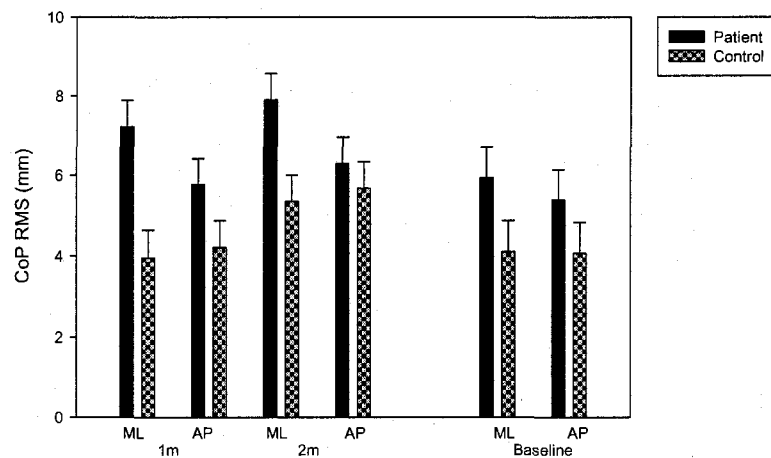


Figure 6. Effects of group, direction and distance (pooled for orientation and target size) on mean CoP variability during precision aiming and baseline quiet stance. Error bars indicate standard error of the mean.

Performance of precision task

Similar to the baseline condition, mean CoP variability was significantly greater in PD patients $F(1, 224) = 17.889, p < 0.001$ (Figure 6). Figure 6 also shows greater mean CoP variability in the 2m target distance condition (distance effect) $F(1, 224) = 4.460,$

$p < 0.05$. Figure 6 also displays the group X direction interaction. As demonstrated, the mean CoP variability in PD patients was greatest in the ML direction; whereas mean CoP variability in control subjects was greatest in the AP direction $F(1, 224) = 3.747, p < 0.05$. No other main or interaction effects were significant for mean CoP variability during the precision aiming task.

Movement (kinematic) variability

Quiet standing

Figure 7 depicts the significant group and direction main effects for movement variability during quiet standing.

Movement variability was significantly greater in PD patients in the head [$F(1, 28) = 4.728, p < 0.05$], sternum [$F(1, 28) = 6.247, p < 0.01$], shoulder [$F(1, 28) = 4.170, p < 0.05$], hip [$F(1, 28) = 6.102, p < 0.05$] and ankle [$F(1, 28) = 5.063, p < 0.05$]; mean movement variability of the knee was not significantly different between groups.

Moreover, movement variability was greater in the AP direction for the head [$F(1, 28) = 5.530, p < 0.05$], sternum [$F(1, 28) = 21.389, p < 0.001$], shoulder [$F(1, 28) = 18.948, p < 0.001$] and hip [$F(1, 28) = 11.113, p < 0.001$]; mean movement variability of the knee and ankle was not significantly different between AP or ML directions.

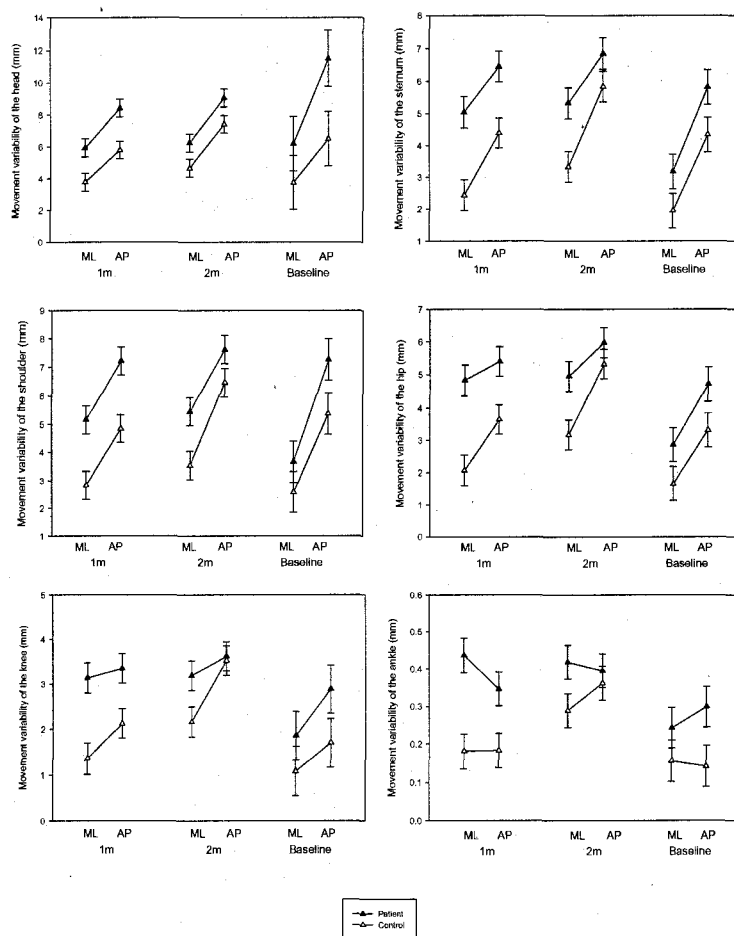


Figure 7. Effects of group, distance and direction (pooled for orientation and target size) on movement variability of the head, sternum, shoulder, hip, knee and ankle during precision aiming and baseline quiet stance. Error bars indicate standard error of the mean.

Performance of precision task

Table 2 presents a summary of statistical tests performed for the dependent variables related to trajectory variability of kinematic markers. These effects are further summarized in Figure 7, which shows group, distance and direction effects for movement variability. These main effects indicate that movement variability of joints from the knee up was greatest in PD patients, in the 2m target condition and in the AP direction.

Table 2

Summary of the main effects of movement variability at the head, sternum, shoulder, hip, knee and ankle during the precision aiming task

Main effect	Group		Direction		Orientation		Distance		Target Size	
	PD	Control	ML	AP	Parallel	Perpendicular	1m	2m	Large	Small
Marker										
Head	7.426***	5.42***	5.158***	7.688***	6.025*	6.821*	5.988*	6.858*	6.518	6.329
Sternum	5.913***	3.997***	4.031***	5.878***	4.883	5.026	4.577*	5.332*	5.079	4.831
Shoulder	6.362***	4.412***	4.241***	6.533***	5.094	5.68	5.011*	5.763*	5.494	5.28
Hip	5.288***	3.547***	3.752***	5.084***	4.618	4.218	3.983**	4.852**	4.601	4.234
Knee	3.321***	2.289***	2.459***	3.151***	3.004	2.606	2.489**	3.121**	2.983	2.627
Ankle	0.399***	0.254***	0.331***	0.322***	0.332	0.321	0.287*	0.366*	0.325	0.328

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

An interaction of group X distance for movement variability of the knee [$F(1,224) = 4.014, p < 0.05$] and the ankle [$F(1,224) = 3.966, p < 0.05$] is evident in Figure 7; variability was consistently greater in PD patients however, both groups showed significant increases in variability in the 2m target condition.

Mean movement variability of the head was significantly greater in the parallel orientation in the ML direction and in the perpendicular orientation in the AP direction [$F(1,224) = 10.019, p < 0.01$]. Meanwhile, movement variability of the hip and knee were greater in the parallel orientation in the AP direction and greater in the perpendicular

orientation in the ML direction, [$F(1,224) = 16.586, p < 0.001$] and [$F(1,224) = 24.720, p < 0.001$], respectively.

Multiple regression analysis

The regression analysis model was 86.9% successful (adjusted $R^2 = 0.869, F(3, 60) = 140.69, p < 0.001$) in predicting ML CoP variability in PD patients based on ML movement variability of three joints. The first predictor was variability of the shoulder $\beta = 2.108, p < 0.001$, the second predictor was variability of the ankle $\beta = -0.457, p < 0.001$ and the third predictor was variability of the sternum $\beta = -0.872, p < 0.01$.

In contrast, the model for predicting CoP variability in the ML direction in control subjects was 76.5% successful (adjusted $R^2 = 0.765, F(2, 61) = 103.48, p < 0.001$) based on ML movement variability at two joints. The first predictor was variability of the hip $\beta = 0.493, p < 0.001$ and the second predictor was variability of the shoulder $\beta = 0.418, p < 0.001$.

The regression analysis explained AP CoP variability in PD patients and control subjects using the same variables. In PD patients, the sternum (first predictor) $\beta = 0.696, p < 0.001$ and the knee (second predictor) $\beta = 0.309, p < 0.001$ predicted 91.6% of AP CoP variability (adjusted $R^2 = 0.916, F(2, 61) = 345.54, p < 0.001$). In controls subjects, the sternum (first predictor) $\beta = 0.643, p < 0.001$ and the knee (second predictor) $\beta = 0.356, p < 0.001$ predicted 92.2% of AP CoP variability (adjusted $R^2 = 0.922, F(2, 61) = 375.56, p < 0.001$). This indicates that the strategies used to control AP CoP might be similar between a PD patient group and a healthy control group.

Principal Component Analysis (PCA)

We will not present the results from the PCA; however, they will be further discussed in a later section.

Average Mutual Information (AMI)

Quiet Standing

Significantly greater amounts of AMI were shared within the torso [$F(1, 28) = 4.360, p < 0.05$] (Figure 8) and head [$F(1, 28) = 13.280, p < 0.001$] segments in the AP direction, indicating greater inter-dependence of the joints within these segments during quiet stance. There was no significant main effect of group.

Performance of precision task

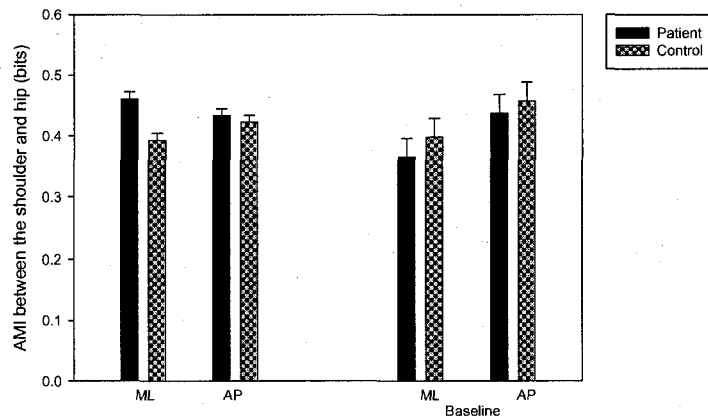


Figure 8. Effects of group and direction (pooled for orientation, distance and target size) on AMI of the torso (shoulder and hip) segment during precision aiming and baseline quiet stance. Error bars indicate standard error of the mean.

PD patients shared greater AMI within the joints of the torso, indicating greater dependence between the shoulder and hip $F(1,224) = 11.453, p < 0.001$, as indicated in Figure 8. Meanwhile, the head and neck (head segment) shared a more dependent relationship in the perpendicular orientation [$F(1,224) = 28.119, p < 0.001$] and in the AP direction [$F(1,224) = 25.187, p < 0.001$].

Figure 9 shows the significant group X orientation interaction for the AMI of the arm segment $F(1,224) = 5.012, p < 0.05$, while Figure 10 shows the same significant interaction for the torso $F(1,224) = 3.948, p < 0.05$. Similar patterns existed for both segments. PD patients showed greater dependence between the joints of the segment in the parallel orientation while control subjects showed greater dependence between the joints in the perpendicular orientation.

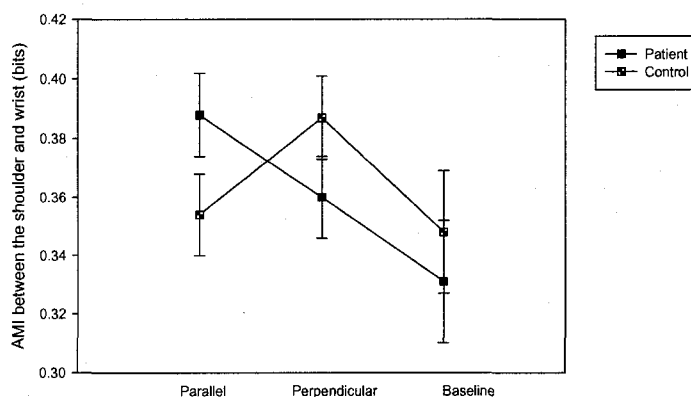


Figure 9. Effects of group and orientation (pooled for direction, distance and target size) on the AMI of the arm (shoulder and wrist) segment during precision aiming and baseline quiet stance. Error bars indicate standard error of the mean.

Figure 8 displays how PD patients exhibit greater inter-dependence of the torso segment in the ML direction while control subjects show greater dependence between the shoulder and hip in the AP direction $F(1,224)=5.835, p<0.05$. This result will be emphasized during the discussion.

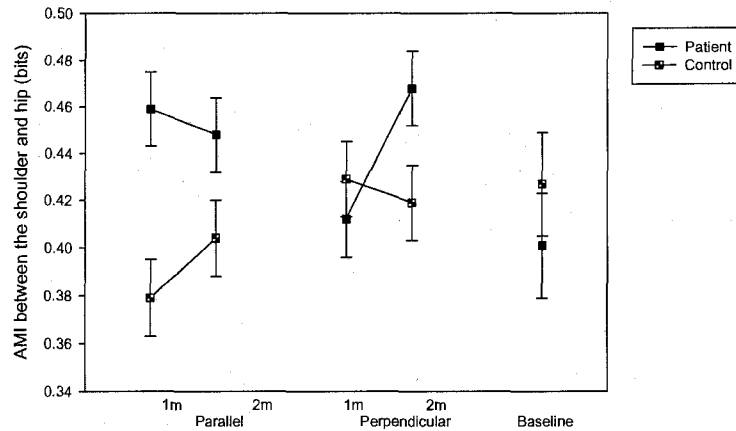


Figure 10. Effects of group, orientation, and distance (pooled for direction and target size) on the AMI of the torso (shoulder and hip) segment during precision aiming and baseline quiet stance. Error bars indicate standard error of the mean.

The hip and the ankle shared a greater dependent relationship in the AP direction in the parallel orientation and in the ML direction in the perpendicular orientation, evidenced by the interaction of orientation X direction $F(1,224)=11.911, p<0.001$. While the head and neck shared a greater dependent relationship in the parallel orientation at the 1m target distance and in the perpendicular orientation at the 2m target distance $F(1,224)=4.035, p<0.05$.

PD patients showed greater AMI of the torso in the parallel orientation in the 1m target condition and in the perpendicular orientation in the 2m target condition.

Conversely, control subjects showed greater AMI of the torso in the parallel orientation at the 2m distance and in the perpendicular orientation in the 1m distance $F(1,224)=4.797$, $p<0.05$. This finding indicates the importance of distance from the target during the precision task.

Additional interactions of distance include increased AMI of the torso in the ML direction at a 2m target distance in the parallel orientation and greater mean AMI in the AP direction in the perpendicular orientation at the same distance $F(1,224)=5.993$, $p<0.05$. Mean AMI of the head in the AP direction was greatest at a 1m target distance in the parallel orientation and greatest in the same direction at a 2m target distance in the perpendicular orientation $F(1,224)=4.997$, $p<0.05$.

Directional coupling

Quiet standing

We found no significant main or interaction effects for DC during quiet stance.

Performance of precision task

Figure 11 shows stronger DC of the head segment in control subjects [$F(1,224) = 12.519$, $p<0.001$], in the parallel orientation [$F(1,224) = 7.168$, $p<0.01$] and in the 1m target distance [$F(1,224) = 4.010$, $p<0.05$]. Negative values indicate activity driven by the head; positive values indicate activity driven by the neck. Therefore, we see that there is a clear effect of the precision aiming task on the organization of the head segment between groups.

Additionally, DC of the torso was stronger in the ML direction $F(1,224) = 45.360$, $p<0.01$; interestingly, the hip drives movement of the shoulder in the ML

direction while the shoulder drives movement of the hip in the AP direction. This finding will be elaborated in the discussion section.

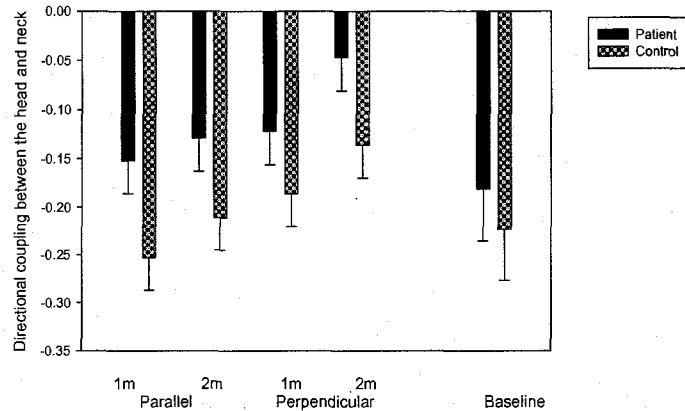


Figure 11. Effects of group, orientation and distance (pooled for direction and target size) on the directional coupling of the head (head and neck) during precision aiming and baseline quiet stance. Error bars indicate standard error of the mean.

Figure 12 shows stronger DC of the arm in PD patients at a 2m target distance and in control subjects at a 1m distance $F(1,224)=4.498, p<0.05$, while Figure 13 shows stronger DC of the arm in PD patients in the AP direction and control subjects showed stronger DC in the ML direction $F(1,224)=4.522, p<0.05$. In all cases, movement of the shoulder was driving the movement of the wrist.

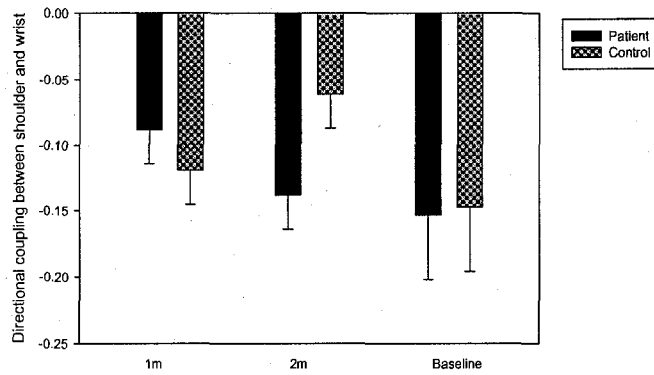


Figure 12. Effects of group and distance (pooled for orientation, direction and target size) on the directional coupling of the arm (shoulder and wrist) during precision aiming and baseline quiet stance. Error bars indicate standard error of the mean.

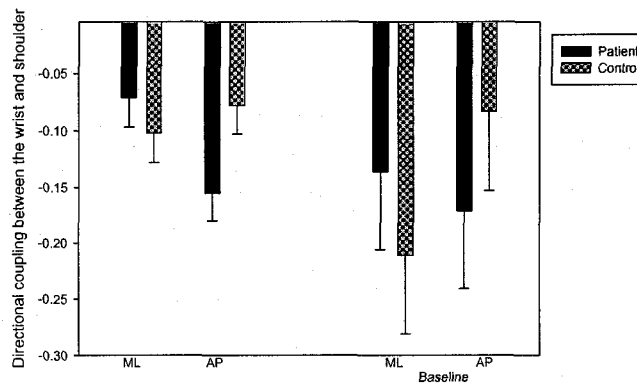


Figure 13. Effects of group and direction (pooled for orientation, distance and target size) on the directional coupling of the arm (shoulder and wrist) during precision aiming and baseline quiet stance. Error bars indicate standard error of the mean.

Analysis of Figure 14 shows a significant group X orientation X direction interaction for the DC of the leg segment $F(1,224)=4.109, p<0.05$. As such, PD patients displayed stronger DC in the parallel orientation in the AP direction, whereas control

subjects showed stronger DC in the parallel orientation in the ML direction. Movement of the hip was driving the movement at the ankle.

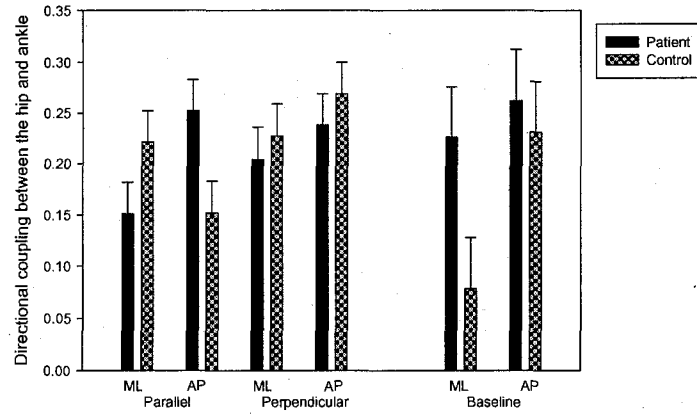


Figure 14. Effects of group, orientation and direction (pooled for distance and target size) on the directional coupling of the leg (hip and ankle) during precision aiming and baseline quiet stance. Error bars indicate standard error of the mean.

Meanwhile, the same interaction exists for the DC of the head $F(1,224)=4.474$, $p<0.05$, indicating that in the perpendicular orientation, PD patients show stronger DC in the ML direction and control subjects show stronger DC in the AP direction. In the parallel orientation, control subjects show stronger coupling in the ML direction, while PD patients show no significant difference between AP and ML (Figure 15).

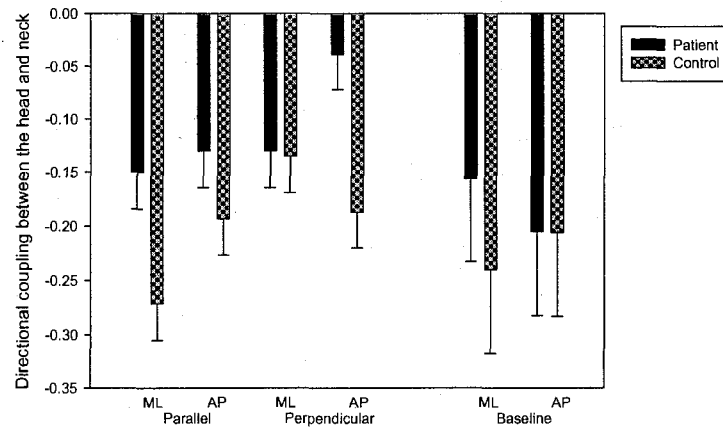


Figure 15. Effects of group, orientation and direction (pooled for distance and target size) on the directional coupling of the head (head and neck) during precision aiming and baseline quiet stance. Error bars indicate standard error of the mean.

Relative phase

Mean Relative phase

Quiet Standing

During quiet stance, the RPmean of the leg segment more significantly approached 0° (in phase) in the ML direction $F(1, 28) = 8.460, p < 0.01$. We found no other significant effects.

Performance of precision task

In contrast to what was seen during quiet stance, the RPmean of the leg segment more closely approached 0° (in phase) in the AP direction [$F(1, 224) = 86.758, p < 0.001$], as did the RPmean of the arm segment [$F(1, 224) = 15.126, p < 0.001$]. However, the RPmean of the torso segment more closely approached 0° (in phase) in the ML direction

$F(1,224) = 6.645, p < 0.01$. Additionally, the RPmean of the arm segment more closely approached 0° (in phase) in the perpendicular orientation $F(1,224) = 7.742, p < 0.01$

An RPmean relationship of the leg segment closer to 0° (in phase) occurred while using the small target $F(1,224) = 4.709, p < 0.05$. This effect is one of the only findings related to target size, which we will attempt to explain in the discussion section.

Figure 16 depicts how a 0° (in phase) relationship of the arm was more closely attained by PD patients in the ML direction than by control subjects in the AP direction $F(1,224) = 4.960, p < 0.05$. Figure 17 shows how the RPmean of the torso approaches 0° (in phase) in PD patients in the parallel orientation and approaches 0° (in phase) in control subjects in the perpendicular orientation $F(1,224) = 5.648, p < 0.05$.

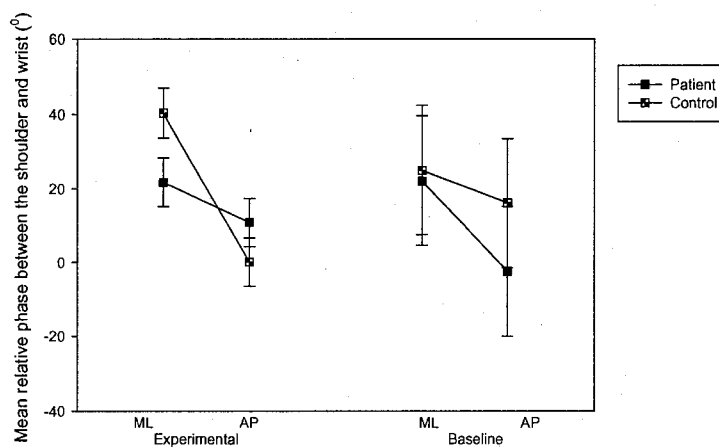


Figure 16. Effects of group and direction (pooled for orientation, distance and target size) on RPmean of the arm segment (shoulder and wrist) during precision aiming and baseline quiet stance. Error bars indicate standard error of the mean.

An additional interaction effect of orientation X direction was found for the RPmean of the arm segment $F(1,224) = 4.173, p < 0.05$. In this case, although the phase

relationship most closely approached 0° (in phase) in the AP direction of both orientations, the phase relationship in the parallel orientation is positive ($M=21.241$), while that in the perpendicular orientation is negative ($M= -10.474$), indicating a phase lag of the leading limb (in this case, the wrist).

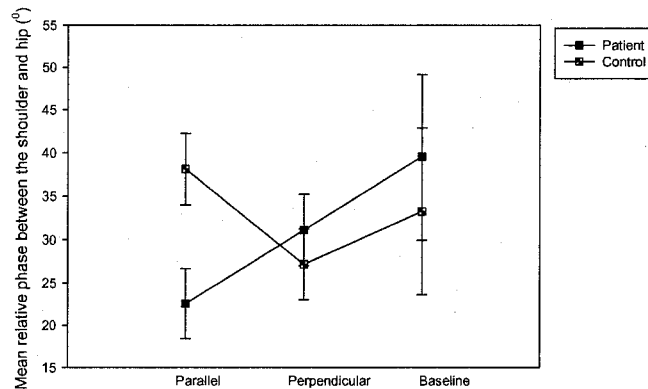


Figure 17. Effects of group and orientation (pooled for distance, direction and target size) on the RPmean of the torso segment (shoulder and hip) during precision aiming and baseline quiet stance. Error bars indicate standard error of the mean.

Relative phase variability

Quiet standing

The head segment had greater RPvar in the ML direction [$F(1, 28) = 7.919$, $p < 0.01$] (Figure 18) while greater RPvar of the arm (Figure 20) and leg segment (Figure 21) occurred in the AP direction [$F(1, 28) = 13.763$, $p < 0.001$] and [$F(1, 28) = 4.530$, $p < 0.05$], respectively. Recall that greater RPvar indicates less stability of the relative phase relationship, perhaps indicating the presence of a phase drift.

Performance of precision task

RPvar in the head segment was greater in PD patients [$F(1,224) = 3.907, p < 0.05$] (Figure 18) and RPvar of the arm segment was greater in control subjects [$F(1,224) = 4.100, p < 0.05$] (Figure 20).

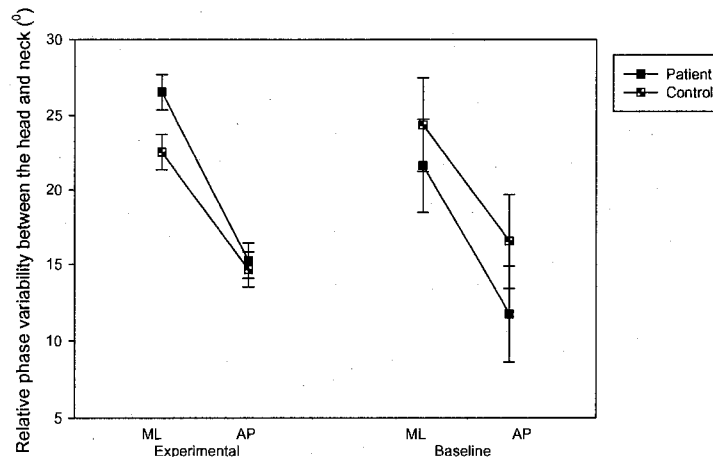


Figure 18. Effects of group and direction (pooled for orientation, distance and target size) on the RPvar of the head segment (head and neck) during precision aiming and baseline quiet stance. Error bars indicate standard error of the mean.

Figures 18 and 19 illustrate how RPvar of the head and torso segments is greater in the ML direction and [$F(1,224) = 66.864, p < 0.001$] and [$F(1,224) = 12.690, p < 0.001$], respectively. However, Figures 20 and 21 illustrate how RPvar of the arm and leg segments is greatest in the AP direction [$F(1,224) = 21.484, p < 0.01$] and [$F(1,224) = 14.511, p < 0.001$], respectively.

Additionally, RPvar of the head segment was greater in the parallel orientation $F(1,224) = 4.924, p < 0.05$.

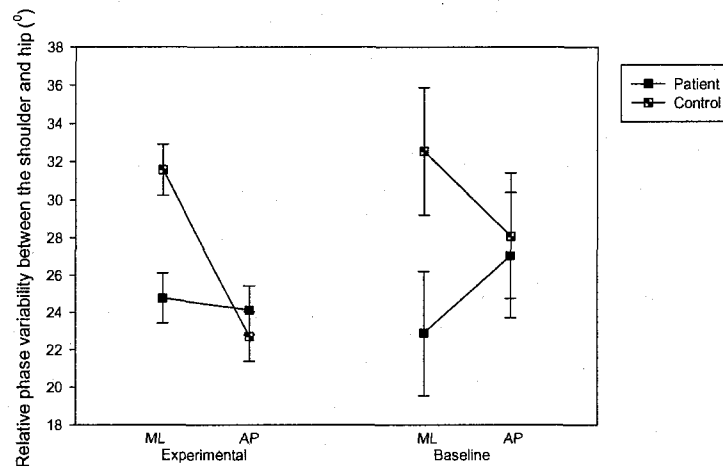


Figure 19. Effects of group and direction (pooled for orientation, distance and target size) on the RPvar of the torso segment (shoulder and hip) during precision aiming and baseline quiet stance. Error bars indicate standard error of the mean.

An interaction of group X direction indicates that the RPvar of the leg segment is greater in PD patients in the ML direction and greater in control subjects in the AP direction $F(1,224) = 16.048, p < 0.001$ (Figure 21). Figures 19 and 20 show the same interaction for RPvar of the torso [$F(1,224) = 9.493, p < 0.001$] and arm segments [$F(1,224) = 7.443, p < 0.01$]; little difference exists between groups in the AP direction but control subjects show significantly greater RPvar in the ML direction.

Additionally, PD patients showed greater RPvar of the leg segment at the 2m target distance while control subjects showed greater RPvar at the 1m target distance $F(1,224) = 5.599, p < 0.05$.

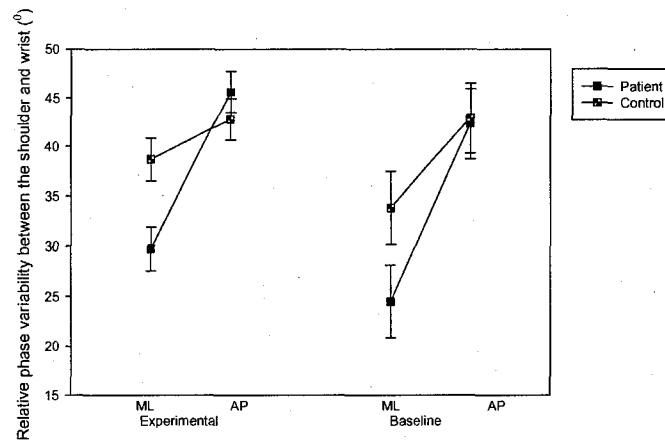


Figure 20. Effects of group and direction (pooled for orientation, distance and target size) on the RPvar of the arm segment (shoulder and wrist) during precision aiming and baseline quiet stance. Error bars indicate standard error of the mean.

The interaction of orientation X direction for RPvar of the torso segment shows that in the perpendicular orientation RPvar in the ML direction is much greater than in the AP direction $F(1,224)=8.266, p<0.01$. No difference existed in the parallel orientation.

The difference in RPvar was significantly greater between directions (AP and ML) while using the small target at a 2m distance and while using the large target at a 1m distance $F(1,224)=7.673, p<0.05$.

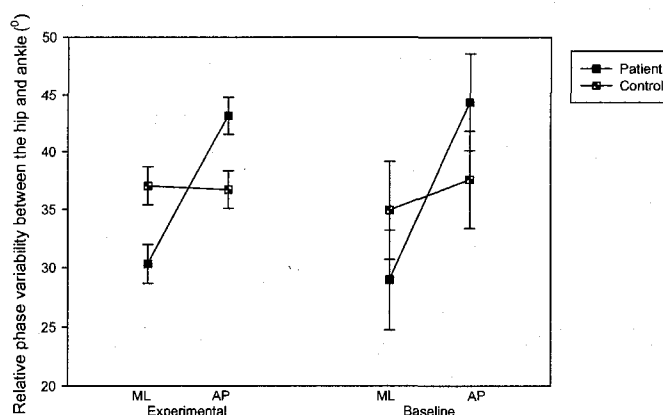


Figure 21. Effects of group and direction (pooled for orientation, distance and target size) on the RPvar of the leg segment (hip and ankle) during precision aiming and baseline quiet stance. Error bars indicate standard error of the mean.

Spectral Coherence

Quiet standing

PD patients showed less coherence of the arm segment (0.013 at a MinF of 2.867 Hz) $F(1, 28) = 6.569, p < 0.05$. No other group effects were found for values of minimum or maximum coherence during quiet stance.

The least amount of coherence of the arm segment (0.013 at MinF of 2.763 Hz) $[F(1, 28) = 5.863, p < 0.05]$ and the leg segment (0.011 at MinF 2.966 Hz) $[F(1, 28) = 4.260, p < 0.05]$ both occurred in the ML direction. This indicates that both the arm and the leg share a minimum coherence in the ML direction.

Maximum coherence of the arm segment (0.760 at MaxF 1.876 Hz) $[F(1, 28) = 9.469, p < 0.01]$, the leg segment (0.763 at MaxF 1.495 Hz) $[F(1, 28) = 8.526, p < 0.01]$, the torso segment (0.785 at MaxF 1.657 Hz) $[F(1, 28) = 26.340, p < 0.001]$ and the head

segment (0.928 at MaxF 1.404 Hz)[$F(1,28) = 31.856, p < 0.001$] all occurred in the AP direction. This indicates greater coherence in all segments in the AP direction.

Performance of precision task

Table 3

Summary of main effects for the values of spectral coherence and the frequency of that coherence during the precision aiming task

Main effect	Group		Direction		Orientation		Distance		Target Size	
Condition	PD	Control	ML	AP	Parallel	Perpendicular	1m	2m	Large	Small
SEGMENT										
Arm										
Min value	0.2**	0.15**	0.016**	0.019**	0.017	0.018	0.017	0.018	0.018	0.017
Min F	2.658	2.743	2.665	2.736	2.629*	2.772*	2.731	2.67	2.685	2.716
Max value	0.709	0.71	0.669***	0.75***	0.696*	0.723*	0.706	0.713	0.696*	0.723*
Max F	1.918	2.016	2.02	1.914	2.067*	1.867*	1.927	2.007	2.015	1.919
Leg										
Min value	0.024**	0.018**	0.013***	0.029***	0.02	0.021	0.023*	0.018*	0.019	0.023
Min F	2.946	2.815	2.718***	3.106***	2.836*	2.989*	2.919	2.905	2.885	2.939
Max value	0.71	0.712	0.645***	0.777***	0.695*	0.727*	0.725*	0.697*	0.7	0.722
Max F	1.723	1.693	1.795**	1.62**	1.768	1.648	1.738	1.677	1.698	1.718
Torso										
Min value	0.025**	0.017**	0.022	0.02	0.02	0.022	0.02	0.021	0.021	0.021
Min F	2.796	2.815	2.74*	2.872*	2.78	2.831	2.751	2.86	2.836	2.775
Max value	0.754***	0.708***	0.704***	0.759***	0.715*	0.747*	0.735	0.728	0.728	0.735
Max F	1.561**	1.74**	1.805***	1.496***	1.672	1.629	1.667	1.634	1.628	1.673
Head										
Min value	0.064**	0.039**	0.027***	0.075***	0.044	0.059	0.051	0.052	0.05	0.052
Min F	3.112	3.161	2.941***	3.332***	3.043***	3.23***	3.074*	3.199*	3.136	3.138
Max value	0.833**	0.864**	0.773***	0.924***	0.822***	0.875***	0.844	0.853	0.847	0.85
Max F	1.649	1.539	1.751***	1.438***	1.622	1.566	1.615	1.573	1.612	1.576

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Control subjects displayed the least amount of coherence for all segments, and had greater coherence of the head segment, while PD patients showed greater coherence of the torso segment.

Similar to baseline, the least amount of coherence for the arm, leg and head segments occurred in the ML direction, while the maximum coherence of all segments occurred in the AP direction.

The maximum value of coherence was consistently greater for all segments in the perpendicular orientation, while the minimum value of coherence was not significantly different between orientations.

The minimum value of coherence of the leg was least in the 2m condition, while the maximum value was greatest in the 1m condition. Meanwhile, maximum coherence of the arm segment occurred while using the small target.

Table 3 shows a summary of the main effects listed above.

Chapter V

Discussion

L-Dopa is the most common medication used in the treatment of primary motor symptoms such as bradykinesia, resting tremor and muscular rigidity in PD patients (Bezard et al., 2001). However, contradicting findings report that L-dopa use in PD patients does not provide benefit for postural instabilities (Carpenter et al., 2002) or performance on postural tasks (Lefebvre & Balasubramaniam, 2007). Indeed, some researchers report increased postural sway variability in PD patients while on L-dopa, leading to increased risks of falling (Rocchi et al., 2002). Recall that postural instability is a primary motor symptom defined by Parkinson in 1817.

Extended use of L-dopa in PD patients may lead to the development of L-dopa induced dyskinesia (LID), a hyperkinetic movement disorder involving involuntary movement production. LIDs are a negative side effect of L-dopa therapy and may interfere with voluntary movement production in PD patients. In light of this evidence, L-dopa has contrasting effects: it improves voluntary movement production, rigidities and tremors but may elicit increased postural instability and LIDs in PD patients.

As previously mentioned, researchers have shown increased postural sway (CoP) variability in PD patients, particularly in the mediolateral (ML) direction (Mitchell et al., 1995), while on L-dopa medication. Increased ML CoP variability might be a contributing factor to the increased postural instability seen in PD patients. Rocchi and colleagues (2004) hypothesized that increased CoP variability while on L-dopa might be a function of clinically unapparent LID in PD patients; however, no studies have confirmed this hypothesis. This study investigates the extent that LIDs affect CoP

variability in PD patients performing precision aiming tasks, and will bridge the gap between effects of pathology and medication induced movement disorders on postural control in PD patients.

Since Redmond and Hegge (1985) showed that PD patients rarely display dyskinesia in limb segments without co-existent axial or trunk dyskinesia, this discussion will focus primarily on the shoulder and hip joint relationships within the torso segment.

Centre of Pressure variability

Our first hypothesis was that PD patients would show greater CoP variability in both the AP and ML directions. Analysis of Figure 6 indicates that during the baseline quiet standing condition, PD patients showed greater AP and ML CoP fluctuations than control subjects. This trend remains consistent during the performance of the precision aiming task, however, PD patients also showed greater ML CoP variability while control subjects showed greater AP CoP variability. Rocchi et al. (2002) attribute the increased ML CoP variability to decreased muscle stiffness (through L-dopa administration) without a concurrent increase in neuromuscular control. Maurer et al. (2003) attribute the increased CoP variability to decreased sway velocity accompanied with decreased axial stiffness; however, we believe that the increase in ML CoP variability might reflect clinically unapparent medication induced dyskinesia in PD patients (Rocchi et al., 2004), particularly in the trunk (Adkin et al., 2005).

Recall that changes in centre of mass correlate to CoP variability (Gage et al., 2004); for this reason, we present CoP variability data to support our fourth hypothesis, which stated that task difficulty would cause dyskinesia amplitude to increase in PD

patients. The study confirmed that CoP variability increased with increasing target distance (2m) in both PD patients and control subjects; however, we failed to see a difference in CoP variability between target sizes. Our finding that CoP variability increases with increasing target distance is corroborated by the Balasubramaniam et al. (2000) study which showed similar results. In this study, the difference in total area of the target sizes was perhaps not sufficient to elicit differences in CoP variability of our subjects; subjects mastered the task regardless of target size.

Our study showed the existence of a trend of reciprocal activity in AP and ML variability in both control subjects and PD patients. Although not statistically significant, control subjects showed greater CoP variability in the parallel orientation in the AP direction, and greater CoP variability in the perpendicular orientation in the ML direction, similar to previous research (Balasubramaniam et al., 2000). PD patients did not exhibit the same modulation of CoP variability; CoP variability was greatest in the ML direction irrespective of orientation. However, PD patients did show reduced AP CoP variability in the perpendicular orientation relative to the parallel orientation. This trend might indicate that the underlying ability to modulate sway in a reciprocal manner still exists in the PD population; however, the baseline CoP variability in the ML direction might overshadow this relationship.

Movement variability

Movement variability of all kinematic markers was greater in PD patients during the precision aiming task (Figure 7) as well as during baseline quiet stance (with the exception of the knee), supporting our second hypothesis. Although the same instructions

were given for all subjects, to 'stand still', the excessive movement variability in PD patients both during quiet stance and the precision aiming task might be due to increased dyskinesia.

Gage et al. (2004) suggested that a linear relationship exists between changes in whole body CoM and CoP variability, and that CoM variability is greater in superior segments in comparison to inferior segments. Careful examination of our results (Figure 7) shows that the magnitude of kinematic variability decreases from the head to the ankle, supporting the Gage et al. (2004) study. Consequently, greater movement variability in superior segments is related to greater CoP variability, while inferior segments are primarily used to fine tune postural sway and response to postural perturbations.

Movement variability of all joints was greatest with the increased target distance of 2m, suggesting an increase in task difficulty in the 2m target distance condition (Figure 7). Likewise, the increase in movement variability in the 2m condition is reflected in the increased CoP variability mentioned earlier. Participants recruited more muscle activity across multiple body segments to keep the laser stationary when the target was further away. Liu et al. (2001) believed that control subjects respond to visual feedback of target tracking errors through voluntary movement correction, while in PD patients error-correcting voluntary movement and dyskinesia combine to produce an over-corrective movement.

Movement variability for all kinematic markers was greatest in the AP direction, a finding supported by previous work (Gage et al., 2004). However, our results section highlights an interaction between orientation and direction for movement variability of the head; variability was greater in the ML direction in the parallel orientation and was

greater in the AP direction in the perpendicular orientation. This is purely an effect of task. When the subjects turned their head 90^0 to the right to look at the perpendicular target, movements recorded along the AP axis were actually occurring in the ML plane.

We also showed that movement variability of both the knee and ankle was greatest in the AP direction in the parallel orientation and in the ML direction in the perpendicular orientation. Interestingly, the direction of greater movement variability was always toward the location of the target square. Horak and Nashner (1986) showed that small disturbances in posture tended to use corrective muscular activation about the ankle, while keeping the knees and hips straight; perhaps the greater movement variability about the knee and ankle were used as fine-tuning adjustments of the postural system to accomplish the precision aiming task.

Relationship between movement and CoP variability

Our multiple regression analysis resulted in a predictive equation for CoP variability based on movement variability in both AP and ML directions. PD patients and control subjects had the same predictive variables for AP CoP variability; the first predictor was movement variability of the sternum, followed by that of the knee. Crenna et al. (1987) explained that slow forward or backward movement of the torso causes a compensatory hyperextension of the knee in a top-down manner to maintain the CoM within the base of support. The predictors of AP CoP variability in our study support the existence of a multi joint top-down coordination synergy in human postural stance (Crenna et al., 1987), particularly during the precision aiming task. Furthermore, this

multi-joint synergy to maintain control of the CoP in the AP direction remains intact in PD patients on L-dopa medication.

Although PD patients and control subjects showed the same predictive measures for AP CoP variability, distinct differences existed between groups in the regression equation for ML CoP variability. ML CoP variability in PD patients was predicted by movement variability of the shoulder, the ankle and the sternum; ML CoP variability in control subjects was predicted by movement variability of the hip and the shoulder. The predictive measures for ML CoP variability in control subjects support the multi-joint bottom-up coordination synergy (Crenna et al., 1987); predictive strength of hip movement variability is stronger than that of shoulder movement variability. However, PD patients do not exhibit the same multi joint control of ML CoP variability; no recognizable coordination synergy exists. The lack of an evident coordination synergy in PD patients may be a result or combination of reactive postural control (as seen in the set shifting hypothesis) (Visser & Bloem, 2005), decreased axial control paired with increased ankle muscle activity/rigidity (Rocchi et al., 2002) or increased trunk sway amplitude caused by medication induced dyskinesia (Adkin et al., 2005).

Our third hypothesis stated that movement variability in superior segments would result in greater ML CoP variability and movement variability in inferior segments would contribute to greater AP CoP variability. The regression equations predicting AP and ML CoP variability do not provide enough support to confirm this hypothesis, however, the predictive trends for CoP variability are worth mentioning. Control subjects seem to adopt a multi-link top-down (sternum to knee) coordination synergy to control AP CoP variability, while ML CoP variability is controlled by a multi-link bottom-up (hip to

shoulder) coordination synergy. Furthermore, PD patients on L-dopa retain the ability to control AP CoP fluctuations by using a top-down coordination synergy, but that the bottom-up coordination synergy to control ML CoP fluctuations does not exist.

Principal component analysis

The PCA was computed by averaging trial types within groups, which resulted in very large inter-trial and inter-subject variability. This large variability indicates that between trial types, subjects adopted different coordination strategies to accomplish the precision aiming task. Likewise, the strategies adopted by one participant were not necessarily the same as those adopted by another participant, increasing the inter-subject variability. The increased inter-trial and inter-subject variability might be a learning function of the task, whereby participants adopted a trial-and-error method of segmental coordination to perform the task. This said, we were unable to identify a universal coordination mode or activation pattern that PD patients or control subjects adopted; hence, our PCA did not provide any meaningful insight regarding the principal components of the system necessary to accomplish the task.

Average mutual information

Average mutual information gives an indication of the amount of information that is mutually shared between two oscillators; greater AMI indicates a dependent relationship, while AMI values approaching 0 indicate an independent relationship. Greater dependence of the shoulder and hip (torso segment) occurred in PD patients in the ML direction and in control subjects in the AP direction (Figure 8). Rocchi et al.

(2002) propose that ML CoP variability is caused by reduced muscle tone in the trunk and hip, leading to a decoupling of trunk and lower limb sway. However, our results show a stronger dependent relationship between the shoulder and hip joints in the ML direction within the torso segment of PD patients, indicating that there might possibly be greater muscle activity occurring within the torso segment. Increased muscle activity and dependence between the shoulder and the hip might be caused by dystonic dyskinesia in the PD population (Adkin et al., 2005), and might not be a constructive means to maintaining control of the torso. Interestingly, this interaction between group and direction is not found for any other body segment, shedding light on the importance of the dependence between the shoulder and the hip in upright postural tasks.

The interaction of the AMI of the torso segment outlined in Figure 10 indicates that the dependence between the shoulder and hip in PD patients was greatest in the parallel orientation at a 1m target distance and in the perpendicular orientation at a 2m distance; control subjects showed the opposite pattern. This shows how the torso organization strategy to accomplish the precision aiming task changes between control subjects and PD patients, particularly as a result of orientation and target distance.

Directional coupling

Multiple group effects and interactions were found for the directional coupling between the joints defining multiple body segments; however, we will only focus the discussion on a select few of these significant effects.

The first interaction of interest was that of group and distance for the directional coupling between the wrist and the shoulder (arm segment); PD patients had a stronger

directional coupling between these joints in the 2m condition, while control subjects had a stronger directional coupling between these joints in the 1m condition. In both cases, movement of the shoulder is driving movement of the wrist. This directional coupling relationship confirms previous research by Burkhard et al. (1999), which showed that movement of the shoulder joint is the most important factor in detecting dyskinesia and relative joint relationships of the whole body. The fact that PD patients required a stronger influence from the shoulder to control movement of the wrists during the 2m target distance condition might indicate that increased task difficulty caused greater variability of the wrists, which needed to be actively controlled by the shoulder. The variability in the wrists might be caused either by choreic or dystonic dyskinesia of the hand as a direct result of the difficulty of the precision aiming task. Control subjects showed little difference between the strength of the directional coupling between target distances, indicating that there was not a significant effect of task difficulty in this group.

The second interaction of interest is that of group and direction for the directional coupling of the arm segment (Figure 13). Not only do PD patients show stronger directional coupling in the AP direction, but also the coupling relationship is severely weakened in the ML direction. In both directions, the shoulder is actively driving movement of the wrist; however, the driving force originating from the shoulder is weakened in the ML direction. This might indicate that the shoulder has less control over variability of the wrist in the ML direction, indicating greater total variability of the arm segment, which might contribute to increased CoP variability in the ML direction in PD patients. Although there is little difference between the strength of directional coupling between directions for the control subjects, we do show that the directional coupling

between the shoulder and wrist is weaker in the AP direction. Our interpretation is that weaker coupling is an indication of greater segment variability, which might be reflected as the observed increase in AP CoP variability in control subjects during the precision aiming task.

Previously, we mentioned the possibility of a multi-link postural strategy, where AP CoP variability was controlled in a top-down manner and ML CoP variability was controlled in a bottom-up manner (Crenna et al., 1987). Analysis of the directional coupling of the torso segment provides distinct evidence that this postural synergy exists. In the AP direction, the shoulder was actively driving the movement of the hip, while in the ML direction the hip was actively driving movement of the shoulder. This effect of direction was not seen in the directional coupling of any other body segment, suggesting that the torso may have an important role in the organization of both AP and ML CoP variability.

Mean relative phase

Recall that the relative phase of a relationship signifies whether the two oscillators, in this case the two joints defining a segment, are in-phase (0°) or anti-phase (180°) with respect to each other (Kelso, 1984). Both in-phase and anti-phase are considered stable relationships, while any value between the two is considered to be in transition.

Analysis of the relative phase of all the body segments did not show any main effects of group, however, there were two interactions where group was involved. This

informs us that for the most part, PD patients and control subjects maintain similar phase relationships between body segments while performing a precision aiming postural task.

However, Figure 16 shows that the mean relative phase of the arm maintains a 0.77° in-phase relationship in control subjects in the AP direction (with PD patients in a 10.79° relationship), while PD patients show a 21.75° relationship approaching in-phase in the ML direction (control subjects maintain a 40.4° phase relationship). Control subjects showed two distinctly different phase relationships of the arm segment between the AP and ML directions, while PD patients did not, perhaps an indication of the PD patients' inability to modulate AP and ML body segment relationships.

The mean relative phase of the torso maintains a 24.43° relationship (approaching in-phase) in the AP direction, while the phase relationship is more transitory in the ML direction at 35.0° . This indicates that in the AP direction, the torso is more likely to maintain a relationship approaching in-phase, while in the ML direction, the phase relationship is more likely to be in transition between in-phase and anti-phase.

During baseline quiet stance, no significant differences between mean relative phase values were noted between PD patients or control subjects. Meanwhile, there was only one significant difference between directions during baseline quiet stance. This indicates that both PD patients and control subjects adopted the same strategies to maintain quiet stance. We see that the presentation of the precision aiming task elicits differences between the groups, indicating how PD patients and control subjects choose alternate coordination strategies to perform the precision aiming task.

Relative phase variability

The analysis of the relative phase variability provided us with the amount of variability (in degrees) that occurred about the mean relative phase; greater relative phase variability indicated that the phase relationship of the segments was less stable.

Relative phase variability of the head segment was greater in PD patients than in controls, indicating less stability of the head (Figure 18). This group difference was not present during the baseline standing condition, indicating that the presentation of the visual target caused a lack of coordination within the head segment in PD patients, possibly a function of dyskinesia of the head. Previous studies have shown that the presentation of a visual target increases dyskinesia in PD patients (Liu et al., 2007). Likewise, the relative phase variability of the head segment was greater in the ML direction, indicating that there is a tighter control of the head segment in the AP direction (Figure 18). Buchanan and Horak (1999) demonstrated that visual information, such as the presentation of the target in our experiment, will stabilize movement of the head, which in turn stabilizes movement of the trunk particularly in the AP plane.

PD patients show very little modulation in the relative phase variability between the AP and ML directions in both the torso (Figure 19) and the arm (Figure 20) segments, while control subjects show significant differences between these two directions. Namely, PD patients show increased relative phase variability in the AP direction while control subjects showed increased relative phase variability in the ML direction. This effect is not present during the baseline quiet standing condition. This shows that greater flexibility exists for control subjects in their control of both the torso and the arm segments during a precision aiming task; they can accomplish the task by exploring more

possible joint configurations or phase relationships while still maintaining less CoP variability overall than PD patients.

In contrast, control subjects show little difference in the relative phase variability between the AP and ML directions in the leg segment, while PD patients showed greater relative phase variability in the AP direction (Figure 21). Rocchi et al. (2002) hypothesized that PD patients on L-dopa experienced decreased ankle muscle stiffness without increased neuromuscular control. The greater relative phase variability of the leg segment seen in PD patients, particularly in the AP direction, might indicate how PD patients require more fine-tuning of the phase relationship between their hip and ankle to accomplish the precision aiming task.

Spectral Coherence

The minimum value of spectral coherence between the shoulder and the hip was 0.017 (2.815 Hz) for control subjects and 0.025 (2.796 Hz) for PD patients, while the maximum value of coherence between these joints was 0.754 (1.561 Hz) for PD patients and 0.708 (1.740 Hz) for control subjects (Table 3). Burkhard et al. (1999) indicated that choreic dyskinesia predominates in the 1.5-3.25 Hz bandwidth, which is the frequency bandwidth for both the maximal and minimal values of coherence of the torso segment in PD patients and control subjects. It seems that PD patients explore a greater range of coherent trunk activity (shoulder and hip) than do control subjects. However, we must clarify that greater coherence does not necessarily indicate greater stability, where PD patients clearly show greater movement variability of the shoulder and hip (Figure 7) than control subjects do.

Summary of main findings

PD patients on L-dopa medication display greater CoP variability than age matched controls while performing a precision aiming task. The increased CoP variability reflects linearly increasing movement variability from the level of the hip upwards. Incidentally, we see that the relationship between movement variability and CoP variability in the ML direction is different between PD patients and control subjects, which is reflected in the increased ML CoP variability seen in PD patients.

We show that the relationship between the shoulder and the hip (defining the torso segment) is altered in PD patients during precision aiming. PD patients show greater dependence (AMI) of these two joints in the ML direction, while control subjects show greater dependence in the AP direction. We also show that PD patients have stronger directional coupling of the arm in the AP direction, suggesting less stability between the shoulder and wrist in the ML direction. PD patients also show less phase stability between the head and neck in the ML direction, indicating tighter control of the head segment in the AP direction.

In summary, ML CoP variability is significantly greater in PD patients compared to age matched controls. We propose that the increased CoP variability is caused by increased prevalence of LID (as identified through the AMI, DC, RP and SC computations) within the torso and arm segments. These body segments share the shoulder as a common joint, perhaps indicating that the LID primarily affects the shoulder. Furthermore, we show that this LID is exacerbated during the performance of the precision task, and that task difficulty by manipulation of target distance and not target size affects stability in PD patients.

Limitations and future directions

The results from this project are limited in scope to PD patients on L-dopa and without consideration of possible asymmetries in neural degeneration between patients. We acknowledge that asymmetries in neural degeneration can translate to motor asymmetries; however, without access to current neuro-imaging results, we could not confirm which side of the brain suffered greater degeneration. Therefore, our analyses were performed using kinematic data from the right side of the body, standardized because the laser pointer was affixed to the right hip.

Likewise, because we did not investigate the kinematics of the left side of the body, we can only presume that the trends seen on the right side of the body translate to the left side. However, the precision aiming task might actually cause greater variability on the left side of the body, where the left side is free to move in order to control and limit movement of the right side of the body.

We must also acknowledge that each of our patients used different medication strategies to control their PD symptoms, potentially affecting postural responses during the precision aiming task. However, the common denominator for patients was the use of L-dopa as part of their treatment.

This thesis served to answer our basic question of whether increased CoP variability in PD patients was due to the presence of clinically unapparent LID; however, we present some possibilities for future research based on our current conclusions. These possibilities include: 1) the validation of the non-linear functions we used to quantify dyskinesia and other movement disorders, 2) determining the joint relationships and segmental contribution to CoP variability in PD patients both on L-dopa and after a 12-

hour washout period. This would be beneficial to determine the actual role of L-dopa in postural control of PD patients, and 3) determining motor asymmetries during the performance of a precision aiming task. This would occur by computing both right and left side motor trajectories and comparing the results to valid neuro-imaging results of PD patients.

Conclusion

Does clinically unapparent L-dopa induced dyskinesia affect CoP variability in PD patients? Our results provide support that PD patients on L-dopa show similar multi-joint coordination synergies for the control of AP CoP variability, but that no clear coordination synergy exists to control ML CoP variability when compared to control subjects. Furthermore, greater ML CoP variability in PD patients on L-dopa reflects decreased joint coordination within the torso, arm and head segments. The decreased joint coordination seen in PD patients on L-dopa provides evidence of clinically unapparent uncoordinated involuntary movements (LID). Moreover, LIDs are aggravated by manipulating task difficulty by changing distance and not target size. In conclusion, CoP variability, particularly in the ML direction, is affected by decreased joint and segment coordination (LID) of the torso, head and arm in PD patients on L-dopa.

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Appendix 1: Extension of research ethics certificate



Université d'Ottawa University of Ottawa
Service de subventions de recherche et déontologie Research Grants and Ethics Services

HEALTH SCIENCES AND SCIENCE RESEARCH ETHICS BOARD

CERTIFICATION OF ETHICS APPROVAL

This is to certify that the University of Ottawa Health Sciences and Science Research Ethics Board (REB) examined the application for extension of ethics approval for the research project **Postural Sway Analysis of Parkinson's Disease Patients (file H 11-05-04)** submitted by Pr. Ramesh Balasubramaniam of the School of Human Kinetics at the University of Ottawa.

This project received initial ethics approval on February 23, 2006 and a renewal on February 27, 2007 by the REB as meeting appropriate ethical standards set out in the Tri-Council Policy Statement and in the Procedures of the University of Ottawa Research Ethics Boards. The University of Ottawa REB members accordingly gave it a one-year extension of ethics approval. This ethics renewal certification is retroactive to February 23, 2008 and **valid until February 23, 2009.**

Germain Zongo
Protocol Officer for Ethics in Research
For Dr. Daniel Lagarec, Chair of the
Health Sciences and Science REB

March 12, 2008

Date

Appendix 2: Health Questionnaire

Health Questionnaire

1. Date: _____
2. Time of Day: _____
3. Participant Initials: _____
4. Age: _____
5. Sex: _____
6. Height: _____
7. Weight: _____
8. Medical conditions:

9. Medications and dosages:

PD patients

1. Year of diagnosis: _____
2. Year of initial medication therapy: _____
3. L-Dopa therapy for how many years? _____
4. Current medications and dosages?

5. History of dyskinesia? _____
6. Do you have a 'worse' side or segment?

Appendix 3: Folstein MMSE

Appendix 4: UPDRS questionnaire

UNIFIED PARKINSON'S DISEASE RATING SCALE

I. MENTATION, BEHAVIOR AND MOOD

1. Intellectual Impairment

0 = None.

1 = Mild. Consistent forgetfulness with partial recollection of events and no other difficulties.

2 = Moderate memory loss, with disorientation and moderate difficulty handling complex problems. Mild but definite impairment of function at home with need of occasional prompting.

3 = Severe memory loss with disorientation for time and often to place. Severe impairment in handling problems.

4 = Severe memory loss with orientation preserved to person only. Unable to make judgements or solve problems. Requires much help with personal care. Cannot be left alone at all.

2. Thought Disorder (Due to dementia or drug intoxication)

0 = None.

1 = Vivid dreaming.

2 = "Benign" hallucinations with insight retained.

3 = Occasional to frequent hallucinations or delusions; without insight; could interfere with daily activities.

4 = Persistent hallucinations, delusions, or florrid psychosis. Not able to care for self.

3. Depression

1 = Periods of sadness or guilt greater than normal, never sustained for days or weeks.

2 = Sustained depression (1 week or more).

3 = Sustained depression with vegetative symptoms (insomnia, anorexia, weight loss, loss of interest).

4 = Sustained depression with vegetative symptoms and suicidal thoughts or intent.

4. Motivation/Initiative

0 = Normal.

1 = Less assertive than usual; more passive.

2 = Loss of initiative or disinterest in elective (nonroutine) activities.

3 = Loss of initiative or disinterest in day to day (routine) activities.

4 = Withdrawn, complete loss of motivation.

II. ACTIVITIES OF DAILY LIVING (for both "on" and "off")

5. Speech

0 = Normal.

1 = Mildly affected. No difficulty being understood.

2 = Moderately affected. Sometimes asked to repeat statements.

3 = Severely affected. Frequently asked to repeat statements.

4 = Unintelligible most of the time.

6. Salivation

0 = Normal.

1 = Slight but definite excess of saliva in mouth; may have nighttime drooling.

2 = Moderately excessive saliva; may have minimal drooling.

3 = Marked excess of saliva with some drooling.

4 = Marked drooling, requires constant tissue or handkerchief.

7. Swallowing

0 = Normal.

1 = Rare choking.

2 = Occasional choking.

3 = Requires soft food.

4 = Requires NG tube or gastrostomy feeding.

8. Handwriting

0 = Normal.

1 = Slightly slow or small.

2 = Moderately slow or small; all words are legible.

3 = Severely affected; not all words are legible.

4 = The majority of words are not legible.

9. Cutting food and handling utensils

0 = Normal.

1 = Somewhat slow and clumsy, but no help needed.

2 = Can cut most foods, although clumsy and slow; some help needed.

3 = Food must be cut by someone, but can still feed slowly.

4 = Needs to be fed.

10. Dressing

- 0 = Normal.
- 1 = Somewhat slow, but no help needed.
- 2 = Occasional assistance with buttoning, getting arms in sleeves.
- 3 = Considerable help required, but can do some things alone.
- 4 = Helpless.

11. Hygiene

- 0 = Normal.
- 1 = Somewhat slow, but no help needed.
- 2 = Needs help to shower or bathe; or very slow in hygienic care.
- 3 = Requires assistance for washing, brushing teeth, combing hair, going to bathroom.
- 4 = Foley catheter or other mechanical aids.

12. Turning in bed and adjusting bed clothes

- 0 = Normal.
- 1 = Somewhat slow and clumsy, but no help needed.
- 2 = Can turn alone or adjust sheets, but with great difficulty.
- 3 = Can initiate, but not turn or adjust sheets alone.
- 4 = Helpless.

13. Falling (unrelated to freezing)

- 0 = None.
- 1 = Rare falling.
- 2 = Occasionally falls, less than once per day.
- 3 = Falls an average of once daily.
- 4 = Falls more than once daily.

14. Freezing when walking

- 0 = None.
- 1 = Rare freezing when walking; may have starthesitation.
- 2 = Occasional freezing when walking.
- 3 = Frequent freezing. Occasionally falls from freezing.
- 4 = Frequent falls from freezing.

15. Walking

- 0 = Normal.
- 1 = Mild difficulty. May not swing arms or may tend to drag leg.
- 2 = Moderate difficulty, but requires little or no assistance.
- 3 = Severe disturbance of walking, requiring assistance.
- 4 = Cannot walk at all, even with assistance.

16. Tremor (Symptomatic complaint of tremor in any part of body.)

- 0 = Absent.
- 1 = Slight and infrequently present.
- 2 = Moderate; bothersome to patient.
- 3 = Severe; interferes with many activities.
- 4 = Marked; interferes with most activities.

17. Sensory complaints related to parkinsonism

- 0 = None.
- 1 = Occasionally has numbness, tingling, or mild aching.
- 2 = Frequently has numbness, tingling, or aching; not distressing.
- 3 = Frequent painful sensations.
- 4 = Excruciating pain.

III. MOTOR EXAMINATION**18. Speech**

- 0 = Normal.
- 1 = Slight loss of expression, diction and/or volume.
- 2 = Monotone, slurred but understandable; moderately impaired.
- 3 = Marked impairment, difficult to understand.
- 4 = Unintelligible.

19. Facial Expression

- 0 = Normal.
- 1 = Minimal hypomimia, could be normal "Poker Face".
- 2 = Slight but definitely abnormal diminution of facial expression
- 3 = Moderate hypomimia; lips parted some of the time.
- 4 = Masked or fixed facies with severe or complete loss of facial expression; lips parted 1/4 inch or more.

20. Tremor at rest (head, upper and lower extremities)

0 = Absent.

1 = Slight and infrequently present.

2 = Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present.

3 = Moderate in amplitude and present most of the time.

4 = Marked in amplitude and present most of the time.

21. Action or Postural Tremor of hands

0 = Absent.

1 = Slight; present with action.

2 = Moderate in amplitude, present with action.

3 = Moderate in amplitude with posture holding as well as action.

4 = Marked in amplitude; interferes with feeding.

22. Rigidity (Judged on passive movement of major joints with patient relaxed in sitting position. Cogwheeling to be ignored.)

0 = Absent.

1 = Slight or detectable only when activated by mirror or other movements.

2 = Mild to moderate.

3 = Marked, but full range of motion easily achieved.

4 = Severe, range of motion achieved with difficulty.

23. Finger Taps (Patient taps thumb with index finger in rapid succession:)

0 = Normal.

1 = Mild slowing and/or reduction in amplitude.

2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.

3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.

4 = Can barely perform the task.

24. Hand Movements (Patient opens and closes hands in rapid succession.)

0 = Normal.

1 = Mild slowing and/or reduction in amplitude.

2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.

3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.

4 = Can barely perform the task.

25. Rapid Alternating Movements of Hands (Pronation-supination movements of hands, vertically and horizontally, with as large an amplitude as possible, both hands simultaneously.)

0 = Normal.

1 = Mild slowing and/or reduction in amplitude.

2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.

3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.

4 = Can barely perform the task.

26. Leg Agility (Patient taps heel on the ground in rapid succession picking up entire leg. Amplitude should be at least 3 inches.)

0 = Normal.

1 = Mild slowing and/or reduction in amplitude.

2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.

3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.

4 = Can barely perform the task.

27. Arising from Chair (Patient attempts to rise from a straightbacked chair, with arms folded across chest.)

0 = Normal.

1 = Slow; or may need more than one attempt.

2 = Pushes self up from arms of seat.

3 = Tends to fall back and may have to try more than one time, but can get up without help.

4 = Unable to arise without help.

28. Posture

0 = Normal erect.

1 = Not quite erect, slightly stooped posture; could be normal for older person.

2 = Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.

3 = Severely stooped posture with kyphosis; can be moderately leaning to one side.

4 = Marked flexion with extreme abnormality of posture.

29. Gait

0 = Normal.

1 = Walks slowly, may shuffle with short steps, but no festination (hastening steps) or propulsion.

2 = Walks with difficulty, but requires little or no assistance; may have some festination, short steps, or propulsion.

3 = Severe disturbance of gait, requiring assistance.

4 = Cannot walk at all, even with assistance.

30. Postural Stability (Response to sudden, strong posterior displacement produced by pull on shoulders while patient erect with eyes open and feet slightly apart. Patient is prepared.)

0 = Normal.

1 = Retropulsion, but recovers unaided.

2 = Absence of postural response; would fall if not caught by examiner.

3 = Very unstable, tends to lose balance spontaneously.

4 = Unable to stand without assistance.

31. Body Bradykinesia and Hypokinesia (Combining slowness, hesitancy, decreased armswing, small amplitude, and poverty of movement in general.)

0 = None.

1 = Minimal slowness, giving movement a deliberate character; could be normal for some persons. Possibly reduced amplitude.

2 = Mild degree of slowness and poverty of movement which is definitely abnormal. Alternatively, some reduced amplitude.

3 = Moderate slowness, poverty or small amplitude of movement.

4 = Marked slowness, poverty or small amplitude of movement.

IV. COMPLICATIONS OF THERAPY (In the past week)

A. DYSKINESIAS

32. Duration: What proportion of the waking day are dyskinesias present? (Historical information.)

0 = None

1 = 1-25% of day.

2 = 26-50% of day.

3 = 51-75% of day.

4 = 76-100% of day.

33. Disability: How disabling are the dyskinesias? (Historical information; may be modified by office examination.)

0 = Not disabling.

1 = Mildly disabling.

2 = Moderately disabling.

3 = Severely disabling.

4 = Completely disabled.

34. Painful Dyskinesias: How painful are the dyskinesias?

0 = No painful dyskinesias.

1 = Slight.

2 = Moderate.

3 = Severe.

4 = Marked.

35. Presence of Early Morning Dystonia (Historical information.)

0 = No

1 = Yes

B. CLINICAL FLUCTUATIONS

36. Are "off" periods predictable?

0 = No

1 = Yes

37. Are "off" periods unpredictable?

0 = No

1 = Yes

38. Do "off" periods come on suddenly, within a few seconds?

0 = No

1 = Yes

39. What proportion of the waking day is the patient "off" on average?

0 = None

1 = 1-25% of day.

2 = 26-50% of day.

3 = 51-75% of day.

4 = 76-100% of day.

C. OTHER COMPLICATIONS

40. Does the patient have anorexia, nausea, or vomiting?

0 = No

1 = Yes

41. Any sleep disturbances, such as insomnia or hypersomnolence?

0 = No

1 = Yes

42. Does the patient have symptomatic orthostasis?

(Record the patient's blood pressure, height and weight on the scoring form)

0 = No

1 = Yes

V. MODIFIED HOEHN AND YAHR STAGING

STAGE 0 = No signs of disease.

STAGE 1 = Unilateral disease.

STAGE 1.5 = Unilateral plus axial involvement.

STAGE 2 = Bilateral disease, without impairment of balance.

STAGE 2.5 = Mild bilateral disease, with recovery on pull test.

STAGE 3 = Mild to moderate bilateral disease; some postural instability; physically independent.

STAGE 4 = Severe disability; still able to walk or stand unassisted.

STAGE 5 = Wheelchair bound or bedridden unless aided.

VI. SCHWAB AND ENGLAND ACTIVITIES OF DAILY LIVING SCALE

100% = Completely independent. Able to do all chores without slowness, difficulty or impairment. Essentially normal. Unaware of any difficulty.

90% = Completely independent. Able to do all chores with some degree of slowness, difficulty and impairment. Might take twice as long. Beginning to be aware of difficulty.

80% = Completely independent in most chores. Takes twice as long. Conscious of difficulty and slowness.

70% = Not completely independent. More difficulty with some chores. Three to four times as long in some. Must spend a large part of the day with chores.

60% = Some dependency. Can do most chores, but exceedingly slowly and with much effort. Errors; some impossible.

50% = More dependent. Help with half, slower, etc. Difficulty with everything.

40% = Very dependent. Can assist with all chores, but few alone.

30% = With effort, now and then does a few chores alone or begins alone. Much help needed.

20% = Nothing alone. Can be a slight help with some chores. Severe invalid.

10% = Totally dependent, helpless. Complete invalid.

0% = Vegetative functions such as swallowing, bladder and bowel functions are not functioning. Bedridden.