THE INFLUENCE OF DRUG-INDUCED DYSKINESIAS ON MANUAL TRACKING IN PARKINSON’S DISEASE

by

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Abstract

The influence of peak-dose drug-induced dyskinesia (DID) on manual tracking (MT) was examined in 10 dyskinetic patients (DPD), and compared to 10 age/gender-matched non-dyskinetic patients (NDPD) and 10 healthy controls. Whole body movement (WBM) and MT were recorded with a 6-degrees of freedom magnetic motion tracker and forearm rotation sensors, respectively. Subjects were asked to match the length of a computer-generated line with a line controlled via wrist rotation. Results show that DPD patients had greater WBM displacement and velocity than other groups. All groups displayed increased WBM from rest to MT, but only DPD and NDPD patients demonstrated a significant increase in WBM displacement and velocity. In addition, DPD patients exhibited excessive increase in WBM suggesting overflow DID. When two distinct target pace segments were examined (FAST/SLOW), all groups had slight increases in WBM displacement and velocity from SLOW to FAST, but only DPD patients showed significantly increased WBM displacement and velocity from SLOW to FAST. Therefore, it can be suggested that overflow DID was further increased with increased task speed. DPD patients also showed significantly greater ERROR matching target velocity, but no significant difference in ERROR in displacement, indicating that significantly greater WBM displacement in the DPD group did not have a direct influence on tracking performance. Individual target and performance traces demonstrated this relatively good tracking performance with the exception of distinct deviations from the target trace that occurred suddenly, followed by quick returns to the target coherent in time with increased performance velocity. In addition, performance hand velocity was not correlated with WBM velocity in DPD patients, suggesting that increased ERROR in velocity was not a direct result of WBM velocity. In conclusion, we propose that over-excitation of motor cortical areas, reported to be present in DPD patients, resulted in overflow DID during voluntary movement. Furthermore, we propose that the increased ERROR in velocity was the result of hypermetric voluntary movements also originating from the over-excitation of motor cortical areas.
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Abbreviations

BG: Basal Ganglia  
CoM: Center of Mass  
COMT inhibitor: Cathecol-O-methyl transferase inhibitor  
DBS: Deep Brain Stimulation  
DA: Dopamine  
DID: Drug-Induced dyskinesias  
DPD: Dyskinetic Parkinson’s disease patients  
FoB: Flock of Birds  
GABA: Gamma-amino-butyric-acid  
GPe: GPe  
GPI: Globus pallidus internus  
L-dopa: Levadopa  
MAOB: monoamine oxidase B  
MT: Manual Tracking  
MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine  
NDPD: Non-dyskinetic Parkinson’s disease patients  
PD: Parkinson’s disease  
PPN: Pedunculopontine nucleus  
SNC: Substantia nigra pars compacta  
STN: Subthalamic Nucleus  
UPDRS: Unified Parkinson’s Disease Rating Scale  
VA/VL: Ventral anterior/ ventrolateral thalamus  
WBM: Whole body movement
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INTRODUCTION

Presently, nearly 100,000 Canadians have been diagnosed with Parkinson's disease (PD) (Statistics Canada, 2005). Parkinson's disease is a progressive neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta (SNc), located within the basal ganglia (Ehringer and Hornykiewicz, 1960). Parkinson's disease is classified as a movement disorder with resting tremor, akinesia, bradykinesia, rigidity, and postural instability presenting as the cardinal symptoms. Although genetic and environmental factors have been linked to the development of Parkinson's disease, there is still no known cause, and subsequently no known cure. There are however, a myriad of treatment options available to alleviate the symptoms. Currently the gold standard treatment option is L-3-4-dihydroxyphenylalanine a precursor to dopamine, commonly referred to as Levodopa (L-dopa), in combination with peripheral dopa decarboxylase inhibitor (Carbidopa), which is employed to increase the availability of dopamine. While L-dopa can be effective in decreasing symptoms in some patients, there are subsequent motor complications associated with its long-term use. One of the most common motor complications has been described as drug-induced dyskinesia (DID) (Filion, 2001; Obeso et al. 2000a). Cotzias et al. (1967) first noted drug-induced dyskinesia while observing Parkinson's disease patients who demonstrated positive benefits from L-Dopa; recording that after initiating the drug approximately 10% of patients per year developed drug-induced dyskinesia. More recent research has revealed that the majority of Parkinson's disease patients develop dyskinesia after 5 –10 years of
treatment (Rascol et al. 2000), with more than 80% of Parkinson’s disease patients experiencing these involuntary motor fluctuations after 10 years (Bass, 2000). The longer the duration of drug therapy, the more frequent and severe dyskinesias become. This increase in frequency and severity limits clinicians’ ability to provide satisfactory control of symptoms.

According to Statistics Canada, the size of the nation’s elderly population is growing. In the next 25 years approximately 9 million people (the entire baby boom generation) will be at least 65 years old. With 85% of those diagnosed with Parkinson’s disease being over the age of 65, this population increase may cause a similar increase in the number of individuals with Parkinson’s disease (Tanner & Goldman 1996). Furthermore, Canadian seniors are living longer than ever before; as a consequence of this increased longevity and increased drug effectiveness, patients will live longer with Parkinson’s disease, increasing the duration of L-dopa therapy, therefore increasing the number of patients that will experience drug-induced dyskinesia during the course of the disease.

Although the pathophysiology, prevalence, incidence, and risk factors associated with dyskinesia have been investigated at length, there is little research describing the movement characteristics of dyskinesia in Parkinson’s disease. However, due to the growing number of individuals who will be diagnosed with Parkinson’s disease and who will experience dyskinesia as a result of a decrease in mortality, an ageing baby boomer population and the increased effectiveness of medications, a better understanding of the full
impact of dyskinesia on voluntary movement is essential. Quantification of drug-induced dyskinesias during voluntary movement will create a deeper understanding of the role of the basal ganglia and motor systems. This understanding may directly affect patient care, contributing to the development of better and more efficient use of medication and ultimately improving the quality of life for the growing number of individuals who will be living with the disease. Therefore, the purpose of the current study was to quantify the effect drug-induced dyskinesia on the performance of a voluntary task.

REVIEW OF LITERATURE

1 Parkinson’s Disease (PD)

Before investigating drug-induced dyskinesias, an overview of the risk factors, aetiology, and symptoms of Parkinson’s disease, as well as normal basal ganglia pathology and dysfunction will be provided.

The cardinal pathological feature of Parkinson’s disease is degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNC) (Kish et al. 1988). Currently, there is no way to stop the loss of nerve cells that produce dopamine or to restore those that have already been lost. Drug treatment such as dopamine, dopamine agonists, anticholinergics, catechol-O-methyltransferase (COMT) and monoamine oxidase B (MAOB) inhibitors as well as surgery can, however, have been engineered in order to help manage the slow decline in motor function.
Parkinson’s disease, which is prevalent in approximately 1% of the population, has a mean age at onset of 55 years (Bedard et al. 1999). Although the risk of developing Parkinson’s disease increases with age, symptoms may appear at any age. Approximately 10% of Parkinson’s disease patients experience the onset of symptoms before 40 years of age (Koller & Lang 1987).

1.1 Aetiology

Although there have been considerable advancements in the knowledge of Parkinson’s disease, the aetiology of the disease remains unknown. While no single factor has been conclusively attributed to its cause, several findings give credibility to the idea that specified environmental agents paired with genetic predisposition may trigger the death of dopaminergic neurons in the substantia nigra. Epidemiological studies indicate that a number of factors both hereditary and environmental may be responsible for an increased risk (Hubble 1993).

1.1.1 Environmental

Exposure to well water (Tanner & Langston 1990; Priyadarshi et al. 2001; Rajput et al. 1986), herbicides and pesticides (Ho et al. 1989; Koler et al. 1990; Lewin 1985; Priyadarshi et al. 2001; Shoenber 1987), proximity to industry (Tanner 1986; Tanner et al. 1989), and living in rural environments (Ho et al. 1989; Schoenber 1987), have each been indicated as possible occupational and environmental risk factors linked to Parkinson’s disease. Some toxins have also been associated with the development of the disease, including trace metals, cyanide, lacquer thinner, organic solvents, carbon
monoxide, and carbon disulfide (Lai et al. 2001). No specific toxins have been found in the brains of Parkinson’s disease patients (Olanow & Tatton 1999). Compelling evidence has been recorded in studies of drug addicts who developed a syndrome that closely resembled Parkinson’s disease, both in its clinical characteristics and in its pathology after the ingestion of 1,2,3,6-methyl-phenyl tetrahydropyridine (MPTP) (Langston et al. 1983). Although this discovery strengthens the possibility that there may be environmental factors that are associated with the development of Parkinson’s disease, to date no substance like MPTP has been found within the brains of Parkinson’s disease patients (Olanow & Tatton 1999).

1.1.2 Genetic

In addition to environmental factors, an autosomal dominant pattern of inheritance has also been recorded in approximately 5-10% of Parkinson’s disease patients with a familial form of Parkinson’s disease (Lu et al. 2001). Support for a genetic factor has also been documented in several studies where the incidence has been recorded to be greater in family members than in age-matched controls (Wood 1998). Several genes have also been associated with an increased risk of Parkinson’s disease, however gene mutations can generally only explain a minute number of cases (Olanow & Tatton 1999). Most likely it is a combination of both genetic and environmental factors which predispose patients to develop Parkinson’s disease. Oxidant stress, mitochondrial dysfunction, excitotoxicity, and glia inflammatory processes are also thought to contribute to the degeneration of dopaminergic neurons (Olanow & Tatton 1999). It is believed that the result of these events is the induction of apoptosis in nigral dopaminergic neurons (Hubble, 1993).
1.2 Basal Ganglia Physiology

Models of the basal ganglia have been devised to help basal ganglia function in Parkinson's disease. In order to gain a comprehensive understanding of the development of drug-induced dyskinesias in Parkinson's disease, it is essential to review the role of the basal ganglia in movement.

The basal ganglia is generally regarded as being comprised of several nuclei, the striatum (the caudate nucleus and putamen), the globus pallidus internal (globus pallidus internus) and external (Globus pallidus externus) segments, subthalamic nuclei (STN), substantia nigra pars reticulata (SNr) and pars compacta (SNC), as well as the pedunculopontine nucleus (PPN) (Albin et al. 1989). The thalamus plays an important role in basal ganglia circuitry as the relay nuclei, but is not formally considered one of the basal ganglia nuclei. Sensorimotor, cognitive and limbic-related information flows from the frontal lobe through the basal ganglia nuclei via five pathways in parallel loops: the motor loop, the oculomotor loop, the limbic loop, and two prefrontal loops (Alexander et al. 1990). The loop with which investigators of Parkinson's disease are most concerned is the motor loop. It is known to be responsible for planning and learning movements. The motor loop begins in the primary sensory cortical, the primary motor, the supplementary motor, and the premotor areas, which have projections to the striatum, specifically the putamen, the input nuclei of the basal ganglia. The output nuclei of the basal ganglia are the globus pallidus internus and substantia nigra pars reticulate (SNr), which target the ventral lateral (VL) and ventral anterior (VA) thalamus. The thalamus in turn projects information back to
the cortex, and then to the brainstem and spinal cord (Fig. 1) (Albin et al. 1989; Alexander et al. 1990).

**Fig. 1 Model of the Basal Ganglia.** This figure outlines the current model of the basal ganglia. The motor loop begins in the primary sensory cortical, the primary motor, the supplementary motor, and the premotor areas, which have projections to the striatum, the input nuclei of the basal ganglia. The output nuclei of the basal ganglia are the Globus pallidus internus and SNr, which target the ventral lateral (VL) and ventral anterior (VA) thalamus. The thalamus in turn projects information back to the cortex, and then to the brainstem and spinal cord.
1.2.1  *Direct and Indirect Pathways*

The motor loop of the basal ganglia has been described in reference to two major pathways, the direct and indirect pathways. Activation of the direct pathway facilitates desired movement via increased thalamocortical activity (Fig 2a). The direct pathway begins in the striatum with inhibitory gabaergic projections, specifically from the putamen, to the motor regions of the Globus pallidus internus and the SNr (Wichmann & DeLong 1993). The Globus pallidus internus then has inhibitory gabaergic projections to the thalamus, the output nuclei of the basal ganglia. Disinhibition of the thalamus results in increased excitatory glutamatergic projections to the motor cortex (Bolam et al. 2000).

Activation of the indirect pathway inhibits undesired movement via decreased thalamocortical activity (Fig 2b). The indirect pathway also begins in the striatum, where inhibitory gabaergic neurons project to the globus pallidus externus. The Globus pallidus externus in turn has inhibitory gabaergic projections to the subthalamic nucleus (DeLong, 1990). The subthalamic nucleus in turn excites the Globus pallidus internus/SNr and Pedunculopontine nucleus (PPN) via glutamatergic projections (Brotchie, 2000). Excitation of the Globus pallidus internus results in inhibitory gabaergic projections to the thalamus. Inhibition of the thalamus decreases excitatory glutamatergic projections to the motor cortex.
Fig 2. Direct and Indirect Pathways The direct pathway (a), begins in the striatum, specifically from the putamen, which has Gabaergic projections to the motor regions of the Globus pallidus internus and the SNr. The Globus pallidus internus then has inhibitory gabaergic projections to the thalamus, the output nuclei of the basal ganglia. The indirect pathway (b), also begins in the striatum, where inhibitory gabaergic neurons project to the globus pallidus externus. The globus pallidus externus in turn has inhibitory gabaergic projections to the subthalamic nucleus where glutamatergic projections then excite the globus pallidus internus/SNr and Pedunculopontine nucleus (PPN). Excitation of the globus pallidus internus results in inhibitory gabaergic projections to the thalamus. Inhibition of the thalamus decreases excitatory glutamatergic projections to the motor cortex.

1.2.2 Role of Dopamine

Dopamine, which is associated with reward-driven learning, functions to execute operant tasks, where rewards are contingent upon movement outcome (Gillies & Arbuthnott 2000). In the motor loop of the basal ganglia, striatal responses to incoming glutamatergic projections from the cortex are mediated by dopamine transmission from the SNc (Gerfen, 1990). The striatum has a heterogeneous organization of dopamine receptors,
with both D1 and D2 receptors situated throughout. Both the direct and indirect pathways arise from these different cellular populations in the striatum, specifically the putamen. The action of dopamine is different depending on the receptors to which it binds. Although striatal projection neurons are GABAergic in both the indirect and direct pathways, binding to D2 receptors in the indirect pathway induces suppression of neuronal activity, whereas binding to D1 receptors in the direct pathway induces facilitation of neuronal activity (Brotchie, 1998).

1.3 Basal Ganglia in Parkinson’s Disease

In idiopathic Parkinson’s disease, the loss of nigrostriatal dopaminergic input to the striatum results in a disinhibition of the output nuclei (globus pallidus internus and SNr) and an increased inhibition of the thalamocortical projection, which leads to a reduction or absence of movement (bradykinesia or akinesia) (Albin et al. 1989; DeLong, 1990).

1.3.1 Impact of Lack of DA on the Direct and Indirect Pathways

The degeneration of dopaminergic neurons causes an imbalance between the direct and indirect pathways. In the direct pathway, the lack of dopamine projected onto excitatory D1 receptors in the striatum results in disinhibition of the globus pallidus internus, which in turn results in increased inhibition of the thalamus and decreased excitation of the motor cortex (Obeso et al. 2000b; DeLong, 1990). In the indirect pathway, the lack of dopaminergic projections onto inhibitory D2 dopamine receptors in the striatum, results in an increased inhibition of the globus pallidus externus, and thus disinhibiting the subthalamic nucleus. The disinhibition of the subthalamic nucleus results in an increased
excitation of the globus pallidus internus, and the same increased inhibition of the thalamus as seen in the direct pathway (DeLong, 1990). The net result is an overall decrease in the excitation of the motor cortex, (Fig. 3).

Fig. 3 Model of the Basal Ganglia in Parkinson’s Disease In the direct pathway, lack of dopamine projected onto excitatory D1 receptors in the striatum causes disinhibition of the globus pallidus internus, which in turn results in increased inhibition of the thalamus and decreased excitation of the motor cortex. In the indirect pathway, lack of dopaminergic projections onto inhibitory D2 dopamine receptors in the striatum, results in an increased inhibition of the globus pallidus externus, and thus disinhibiting the ST, resulting in an increased excitation of the globus pallidus internus, and the same increased inhibition of the thalamus as seen in the direct pathway. The net result is an overall decrease in the excitation of the motor cortex.
Although the current model of the basal ganglia gives insight into the mechanisms of Parkinson’s disease it is still incomplete. It does not account for why symptoms present differently in some patients, or the spectrum of responses to L-dopa and other therapies (Obeso et al. 2000a). Of particular importance to the present study, the model does not account for the development of dyskinesias in some patients and not others.

1.4 Motor Symptoms

Parkinson’s disease is clinically characterized by slowness of movement (bradykinesia), the inability to initiate movement (akinesia), muscular rigidity, resting tremor, and postural instability (Lang & Lazano 1998).

1.4.1 Akinesia

The term akinesia is used clinically to describe the inability to initiate movement. It has been hypothesized that akinesia is a result of the abnormal thalamocortical activation that occurs in Parkinson’s disease patients with the progressive loss of dopaminergic neurons in the substantia nigra pars compacta, and can be confirmed by findings that antidopaminergic drugs can induce akinesia, and dopaminergic drugs have a powerful effect of reducing akinesia (Wichmann & DeLong 1993).

1.4.2 Rigidity

Rigidity in Parkinson’s disease is clinically defined as the inability to fully relax or to completely stretch ones muscles. Exaggerated long-latency reflex or decreased lb
inhibition of the spinal reflex network has been suggested to underlie rigidity (Tatton & Lee 1975).

1.4.3 *Tremor*

The central oscillators for parkinsonian tremor have been localized in the basal ganglia circuit, and possibly the cerebellar-thalamic system (Pare et al. 1990, Duval et al 2001). Changes in the firing pattern within the basal ganglia, thalamus, and possibly the cerebellum may modify the cortico-spinal activity.

1.4.4 *Bradykinesia*

Bradykinesia is the cardinal feature of Parkinson’s disease. The slowness of movement is overtly evident, and is quite possibly one of the most systematically present symptoms in Parkinson’s disease. Bradykinesia has been suggested to result from increased activity and altered firing patterns of the output nuclei of the basal ganglia (Bergman & Duelsch 2002). It is hypothesized that increased tonic inhibition of thalamocortical neurons reduces the responsiveness of cortical mechanisms (Berardelli et al. 2001). Bradykinesia is strongly associated with velocity generation and movement accuracy. Patients have been reported to experience difficulty generating adequate agonist activity during rapid limb movement, and perform movements with larger amplitude and lower velocities than controls (Flowers, 1976; Hallett & Knoshbin 1980; Baroni, 1984; Berardeli et al. 1986; Whichman & DeLong 1993).
1.5 Treatments

Although there are hypotheses about the aetiology of Parkinson’s disease and the dysfunction of the basal ganglia in Parkinson’s disease has been modeled, there is still no cure for Parkinson’s disease. There are, however, treatments centered on the administration of medication to relieve the previously mentioned motor symptoms. Medication selection and dosage are tailored to each patient. Factors such as severity of symptoms, age, and presence of other medical conditions are considered when determining the appropriate drug therapy. As Parkinson’s disease progresses, physicians are required to modify drug doses and constantly change medication regimens, usually requiring the administration of a combination of drugs.

1.5.1 Levodopa (L-dopa)

Medical administration of dopamine itself is ineffective since it is unable to cross the blood brain barrier. L-dopa, a metabolic precursor of dopamine, which does enter the brain via the bloodstream, is thus used in the treatment of Parkinson’s disease. Levodopa (L-dopa) has been established as one of the most effective antiparkinsonian agents, documented by several landmark clinical studies (Birkmayer & Hornykiewicz 1961; Cotzias et al 1967; Muenter & Tyce 1971). The plasma half-life of L-dopa, influenced mostly by distribution in tissues such as skeletal muscle, usually ranges from 1-2 hours; therefore much of L-dopa is metabolized before it reaches the brain, with less than 5% - 8% of an oral dose being delivered (Nutt et al. 1984).
Once produced, L-dopa does not accumulate because it is rapidly converted to dopamine by L-amino acid decarboxylase (L-AAD). If L-dopa is not administered with an inhibitor (L-AAAD or catechol-O-methyltransferase COMT), a large proportion of each oral dose will be diverted to the products of those enzymes (Chase, 1998). Therefore L-dopa and dopa-decarboxylase combined are the gold standard of treatment for Parkinson’s disease. Use of inhibitors, such as carbidopa, permit an approximately four-fold reduction of L-dopa doses needed for optimal control of Parkinson’s disease symptoms (Nutt et al. 1985). Tracking studies employed to determine the effectiveness of L-dopa have noted increased velocity and initial agonist EMG burst of velocity of self paced movements after L-dopa administration (Johnson et al. 1996).

1.5.2 COMT (catechol-O-methyl transferase) Inhibitors

COMT Inhibitors enhance L-dopa therapy by inhibiting the COMT enzyme, which metabolizes L-dopa before it reaches the brain. They are only effective when used with L-dopa, and prolong the duration of the L-dopa response about 1.7 times, while not increasing the peak plasma level of L-dopa (Kurth & Adler 1998). It has been recorded that COMT inhibitors reduce ‘off’ time, and increase ‘on’ time similar to dopamine agonists and greatly reduce motor fluctuations (Hely et al. 2000).

1.5.3 MAOB Inhibitors

Dopamine is also oxidized in the synaptic cleft by monoamine oxidase B (MAO-B). MAO-inhibitors also increase the amount of available dopamine in the brain, enhancing the effects of L-dopa (Lang & Lee 2002).
1.5.4 Dopamine Agonists

Although L-dopa has had many years of clinical success and is the gold standard treatment, dopamine agonists also mimic dopamine’s function in the brain, and are used primarily as adjuncts to L-dopa/carbidopa therapy.

1.5.5 Anticholinergics

Anticholinergics are able to reduce the over activity of the neurotransmitter acetylcholine to balance diminished dopamine. They are most effective in the control of tremor, and are used in addition to L-dopa (Cooper et al. 1992).

1.5.6 Surgery

Due to the shortfalls of current medications, technical improvements in neurosurgical techniques and devices have increased the safety and accuracy of surgery, however only about 10% of Parkinson’s patients are estimated to be suitable candidates for surgery. Patients who have had no response to, or responded very poorly to L-dopa/carbidopa are not good candidates for surgical interventions (Obeso et al. 1999). Accepted surgical procedures for the treatment of Parkinson’s disease include ablative surgery, or deep brain stimulation (DBS), and transplantation or restorative surgery.

2 Drug-Induced Dyskinesias (DID)

Although L-Dopa is the most effective treatment for the symptomatic relief of Parkinson’s disease, as the disease progresses the effectiveness of L-dopa becomes limited, resulting in narrowing of its therapeutic window (Linder et al. 1996). L-dopa has a
"honeymoon" period, between 3-5 years, in which patients experience maximum symptomatic relief. Subsequent wearing off necessitates drug ingestion at shorter time intervals with increased doses and the development of motor fluctuations, on-off phenomenon, and peak-dose drug-induced dyskinesias (Chase et al. 1994; Bravi et al. 1994; Koller, 1996). Motor fluctuations become evident through the time course of a single dose.

2.1 Risk Factors and Frequency of Drug-induced Dyskinesias

Drug-induced dyskinesias generally occur in patients who have good therapeutic response to L-dopa, and appear sooner and more severely on the side most affected by Parkinson’s disease (Grandas at al, 1999). Risk factors are generally associated with L-dopa treatment and patient category, such as length of treatment and disease stage, gender, duration of disease, daily dose of L-dopa, and most importantly for this study, age at onset of Parkinson’s disease.

The risk of developing dyskinesias increases for patients in more advanced stages of the disease, with H&Y stage III patients developing dyskinesias significantly earlier than those patients whose onset of L-dopa therapy commenced in stages I and II of Parkinson’s disease (Kostic et al. 2002). The amount of L-dopa administered daily is also a factor that increases the risk; the higher the dose the more dyskinetic the patient (Rascol & Fabre 2001). The use of dopamine agonists as an initial treatment are reported to reduce the risk of drug-induced dyskinesias, with patients who begin therapy with a dopamine agonist less likely to develop dyskinesias as early as patients who begin treatment with L-dopa (Rascol
& Fabre 2001). Grandas et al 1999, report age at onset and initial dose of L-dopa as the major independent predictors for the development of drug-induced dyskinesia.

2.2 Classification of Drug-Induced Dyskinesias

In order to quantify dyskinesias during voluntary movement it is essential to understand the different types of dyskinetic movements.

2.2.1 Choreic Type

Choreic movement is the most common form of drug-induced dyskinesias. Chorea refers to the involuntary movements that flow from one body part to another, and are movements considered to be purposeless, non-rhythmic, abrupt, rapid, irregular, and unsustained (Fahn, 2000). The characteristic feature of chorea is that the movements are considered to be random. Choreic movements can also be classified as overflow dyskinesia; drug-induced dyskinesias that generally occurs in inactive body segments while patients are performing voluntary movements. Overflow dyskinesia is not generally observable at rest (Fahn, 2000). Reasons for the increase in severity of dyskinesias during motor tasks is unknown, but it has been observed that stress may increase abnormal movements such as resting parkinsonian tremor, focal and generalized dystonia, and chorea (Durif, 1999). The influence of stress, however, is not necessarily the primary cause. Attentional processes, known to be under the influence of limbic structures projecting to basal ganglia, may play a role in the aggravation of drug-induced dyskinesias (Fahn, 2000). Another hypothesis is that the activation of the cortical motor areas during motor tasks could be excessive in patients with dyskinesia (Durif, 1999).
Supporting results have been recently reported during motor tasks where a significant over-activation of the supplementary and primary motor cortical areas have been recorded in patients with dyskinesia when compared with patients without dyskinesia and control subjects (Rascol et al. 1998).

2.2.2 Dystonia

Dystonia is the second most common form of drug-induced dyskinesia, peak dose dystonia is characterized by sustained muscle contractions commonly present in muscles such as those of the arm or leg, in the trapezius, and in facial muscles (Ilson et al. 1984; Fahn 2000). Another particular manifestation of dystonia, “off” dystonia, is commonly observed in the foot in early morning when patients are “off”, but can also occur during the day and are long lasting and very often exceedingly painful (Ilson et al. 1984; Fahn 2000).

2.2.3 Ballism

Ballism, exceptionally large amplitude choreic movements that occur in the proximal section of the limbs is another form of drug-induced dyskinesia (Vidailhet et al. 1999). Although ballism is not commonly observed in Parkinson’s disease patients with dyskinesia, when present it has been noted to be both unilateral on the side most affected by Parkinson’s disease, and appears bilaterally in patients with more severe Parkinson’s disease affecting the entire body (Fahn, 2000).
2.2.4 **Myoclonus**

Drug-induced dyskinesias can also present in the form of myoclonus, characterized as abrupt, momentary, shock-like movements occurring as single, unilateral or bilateral, jerks in the limbs (Klawans et al. 1975). This manifestation of dyskinesia is usually due to an overdose of levodopa, and generally occurs while patients are sleeping, but can also occur during the day (Fahn, 2000). These manifestations of dyskinesia can be classified into, off-period dystonia, bi-phasic drug-induced dyskinesia, and peak-dose drug-induced dyskinesia. Off-period dystonias are painful involuntary movements involving the foot and lower limbs, and are associated with low L-dopa plasma levels in the morning or at the end of doses during the day (Rascol et al. 2001).

On-period drug-induced dyskinesia, such as peak-dose dyskinesia, are characterized by the onset of involuntary movements occurring during the time period in which the L-dopa medication is most effective. These dyskinesias are primarily choreic, usually involving the upper limbs more than the lower limbs, face and trunk (Cubo et al. 2001). Choreic movements accompanied by akathisia or jerking movements have also been observed and are considered to be bi-phasic dyskinesia, occurring during the stages when dopamine levels rise and fall. However, the occurrence of bi-phasic dyskinesia is very rare (Baas, 2000).

2.3 **Possible Neural Mechanisms Responsible for Drug-Induced Dyskinesia**

Although the pathophysiology of drug-induced dyskinesia is not yet fully understood, the current models of the basal ganglia in the functional state and with
degeneration associated with Parkinson’s disease, give a comprehensive view of the neural mechanisms that may be altered. The current model of the basal ganglia with drug-induced dyskinesia suggests that increased inhibition of the globus pallidus internus results in decreased inhibitory influence of the globus pallidus internus on the VL thalamus, which in turn causes increased excitation of the motor cortex, (Fig. 4) (DeLong, 1990; Crossman, 1987, Wichman & DeLong 1996). Support for this model has been presented in studies wherein dyskinesias were induced in MPTP-treated monkeys via excitotoxic lesions of the subthalamic nucleus, disinhibition of the globus pallidus externus by GABA antagonist bicuculine, and inhibition of the subthalamic nucleus or globus pallidus internus with GABA agonist musimol (Hamada & DeLong 1992; Matsumura et al 1995; Burbaud et al 1998). Apomorphine infusions have also been reported to induce dyskinesia associated with decreased firing rate in the globus pallidus internus in both MPTP-treated monkeys and Parkinson’s patients (Filion et al 1991; Merello et al 1999; Hutchinson et al 1997; Lozano et al 2000).
Fig. 4 Model of the Basal Ganglia in Parkinson’s disease with Drug-Induced Dyskinesia

Increased inhibition of the globus pallidus internus results in decreased inhibitory influence of the globus pallidus internus on the VL thalamus, which in turn causes increased excitation of the motor cortex.

This simplistic explanation of the altered neurological mechanisms responsible for the development of dyskinesia does not expose the complexity of the changes that may occur with L-dopa therapy. It has been hypothesized that the appearance of dyskinesia is due to a combination of the extent of the loss of dopaminergic neurons in the substantia nigra and L-Dopa treatment (Jenner, 2000). Evidence for the occurrence of dyskinesia due
to the loss of dopamine neurons in the substantia nigra pars compacta has been recorded in animal studies, linking the degree of loss of dopamine neurons to the development of dyskinesia (Schneider & Yuwiler 1989; Voyce et al. 1990). In MPTP treated animals, the appearance of dyskinesia usually require daily doses lasting for a period of several months (Calon, 2000). For instance, in the MPTP monkey model, drug-induced dyskinesia appear after doses of between 50 – 100 mg administered daily for several weeks (Bedard, et al. 1986). The long-term development of dyskinesia after L-dopa therapy has also been recorded to be very rapid in MPTP-exposed drug addicts (Bellard, 1985), further strengthening the previous association between nigral pathology and the development of dyskinesia found in MPTP treated monkeys. Studies, however, involving Parkinson’s patients have shown a 17% reduction in the duration of L-dopa dose motor benefits after three years on the drug (Hughes et al. 2001). Due to the lesser extent of dopamine neuron loss in Parkinson’s patients than in MPTP monkeys and drug addicts, the assumption is that the more severe the nigral pathology the lower the dose of L-dopa required to induce dyskinesia, and the quicker dyskinesia appears (Jenner, 2000).

2.3.1 Receptor Hypersensitivity

The previously presented association between dopaminergic neuron loss and the dopamine receptor action of L-dopa led researchers to believe that dyskinesia could be caused by altered dopamine receptor function, specifically that L-dopa may induce dyskinesia by excessively inhibiting striatal GABA neurons, thus disinhibiting the globus pallidus externus (Obeso et al 2000a). Crossman et al demonstrated that choreiform dyskinesia could be induced by blocking the stiato-pallidal inhibitory pathway, and that this
was associated with excessive subthalamic nucleus inhibition (Crossman et al 1989). A lack of consensus, however, emerged over which dopamine receptor subtype was responsible since a vast number of dopamine agonists with selective D-1 and D-2 agonist activity are capable of producing dyskinesia in MPTP treated monkeys (Bedard et al. 1992). That is to say that the direct pathway mediated by D1 receptors, but not the D2 receptors mediated indirect pathway, may be overcompensated causing a hyperactive response from the direct pathway (Baas, 2000). This has been supported by research noting that L-dopa acts as a D1 and a D2 receptor agonist, while other dopamine agonists, such as Bromocriptine induce dyskinesias to a lesser extent (Bedard, 1986). In post mortem tissue of untreated Parkinson’s patients, (Lee et al. 1978) and MPTP monkeys (Bedard et al. 1986), D2 receptor binding sites are increased. However, dyskinesias are virtually never observed after the first dose of L-dopa when this hypersensitivity is liable to be present, and there has not been sufficient data to correlate hypersensitivity with the occurrence of dyskinesia (Calon, 2000). This does not discount hypersensitivity as a possible mechanisms for the development of dyskinesia. It may, however, suggest the role of other dopamine subtypes, or changes downstream from dopamine receptors at the level of intracellular cell signaling mechanisms to be associated with the hypersensitivity hypothesis. Specifically, recent studies suggest that dyskinesia are not only associated with changes in globus pallidus internus firing frequency, but also changes in the firing pattern, such as changes in the degree of synchrony of neuronal firing, the number and duration of firing bursts, and the extent of inhibitory surround (Wichmann & Delong 1996; Obeso et al 1997; Vitek et al 1999).
2.3.2 Pulsatile dopamine Receptor Stimulation

Recent advancements have since directed attention away from the simple solutions of postsynaptic dopamine receptor hypersensitivity due to presynaptic denervation, or more specifically D1 receptor hypersensitivity. Research now suggests an association between the development of drug-induced dyskinesia and pulsatile stimulation of dopamine receptors, due to the fact that both short acting selective D1 agonists and selective D2 agonists given by repeated pulsatile administration produce more intense dyskinesia than continuous receptor stimulation induced by subcutaneous infusion (Nutt et al. 2000; Bezard et al. 2001). Supportive evidence from animal-based studies suggests that this chronic intermittent dopaminergic stimulation, which does not duplicate the physiological pattern of the actual neurotransmitter secretion, results in drug-induced dyskinesia and motor fluctuations after prolonged L-dopa use (Chase, 1998; Wade et al. 1973). Administration of L-dopa via a mini pump system provides a continuous flow of dopamine, and has been recorded to be associated with reduced incidence of dyskinesia (Olanow et al. 2000). The pulsatile administration of L-dopa has also been hypothesized to result in subsequent deregulation of genes and proteins in downstream neurons, with a net result of changes in the patterns of firing of neurons within the nuclei of the basal ganglia (Obeso et al. 2000a; Brotchie, 2000).

In support of this hypothesis, it has been recorded that once dyskinesia has appeared, it will return with the initiation of one dose after treatment has been stopped for several weeks, indicating that long lasting modifications in the basal ganglia have been made in response to dopamine, suggesting a learning phenomenon similar to long-term
potentiation (Calon, 2000). Experimental evidence indicates that physiological changes in rat corticospinal plasticity associated with dopamine denervation and L-dopa treatment differ depending on whether or not dyskinesias develop (Picconi at al. 2003), supporting the hypothesis that pulsatile stimulation may cause complex mechanistic changes in basal ganglia circuitry to cause dyskinesia.

RATIONALE

Several studies have used visually guided motor tasks, specifically manual tracking (MT), to investigate the ability of Parkinson’s disease patients to make changes in kinematics, control strategies and movement accuracy (Flowers 1976; Flowers 1978; Hallett & Knoshbin 1980; Baroni et al. 1984; Beradelli et al. 1986; Johnson et al. 1994; Johnson et al. 1996; Liu et al. 2001). In particular, MT has been used extensively to evaluate the reduced movement velocity associated with bradykinesia. Higher levels of tracking errors have been recorded in patients when compared to controls and have been hypothesized to be a result of mostly reduced movement amplitude, rather than reduced movement velocity (Hufschmidt & Lurking 1995). Therefore, it has been suggested that the tracking impairment in patients with Parkinson’s disease may be independent of movement speed (Hocherman & Aharon-Peretz 1994). Johnson et al. (1994) have reported that treatment with L-dopa increases movement velocity during wrist tracking, but does not improve tracking accuracy. Identical findings have been reported in Johnson et al. (1999), who noted that wrist tracking under different viscous loads affected movement velocity with no effect on tracking accuracy after L-dopa. The fact that
improved velocity with L-dopa administration has been recorded, the lack of improvement in tracking accuracy has created some debate as to whether Parkinson's patients are able to make visuomotor adaptations during voluntary movement performance. Hocherman and Giladi (1998) have reported evidence of significant visuomotor improvement in all aspects of visuomotor tracking, specifically velocity and directional mismatches (a measure of accuracy), 30 min post L-dopa administration. These findings may be supported by the fact that the basal ganglia and lateral cerebellum are engaged in different processes, specifically during visuomotor adaptation (Jueptner & Weiller 1998). Following a change in movement parameters such as visual feedback or due to abnormal motor output, the basal ganglia may initially be active in searching and selecting a behaviorally appropriate visuomotor map; however, once an appropriate map is selected, the lateral cerebellum may function to adapt or fine-tune the selected map via error-correction mechanisms (Mial et al 1987; Desmurget et al 2004). This may be evidence of intact cerebellar circuits that enable Parkinson's patients to employ error detection and correction mechanisms to make adjustments in visuomotor control in the presence of basal ganglia dysfunction.

According to the aforementioned studies, L-dopa seems to improve some aspects of MT such as velocity, and in some circumstances, accuracy. However, the impact of hyperactivity of dopaminergic functions, resulting in dyskinetic movements, on MT has only been investigated in a few studies. For instance, Liu et al. (2001) showed that patients had increased positional mismatches when compared with controls (Liu et al. 2001). With visual feedback, patients with dyskinesia had increased variation in tracking
velocity. Increased positional mismatches in the presence of visual feedback compared to the no-visual feedback condition were also observed, suggesting that the cerebellum was active in voluntary error correction. They suggested that these corrections may have been exaggerated or excessive, hence increasing error. Liu et al. 2001 proposed that the low frequency of dyskinesia, between 1-5 Hz, allowed patients to initiate error correction.

HYPOTHESIS I

Based on the above mentioned findings, it is reasonable to assume that if increased magnitude of dyskinesia was to be systematically associated with increased errors in the tracking performance, dyskinesia could be considered to be the main source of error. However, if there were no relationships between dyskinesia magnitude and error, the source of the latter may indeed originate from a combination of dyskinesia and voluntary error corrections employed by an intact cerebellar system.

It has also been reported that Parkinson's patients with dyskinesia experience increased dyskinetic movements during motor and mental tasks. As previously mentioned, it has been hypothesized that stress, attentional processes, and excessive cortical activation may each play a role in the aggravation of dyskinesia (Fahn, 2000; Durif, 1999; Rascol et al. 1998). However, no studies to date have systematically assessed in an objective manner the observed increase in dyskinetic movement during motor tasks. For instance, in their study, Liu et al. (2001) suggested that there was a significant increase in magnitude of dyskinesia. However, they assessed this increase by
determining the level of smoothness of MT, not by direct quantification of drug-induced dyskinesia. Accordingly, they were not able to make a direct association between any increased dyskinesia magnitude and the observed error. It is essential to account for this phenomenon in order to determine the true relationship between drug-induced dyskinesia and voluntary movement.

HYPOTHESIS II

Based on the above mentioned findings, it can be hypothesized that dyskinesia magnitude will indeed increase during MT.

Although attempts have been made to quantify speed, peak magnitude, frequency, and consistency of movement of dyskinesia via kinematics technology such as EMG, Doplar Radar, accelerometer, and rotation sensitive monitors (Goetz, 1999), data has generally only been of value if obtained at rest, or when derived from body segments that are not involved in voluntary movements (Burkhard et al. 1999; Hoff et al. 2001). Currently the movement analysis of dyskinesia relies mainly on subjective scales of measurement, such as section IV-A of the Unified Parkinson’s Disease Rating Scale (UPDRS) (Fahn et al. 1987). Quantitative measures for the influence of drug-induced dyskinesia on voluntary movements and vice versa are still lacking.

It is clear that there is a need for more in depth quantitative assessment of the entire body in order to truly be able to further understand the nature of DID and overflow...
phenomenon, and to be able to dissect the influence of these abnormal involuntary movements on voluntary motor performance. Therefore, the present study’s aim was to quantify whole body dyskinesia using 3 dimensional magnetic tracking technology. Quantifying error in performance and magnitude of drug-induced dyskinesias during a manual tracking (MT) task, may present a better understanding of the relationship between tracking performance, a visuomotor task under cerebellar control (Miall et al. 1987), and dyskinesia, abnormal involuntary movements resulting from dysfunction in basal ganglia circuitry (DeLong, 1990; Crossman, 1987, Wichman & DeLong 1996).

METHODOLOGY

Whole body movement was measured in 30 participants, 10 patients with ideopathic Parkinson’s disease exhibiting mild to moderate, primarily choreic drug-induced dyskinesia (mean age of 65.7 SD 10.37), 10 age-matched Parkinson’s patients (mean age of 67.4 SD 8.98), and 10 age-matched controls (mean age of 67.77 SD 10.34). Participants with predominantly dystonic dyskinesia, high amplitude tremor, presence of metal in the body, previous brain surgery (DBS) or psychiatric complications were excluded from the study. All participants were required to sign an informed consent document, as approved by Brock University Ethics Board, and Western University Ethics Review Board, prior to participation.
3 Quantification of Whole Body Movement

In order to capture whole-body movement (WBM) in 3 dimensions, a 6 degree of freedom electromagnetic measurement system, the Flock of Birds (Innovative Sports Training, IL) magnetic motion tracker, was employed. The magnetic tracker consists of an extended range transmitter that permits accurate recordings to be taken with a 12’ radius of the fixed transmitter. Within this 12’ radius the system operates with an accuracy and resolution of .5 degrees and .1 degrees in rotation and .25cm and .08cm in translation, respectively (Innovative Sports Training, IL). In order to obtain the most accurate readings a smaller recording space (91.45cm x 121.8cm x 121.8cm) was mapped using 100 defined points taken at equally spaced intervals of 30.45cm in the x, y and z direction. The actual values (x, y, z) were related to the measured values and the relationship between the two was determined via a standard regression of the actual values (dependent) and the measured values (independent). After implementing the automated correction algorithms to compensate for field distortion, resolution was determined to be 0.4mm in translation, with an accuracy of 0.8 cm in translation.

Prior to recording, 15 receivers acquiring time series signals of both position (x, y, z) and orientation (pitch, yaw, roll) were positioned adjacent to the joint axes of each limb under consideration. Affixed to a custom shirt, pair of shoes, gloves, and using Velcro bands, sensors were located on the posterior surface of the head, first thoracic vertebrae, sacral bone, superior spinae of the scapula, lateral surface of the forearms and upperarms, back of the hands, as well as, the lateral aspects of the calves and dorsal surface of the feet (Fig 5).
Patient height and weight were entered manually into the system. In order to ascertain the orientation of the patients, a neutral position was selected as the standard operating position. Neutral is defined as arms at sides, palms medial and thumbs pointing
anterior. Following the establishment of a neutral position, axes were created from anatomical landmarks by digitizing those landmarks.

3.1 Digitization

Using a stylus receiver, bony landmarks were palpated, and the centroid method was used to form coordinate systems at the CoM of each segment (Fig. 6).

![Digitization](image)

**Fig. 6 Digitization.** The picture above illustrates the stylus sensor being used to mark reference points on bony landmarks.

These variables were used to ascertain appropriate anthropometrical data, yielding patient bone lengths and body proportions, which were then displayed as a 3D skeletal representation, (Fig. 7).
Fig. 7 3D skeletal representation. The digitization of specific bone landmarks created a 3D skeletal representation which could then be viewed in real time. Red, Yellow and Blue arrows indicate the direction of the world axis.

4 Quantification of Manual Tracking (MT)

In order to obtain a measure of MT performance, two forearm rotation sensors (FRS), with an accuracy of 0.3 degrees, were employed. Wooden dowels attached to two
foam balls were fastened to the FRS to measure the pronation and supination at the wrist as the participants performed the MT task. The MT task required that participants match the performance of a computer generated target line, with a line they control via pronation and supination of the forearm on the dominant side only. The target line followed a sign wave pattern with a frequency between 0.25 and 0.75 HZ and amplitude ranging from 20 to 120 degrees generated by DasyLab8.0 (DASYTEC, National Instruments Company, Amherst, NH). Although the sign wave remained similar between trials, it was difficult for patients to anticipate changes of either amplitude or frequency due to the irregular nature of the target line displacement. Both the target line and the subject controlled line were displayed on a large screen (1 x 0.5m) positioned approximately 1.5m from the subjects’ seated position.

Fig. 8 MT task. The MT task, generated by DasyLab 8.0 software, consisted of a computer generated line (Black), generated via the summation of three different sign waves oscillating between .25 and .75 Hz with amplitudes between 20 and 120 degrees. These signals were summated in order to obtain random target display. The patient controlled line (Red) was controlled via pronation and supination at the wrist while patients held foam balls positioned at the end of wooden dowels attached to forearm rotation sensors (FRS).

5 Procedure

Patients were instructed to arrive for testing preceding the L-dopa dose in which they deemed to be followed by their most dyskinetic period; most of which occurred in the
afternoon when consecutive doses had accumulated. Parkinson’s patient groups were instructed to take their usual dose of antiparkinsonian medication upon arrival, after which the first recording was taken to ascertain a base level of dyskinesia. Once the medication was taken, the FoB sensors were positioned adjacent to the joint axes to define each segment under consideration. Following the digitization, patients were asked to be seated, arms and legs bent at 90°, holding onto the foam handballs attached to the left and right FRS. Recordings were taken at rest and while subjects performed the MT task for a period of 50 seconds. During the MT task and resting condition, subjects were asked to refrain from any voluntary movement and not to suppress any involuntary movement. Immediately after the first recording, the motor component of the Unified Parkinson’s Disease Rating Scale (UPDRS) was performed, approximately 30 min post dose. The second recording took place approximately 1.5 h hours post dose, and was followed by the administration of a second UPDRS assessment. In order to ascertain which of the two recordings most represented the individual patients’ peak-dose dyskinesia, the following guidelines were followed during the testing period. Participants were monitored and asked to provide feedback with respect to their dyskinesia severity, additionally, during data analysis, whole body movement magnitude was evaluated for each recording period, indicating the recording in which Parkinson’s patients exhibited a greater dyskinesia magnitude. This recording was then compared to UPDRS scores to verify the recording that represented the best measure of peak-dose drug-induced dyskinesia. Based on dyskinesia magnitude and UPDRS scores, the second recording was kept for analysis in all cases but two. Control subject recordings were carried out with the same time frame as Parkinson’s patients, excluding the L-dopa dose and UPDRS assessments.
6 Analysis

6.1 Signal Analysis

The magnitude of movement in each body segment was quantified by calculating the root mean square (RMS) for each x, y, and z, coordinate in all sensors. The mean RMS value of the x, y, z coordinates were then squared before being averaged. The square root was subsequently taken, resulting in a 3D vectorial magnitude for each sensor (Fig. 9). To obtain a measure of whole body movement, the sum of the magnitude of movement in all body segments (excluding the sacrum, performance hand, forearm, and upper arm) was calculated. Whole body movement was calculated in both displacement (m) and velocity (m/sec).

\[
\text{Magnitude} = \sqrt{\frac{(X^2 + Y^2 + Z^2)}{3}}
\]

*Fig. 9 Whole Body Magnitude* The RMS values for movement in each axes was calculated and then averaged, yielding a 3D vectoral magnitude of movement in that particular sensor.

To quantify ERROR in the MT performance, the target line was subtracted from the subjects' performance (Fig. 10) and the mean of the remaining signal (absolute value in degrees) was computed (Fig. 11).
Fig. 10 Manual Tracking In order to calculate ERROR in performance, the target line was subtracted from the patients' performance resulting in the mean of the remaining signal (absolute value in degrees).

ERROR velocity was also calculated by subtracting the absolute value of the velocity of performance from the absolute value of velocity of the target, obtaining an ERROR value in degrees.

Fig. 11 ERROR Mean of the remaining ERROR (absolute value in degrees) in displacement and velocity (absolute value in degrees/sec) was calculated after the target line displacement was subtracted from the patients' performance displacement.
In order to determine the influence of DID on performance, the performance signal was analyzed in two separate target pace segments, a SLOW segment (Fig 12) (mean velocity of 3.058 degrees • sec) and a FAST segment (mean velocity of 10.602 degrees • sec) (Fig. 13). ERROR displacement and velocity as well as whole body movement displacement and velocity were computed for these segments.

**Fig. 12 SLOW Target pace segment** The target was divided into two distinct SLOW sections. These sections were then averaged in order to determine the SLOW segment of the target. (mean velocity of 3.058889 degrees • sec)
Fig. 13 FAST Target pace segment. The target was divided into two distinct FAST sections. These sections were then averaged in order to determine the FAST segment of the target (mean velocity of 10.60203 degrees • sec).

6.2 Statistical Analysis

A previous study using a similar MT task to compare motor performance between 10 patients with PD and 10 healthy age-matched controls has shown significant differences between these two groups (Duval et al. 2005). Patients in that study were tested in the OFF condition (12 hours free of anti-parkinsonian drugs). Based on this study, we have determined that in order to obtain a power of 0.80, 4 subjects are required in the present study. Any lack of difference between groups would be interpreted as being the result of testing patients in the ON condition. Whole-body magnitude and motor performance were compared in the rest and MT condition (within groups) and between groups using two-way analysis of variance (ANOVA) (Group x Condition) with repeated measures on the last factor (Condition). Post Hoc pairwise multiple comparisons were calculated using the Student-Newman-Keuls method to determine which comparisons yielded statistical significance. The same was done for ERROR in
displacement and velocity. Spearman’s Rank correlation was used to assess the possible effect of age and years since diagnosis on motor performance. In addition, rank correlation was used to assess the relationship between motor performance and whole-body magnitude within groups. The p value threshold was set at 0.05.

In order to determine the frequency relationship between ERROR in displacement and whole body movement displacement, as well as, the frequency of ERROR in velocity and the frequency of whole body movement velocity, coherence between the frequency of ERROR and the frequency of whole body movement in each sensor was also calculated in the x, y, z coordinates for each sensor.
The influence of drug-induced dyskinesias on manual tracking in Parkinson’s disease

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Abstract

The influence of peak-dose drug-induced dyskinesia (DID) on manual tracking (MT) was examined in 10 dyskinetic patients (DPD), and compared to 10 age/gender-matched non-dyskinetic patients (NDPD) and 10 healthy controls. Whole body movement (WBM) and MT were recorded with a 6-degrees of freedom magnetic motion tracker and forearm rotation sensors, respectively. Subjects were asked to match the length of a computer-generated line with a line controlled via wrist rotation. Results show that DPD patients had greater WBM displacement and velocity than other groups. All groups displayed increased WBM from rest to MT, but only DPD and NDPD patients demonstrated a significant increase in WBM displacement and velocity. In addition, DPD patients exhibited excessive increase in WBM suggesting overflow DID. When two distinct target pace segments were examined (FAST/SLOW), all groups had slight increases in WBM displacement and velocity from SLOW to FAST, but only DPD patients showed significantly increased WBM displacement and velocity from SLOW to FAST. Therefore, it can be suggested that overflow DID was further increased with increased task speed. DPD patients also showed significantly greater ERROR matching target velocity, but no significant difference in ERROR in displacement, indicating that significantly greater WBM displacement in the DPD group did not have a direct influence on tracking performance. Individual target and performance traces demonstrated this relatively good tracking performance with the exception of distinct deviations from the target trace that occurred suddenly, followed by quick returns to the target coherent in time with increased performance velocity. In addition, performance hand velocity was not correlated with WBM velocity in DPD patients, suggesting that increased ERROR in velocity was not a direct result of WBM velocity. In conclusion, we propose that over-excitation of motor cortical areas, reported to be present in DPD patients, resulted in overflow DID during voluntary movement. Furthermore, we propose that the increased ERROR in velocity was the result of hypermetric voluntary movements also originating from the over-excitation of motor cortical areas.
6.3 Introduction

L-3-4-dihydroxyphenylalanine, (Levodopa, or L-dopa), in combination with peripheral
dopa decarboxylase inhibitor (Carbidopa) remains one the most effective treatments for
symptom alleviation in Parkinson’s disease (PD) (Jankovic & Marsden 1999). However, long-
term L-dopa therapy can result in motor complications such as drug-induced dyskinesias (DID)
(Cotzias et al 1969; Yahr et al 1969; Klawans et al 1975), recorded to occur in approximately
50 to 80% of PD patients receiving L-dopa for more than 5 to 10 years (Marsden & Parks
1977, Rajput et al 2002). There are several different classifications or types of DID, such as
dystonic, ballism and myoclonus (Klawans et al 1975; Meunter et al 1977; Melamed 1979;
Fahn 2000). However, the most common type of DID remains choreic-type movements,
involuntary movements that are considered to be purposeless, non-rhythmic, abrupt, rapid,
irregular, and un-sustained (Fahn, 2000). Choreic movements can also be classified as
overflow DID; DID that generally occurs in otherwise inactive body segments while patients
are performing voluntary movements (Fahn, 2000).

In order to assess motor dysfunction in PD, several studies have used visually-guided
motor tasks, specifically manual tracking (MT), to investigate the ability of PD patients to
make changes in kinematics, control strategies and movement accuracy (Flowers 1976;
Hallett & Knoshbin 1980; Baroni et al. 1984; Beradelli et al. 1986, Johnson et al. 1994;
Johnson et al. 1996; Liu et al. 2001). In particular, MT has been used extensively to evaluate
the reduced movement velocity associated with bradykinesia (Draper & Johns, 1964; Flowers, 1976, Hallett & Khoshbin, 1980; Marsden 1982; Baroni et al, 1984; Beradelli et al 1986). Higher tracking errors have been recorded in patients when compared to controls, and are suggested to be mainly a consequence of reduced movement amplitude as opposed to reduced movement velocity (Hufschmidt & Lurking 1995). Therefore, it has been suggested that the tracking impairment in patients with PD may be independent of movement speed (Hoehman & Aharon-Peretz 1994). L-dopa has been reported to increase the velocity of step movements (Baroni et al, 1984; Beradelli et al 1986; Weinrich et al 1988; Pastor et al 1992) as well as the velocity of self paced movements (Johnson et al 1994). However, Johnson et al, 1994 reported that while treatment with L-dopa increased movement velocity during wrist tracking, it did not improve tracking accuracy. The possibility of an inherent deficit in error correction in patients with PD is not easily differentiated from pathologically-induced reduction in movement velocity. However, a recent study by Hoehman and Giladi (1998) reported evidence of significant visuomotor improvement in all aspects of visuomotor tracking, specifically velocity and directional mismatches (a measure of accuracy) 30 min post L-dopa administration, suggesting that patients with PD were able to make visuomotor adaptations during MT after L-dopa. These findings may be supported by the fact that the basal ganglia and lateral cerebellum are engaged in different processes, specifically during visuomotor adaptation (Jueptner & Weiller 1998).
According to the aforementioned studies, L-dopa seems to improve some aspects of MT such as velocity and accuracy. However, the impact of cortico-motor overactivation associated with DID (Rascol et al. 1998) on the performance of MT has only been investigated in a one study. Liu et al. (2001) showed that patients had increased variation in tracking velocity and positional mismatches when compared with controls. Patients with DID also showed increased variation in tracking velocity and increased positional mismatches in the presence of visual feedback compared to the no-visual feedback. It was suggested that patients made positional corrections during the motor task and that error may have been derived from both DID and these voluntary error corrections. Liu et al (2001) based this assumption primarily on the fact that with visual feedback, patients with DID showed increased error. In their study however, Liu et al, did not quantify DID itself. It would be reasonable to assume that if increased DID magnitude was to be systematically associated with increased errors during MT, DID could be considered as the main source of error in the motor performance.

It has also been reported that PD patients with DID experience increased dyskinetic movements during motor and mental tasks (Fahn, 2000; Durif, 1999; Rascol et al. 1998). However, no studies to date have systematically assessed in an objective manner, the observed increase in dyskinetic movement during motor tasks. Accordingly, the goals of the present study were to compare the motor performance and whole-body movement magnitude during a MT task between patients with PD showing mild to moderate DID with those of
patients without DID and matched controls. Also, we intended to quantify possible increase in whole-body movement during motor performance.

6.4 Methodology

Whole body movement was measured in 30 participants, 10 patients with idiopathic PD exhibiting mild to moderate, primarily choreic dyskinesias (DPD group) (mean age of 67.5 SD 10.37), 10 age-matched PD patients who have not yet experienced DID in their lifetime (NDPD group) (mean age of 67.4 SD 8.98), and 10 age-matched controls (mean age of 66.5 SD 10.34). Exclusion criteria included the presence of predominantly dystonic DID, high amplitude tremor, presence of metal in the body, previous brain surgery (DBS) or psychiatric complications. All participants were required to read and sign an informed consent document, as approved by Brock University Ethics Board, and Western University Ethics Review Board, prior to participation.

6.4.1 Quantification of Whole Body Movement

In order to capture full body DID in 3 dimensions, a 6 degrees-of-freedom electromagnetic measurement system, the Flock of Birds (FoB) magnetic motion tracker was employed, (Innovative Sports Training, Chicago, Illinois). The magnetic tracker consists of an extended range transmitter that permits accurate recordings to be taken within a 12’ radius of the fixed transmitter. Within this 12’ radius, the system operates with an accuracy (distance measured between two sensors) of 0.5 degrees in rotation and 0.25cm in translation. The
standard resolution is 0.1 degrees in rotation and 0.08cm in translation. In order to improve upon these values, a smaller area (3' x 4' x 4', from the floor and up) was mapped using 100 defined points taken at equally spaced intervals of 30.45cm in the x, y and z direction. After implementing the automated correction algorithms to compensate for field distortion, resolution was determined to be 0.08 cm in translation, with an accuracy of 0.8 cm in translation.

Prior to recording, 15 sensors (receivers) acquiring time series signals of both position (x, y, z) and orientation (pitch, yaw, roll) were positioned adjacent to the joint axes of each limb under consideration. Affixed to a custom shirt, pair of shoes, gloves, and using Velcro bands, sensors were located on the posterior surface of the head, the first thoracic vertebrae, sacral bone, the superior spinae of the scapula, lateral surface of the forearms and upper-arms, back of the hands, as well as, the lateral aspects of the calves and dorsal surface of the feet. Each sensor was then assigned to the Center of Mass (CoM) of the limb by way of a digitization process. Using a stylus receiver, bony landmarks were palpated, and the centroid method was used to form coordinate systems at the CoM of each segment. Based on the height and weight of the subject, an automated algorithm assigned a particular sensor to the CoM of the limb on which it was positioned.
6.4.2 Quantification of Manual Tracking (MT)

MT performance was quantified using two forearm rotation sensors (FRS) with an accuracy of .3 degrees in rotation. Two wooden dowels attached to foam balls were fastened to the FRS to accurately quantify the pronation-supination movements at the wrist. The MT task required that subjects match the performance of a computer generated target line, with a line they controlled via pronation-supination movement of the dominant hand only. The target line followed a sign wave pattern with a frequency between 0.25 and 0.75 HZ and amplitude ranging from 20 to 120 degrees generated by DasyLab8.0 (DASYTEC, National Instruments Company, Amherst NH). Although the sign wave remained similar between trials, it was difficult for subjects to anticipate changes of either amplitude or velocity due to the irregular nature of the target line displacement. Both the target line and the subject controlled line were displayed on a large screen positioned approximately 1.5m from the subjects’ seated position.

6.5 Procedure

Patients were instructed to arrive for testing preceding the L-dopa dose in which they deemed to be followed by their most dyskinetic period; most of which occurred in the afternoon when consecutive doses had accumulated. The patients were instructed to take their usual dose of antiparkinsonian medication upon arrival, after which the first recording was taken to ascertain a base level of DID. Once the medication was taken, patients were asked to be seated, arms and legs bent at 90°, holding onto the foam handballs attached to the left and right FRS. Recordings were taken at rest, and while subjects performed the manual tracking
task for a period of 60 seconds. During the MT task and resting condition, subjects were asked to refrain from any voluntary movement and not to suppress any involuntary movement. Immediately after the first recording, the motor component of the Unified Parkinson's Disease Rating Scale (UPDRS) was performed, approximately 30 min post dose. The second recording was taken approximately 1.5 hrs post dose, and was followed by the administration of a second UPDRS assessment. In order to ascertain which of the two recordings most represented the individual patients' peak-dose DID, the following guidelines were followed during the testing period. Participants were monitored and asked to provide feedback with respect to their DID severity, additionally, during data analysis, WBM magnitude was evaluated for each recording period, indicating the recording in which PD patients exhibited a greater DID magnitude. This recording was then compared to UPDRS scores to verify the recording represented the best measure of peak-dose DID. Based on DID magnitude and UPDRS scores, the second recording was kept for analysis in all cases but two. Control subject recordings were carried out with the same time frame as PD patient recordings, excluding the L-dopa dose and UPDRS assessments.

6.5.1 Signal Analysis

The magnitude of movement in each body segment was quantified by calculating the root mean square (RMS) for each x, y, and z coordinate in all sensors. The mean RMS value of the x, y, z coordinates were then squared before being averaged. The square root was subsequently taken, resulting in a 3D vectorial magnitude for each sensor. To obtain a measure
of WBM, the sum of the magnitude of movement in the all body segments (excluding the sacrum, performance hand, forearm, and upper-arm) was calculated. WBM was calculated in both displacement (meters) and velocity (m*s\(^{-1}\)).

To quantify ERROR displacement (degrees) in the MT performance, the target line was subtracted from the subjects’ performance. Then, the mean of the absolute values of the remaining signal was computed. ERROR velocity was also calculated by subtracting target velocity from the velocity of performance, obtaining an ERROR value in degrees per second. The goal was to determine if differences existed between groups in their ability to match target velocity. Additionally, to further investigate motor performance, the target performance was separated into 2 distinct pace segments, SLOW (mean velocity of 3.05 degrees*sec) and a FAST segment (mean velocity of 10.60 degrees*sec). ERROR was subsequently calculated for each segment. WBM was also analyzed in both SLOW and FAST segments.

6.5.2 Statistical analysis

A previous study using a similar MT task to compare motor performance between 10 patients with PD and 10 healthy age-matched controls has shown significant differences between these two groups (Duval et al. 2005). Patients in that study were tested in the OFF condition (12 hours free of anti-parkinsonian drugs). Based on this study, we have determined that in order to obtain a power of 0.80, 4 subjects are required in the present study. Any lack of difference between groups would be interpreted as being the result of testing patients in the ON
condition. Whole-body magnitude and motor performance were compared in the rest and MT condition (within groups) and between groups using two-way analysis of variance (ANOVA) (Group x Condition) with repeated measures on the last factor (Condition). *Post Hoc* pairwise multiple comparisons were calculated using the Student-Newman-Keuls method. Spearman’s Rank correlation was used to assess the possible effect of age and years since diagnosis on motor performance. In addition, rank correlation was used to assess the relationship between motor performance and whole-body magnitude within groups. The p value threshold was set at 0.05 for each of the aforementioned statistical tests.

6.6 Results

Due to the age-gender match of each DPD subject with a NDPD patient and control subject, no significant difference was found in mean age between groups. Subject characteristics are displayed in table 1.
Table 1. Subject characteristics. UPDRS: Unified Parkinson’s disease rating scale.

<table>
<thead>
<tr>
<th>Patients #</th>
<th>Gender</th>
<th>Age (years)</th>
<th>Years since diagnosis</th>
<th>Motor score (UPDRS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPD1</td>
<td>M</td>
<td>66</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td>DPD2</td>
<td>M</td>
<td>70</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>DPD3</td>
<td>M</td>
<td>75</td>
<td>20</td>
<td>14</td>
</tr>
<tr>
<td>DPD4</td>
<td>F</td>
<td>80</td>
<td>18</td>
<td>45</td>
</tr>
<tr>
<td>DPD5</td>
<td>F</td>
<td>56</td>
<td>11</td>
<td>17</td>
</tr>
<tr>
<td>DPD6</td>
<td>M</td>
<td>59</td>
<td>6</td>
<td>19.5</td>
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<td>DPD7</td>
<td>M</td>
<td>65</td>
<td>21</td>
<td>36</td>
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<tr>
<td>DPD8</td>
<td>F</td>
<td>76</td>
<td>21</td>
<td>53</td>
</tr>
<tr>
<td>DPD9</td>
<td>M</td>
<td>44</td>
<td>6</td>
<td>16.5</td>
</tr>
<tr>
<td>DPD10</td>
<td>F</td>
<td>70</td>
<td>24</td>
<td>25</td>
</tr>
<tr>
<td>Mean:</td>
<td></td>
<td>66.1</td>
<td>15.6</td>
<td>24.6</td>
</tr>
<tr>
<td>SD:</td>
<td></td>
<td>10.76</td>
<td>6.45</td>
<td>15.52</td>
</tr>
<tr>
<td>NDPD1</td>
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<tr>
<td>NDPD6</td>
<td>M</td>
<td>68</td>
<td>6</td>
<td>46.5</td>
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<td>72</td>
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<td>24.5</td>
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<td>NDPD10</td>
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<tr>
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<td>6</td>
<td>29.6</td>
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<tr>
<td>SD:</td>
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<td></td>
</tr>
<tr>
<td>CON2</td>
<td>F</td>
<td>52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CON3</td>
<td>M</td>
<td>56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CON4</td>
<td>F</td>
<td>73</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CON5</td>
<td>F</td>
<td>77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CON6</td>
<td>M</td>
<td>47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CON7</td>
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<tr>
<td>CON8</td>
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<tr>
<td>CON9</td>
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<tr>
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<td>69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean:</td>
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<td>66.5</td>
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<tr>
<td>SD:</td>
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<td>10.92</td>
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</tbody>
</table>
Correlations (Spearman's Rank) have revealed that when all subjects were pooled, age was not correlated with motor performance (Rho = 0.05, p = 0.77). Also, within the patients groups there were no correlations between age and motor performance (Rho = 0.03, P = 0.88). However, as expected, years since diagnosis was correlated with WBM (Rho = 0.744, P = 0.000) and weakly correlated with error in velocity (Rho = 0.539, P = 0.01).

For WBM in displacement (Fig 13), ANOVA revealed a significant difference between Group (F(2,30) = 12.815, P<0.001), Condition (F(1,30)= 42.615, P<0.001) and Group x Condition (F(2,30)= 6.976, P=0.006). More specifically, Post hoc analysis indicated that DPD patients showed significantly more WBM displacement at rest and during MT than both NDPD and control groups (p<0.05). In addition, DPD and NDPD patients demonstrated a significant increase in WBM displacement from rest to active conditions (p<0.05). DPD subjects also showed a greater absolute increase in WBM displacement from rest to active (0.125 m) as compared to NDPD (0.0431 m) and controls (0.0352 m). No significant differences were observed between NDPD patients and controls.
Fig. 14 WBM Displacement. Whole body movement at rest (in black), and during MT (in grey). Note that the difference in the mean values between rest and active conditions was significant for DPD and NDPD patients. Significant differences within groups are indicated by a single star (*), differences of interests between groups are indicated by double stars (**).

For WBM in velocity (Fig 14), ANOVA revealed a significant difference between Group (F(2,30) = 10.387, P = 0.001), Condition (F(1,30) = 14.213, P = 0.004) and Group x Condition (F(2,30) = 6.291, P = 0.008). More specifically, Post hoc analysis indicated that DPD patients showed significantly more WBM velocity at rest and during MT than both NDPD and control groups (p<0.05). In addition, only DPD patients demonstrated a significant increase in WBM velocity from rest to active conditions (p<0.05). DPD subjects also showed a
greater absolute increase in WBM velocity from rest to active (0.0294 m·s⁻¹) as compared to NDPD (0.00467 m·s⁻¹) and controls (0.00167 m·s⁻¹). No significant differences were observed between NDPD patients and controls.

![Graph showing WBM Velocity](image)

**Fig. 15 WBM Velocity.** Whole body movement at rest (in black), and during action (in grey). Note that only DPD patients demonstrated significantly more WBM velocity during action than at rest (p<0.05). No significant differences were observed between NDPD patients and controls.

Significantly greater WBM velocity can be observed in individual power spectral traces of non-performance limbs, such as the shank (Fig.15).
Fig. 16 DPD patient shank Velocity. Power spectrums indicate frequency components in the Shank of a DPD patients (a) not observed in a NDPD patient (b) and control subjects (c).

For motor performance (Figure 16), ANOVA revealed no significant difference in ERROR in displacement between groups.
**Fig. 17 ERROR in Displacement.** The above graph indicates the magnitude of ERROR in displacement (positional mismatch with target). Although there was a trend indicating increased ERROR in the DPD patient group, no significant difference was found between DPD patients, NDPD patients and controls.

When ERROR in velocity (a measure of the ability of the subject to match the target velocity) was considered (Fig.17), *ANOVA* revealed significant differences between *Groups* ($F(2,30) = 9.997, P < 0.001$). *Post Hoc* analysis indicated significantly more ERROR in velocity in DPD patients than NDPD patients and controls. No significant difference in ERROR in velocity was observed between NDPD patients and controls.
**Fig. 18 ERROR in Velocity.** The above graph indicates the magnitude of ERROR in velocity (velocity mismatch with target). Only DPD patients showed significantly more ERROR in velocity. No significant differences were shown between NDPD patients and controls.

In an attempt to uncover the source of ERROR, ERROR in displacement in MT performance was considered in the FAST and SLOW segments (Fig 18). Consistent with the previous analysis of the entire performance trace, ANOVA revealed no significant difference between Group or Condition.
**Fig. 19** ERROR in displacement SLOW and FAST. The above graph indicates the difference in ERROR in displacement in SLOW (black bars) and FAST (grey bars). No significant difference was recorded for ERROR in displacement in either the SLOW or FAST target pace segments.

For ERROR in velocity in SLOW and FAST segments (Fig 21), ANOVA revealed significant differences between *Group* (F(2,30) = 11.973, P < 0.001) and *Condition* (F(1,30) = 10.670, P = 0.010). *Post Hoc* analysis further revealed that DPD subjects demonstrated a significantly greater ERROR in velocity in both the SLOW and FAST segments as compared to NDPD subjects and controls (P<0.05). DPD patients and NDPD patients also exhibited significantly more ERROR in the FAST segment as compared to the SLOW segment (p<0.05). No significant differences were observed between NDPD patients and controls.
Fig. 20 ERROR in Velocity SLOW and FAST. The above graph illustrates significantly greater ERROR in velocity in DPD patients in both the SLOW tracking segment (black bars) and in the FAST tracking segment (grey bars). Note that both DPD and NDPD patients exhibited significant increases in ERROR in velocity from SLOW to FAST segments.

In order to determine whether ERROR in velocity was the result of decreased velocity or excessive velocity in reference to target velocity, ERROR (performance – target) of the true velocity values was calculated in order to maintain both positive and negative velocity values (Fig.20). ANOVA revealed a significant difference between Group (F(2,30) = 6.074, P = 0.010). No significant difference was revealed for Condition, or Group x condition. More specifically, Post Hoc revealed DPD patients to have significantly greater ERROR velocity (faster than target) than NDPD patients and controls (p<0.05). No significant differences were
revealed between SLOW and FAST segments. In addition, no significant differences were revealed between NDPD patients and controls.

![Graph](image)

**Fig. 21. Positive and negative ERROR Velocity.** The above graph illustrates positive or negative ERROR velocity (mean velocity of performance – mean velocity of target), indicating whether subjects were on average performing with more, the same, or with less velocity than the target. Note that DPD patients moved with greater velocity than the target significantly more than NDPD patients and controls. In all groups, there were no significant differences between SLOW and Fast segments. In addition, no significant differences were evident between NDPD patients and controls.

Analysis of individual target and performance traces also indicated increases in velocity of performance coherent in time with deviations from the target (Fig. 22).
Fig. 22 Individual subject performance and target trace. The above graphs illustrate examples of the difference in tracking ability of several DPD patients (a, b, c) as compared to a NDPD patient (d) and a control subject (e). Performance traces (red) have been plotted overlaying the target trace (black). Above the target and performance traces are the absolute values of the velocity of the performance (blue). The velocity traces reveal large increases in velocity coherent in time with the deviations from the target in DPD patients.
For velocity of movement in the performance hand (Fig. 23), ANOVA revealed a significant difference between Groups (F(2,30) = 3.931, P = 0.038), no significant differences were shown between Condition or Group x Condition. Post Hoc analysis indicated significant differences between DPD patients and NDPD patients, as well as between DPD patients and controls (p<0.05). DPD patients were also shown to have significantly greater performance hand velocity during the FAST segment as compared to the SLOW segment (p<0.05). No significant differences were observed between NDPD patients and controls.

**Fig. 23 Performance Hand Velocity.** The above graph illustrates the velocity of hand performance for DPD, NDPD and control subjects. Note that DPD patients exhibit significantly greater performance hand velocity in both SLOW and FAST segments as compared to NDPD patients and controls.
Spearman’s rank order correlation revealed no correlation between performance hand velocity and WBM velocity in DPD patients. However, a strong positive correlation was evident in NDPD patients, along with a negative correlation in controls.

Table 2. Spearman Rank Order Correlation: Performance hand velocity and WBM.

<table>
<thead>
<tr>
<th></th>
<th>WBMSLOW (velocity)</th>
<th>WBMFAST (velocity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPD HAND</td>
<td>r = 0.127</td>
<td>NA</td>
</tr>
<tr>
<td>SLOW</td>
<td>p &lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>DPD HAND</td>
<td>NA</td>
<td>r = -0.0909</td>
</tr>
<tr>
<td>FAST</td>
<td></td>
<td>p &gt; 0.05</td>
</tr>
<tr>
<td>NDPD HAND</td>
<td>r = 0.745</td>
<td>NA</td>
</tr>
<tr>
<td>SLOW</td>
<td>p &lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>NDPD HAND</td>
<td>NA</td>
<td>r = 0.685</td>
</tr>
<tr>
<td>FAST</td>
<td></td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>CON HAND</td>
<td>r = -0.745</td>
<td>NA</td>
</tr>
<tr>
<td>SLOW</td>
<td>p &lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>CON HAND</td>
<td>NA</td>
<td>r = -0.745</td>
</tr>
<tr>
<td>FAST</td>
<td></td>
<td>p &lt; 0.05</td>
</tr>
</tbody>
</table>
For WBM displacement in the SLOW and FAST segments (Fig. 24), ANOVA revealed significant differences between Group ($F(2,30) = 12.815, P = 0.001$). More specifically, Post Hoc analysis revealed WBM in DPD patients to be significantly greater than NDPD patients and controls ($p < 0.05$), no significant differences were observed between NDPD patients and controls. A significant increase in WBM displacement from SLOW to FAST was also evident in DPD patients ($p < 0.05$). There were no significant increases from SLOW to FAST in either NDPD patients or controls.

![Figure 24. WBM (SLOW/FAST) displacement.](image)

*Fig. 24. WBM (SLOW/FAST) displacement.* The above graph illustrates WBM displacement during both SLOW (in black) and FAST (in grey) target pace segments. Note that a significant increase in WBM displacement from SLOW to FAST is only present in the DPD group.
For WBM velocity in the SLOW and FAST segments (Fig. 25), ANOVA revealed significant differences between Group (F(1,30) = 3.931, P = 0.038). More specifically, Post Hoc analysis revealed WBM velocity in DPD patients to be significantly greater than NDPD patients and controls (p<0.05), no significant differences observed between NDPD patients and controls. A significant increase in WBM velocity from SLOW to FAST was also evident in DPD patients (p<0.05). There were no significant increases from SLOW to FAST in either NDPD patients or controls.

*Fig. 25. WBM (SLOW/FAST) velocity.* The above graph illustrates WBM velocity during both SLOW (in black) and FAST (in grey) target pace segments. Note that a significant increase in WBM displacement from SLOW to FAST is only present in the DPD group.
Spearmans' rank order correlation revealed significant correlation between WBM and ERROR velocity (Rho = .737, p = 0.000).

6.7 Discussion

The goals of the present study were to compare the motor performance and whole-body movement magnitude during a MT task between mild to moderate dyskinetic PD patients (DPD) to those of non-dyskinetic PD patients (NDPD) and control subjects; to determine if increased DID was systematically associated with increased error and to assesses the change in amplitude of DID during MT.

6.7.1 Influence of voluntary movement on WBM

The current results indicate that DPD patients had significantly greater WBM at rest and during MT, indicative of the presence of DID in the DPD group. Although both DPD and NDPD groups had significantly greater WBM during MT performance as compared to the resting condition, DPD patients demonstrated an excessive increase in WBM displacement and velocity from rest to MT, as compared to the NDPD and control groups. It can be postulated that this excessive increase in WBM is due to the observed phenomenon of overflow DID, reported to occur in inactive body segments while patients perform voluntary movements (Durif et al 1999, Lhermitte et al 1978, Nutt 1990, Rascol et al 1998). Slight increase of WBM in controls may be explained by the fact that motor overflow has been reported to occur in normal adults under effort-induced conditions (Armatas et al. 1994; Aranyi & Rosler, 2002).
The significant increase seen in NDPD patients has also been observed in previous studies (Cincotta et al 2002, Rascol et al 1994). Reasons for the increase in severity of motor overflow in PD is unknown, however, stress and attentional processes, known to be under the influence of limbic structures projecting to the basal ganglia, have been implicated in the aggravation of involuntary movements with motor and mental tasks (Marsden 1982, Hardie et al 1984, Durif et al 1999). It has been reported that stress may increase abnormal movements in PD patients, such as resting tremor, as well as focal and generalized dystonia (Marsden 1982). Specifically, the excess increase in WBM in DPD patients, overflow DID, has been previously reported to occur with mental stress and motor activity (Marsden 1982, Hardie et al 1984, Durif et al 1999). Additionally, excessive activation of cortical motor areas during motor tasks has also been implicated (Roland et al 1980, Colebatch et al 1991, Rascol et al. 1998). It has been hypothesized that impaired inhibitory activity or hyper-excitability of motor circuits in PD patients may lead to excessive cortical activation (Kleine et al 2001, Hoy et al 2004). The current model of the basal ganglia in DID suggests that increased inhibition of the globus pallidus internus results in decreased inhibitory influence of the globus pallidus internus on the VL thalamus, which in turn causes increased excitation of the motor cortex (Rascol et al 1998). It can be suggested then, that over-activation of motor cortical areas in PD patients with DID, specifically the supplementary and primary motor cortical areas, would likely result in overflow DID with voluntary movement. The current results seem to support the later explanation of over-activation of motor cortical areas given that the attentional demands of the task and stress of the situation were not manipulated between groups.
Further analysis also indicated that with increased speed of movement (from SLOW to FAST), there was a significant increase in WBM displacement and velocity only in the DPD group. It can be suggested that with voluntary movement, (rest to MT) motor overflow manifested in NDPD patients and overflow DID manifested in DPD patients. However, with increased task speed from SLOW to FAST, it can be postulated that the increased attentional demands of the task may have resulted in increase overflow DID. In addition, due to the fact that WBM did not increase in controls and NDPD patients with task speed, it is reasonable to assume that the same over-excitation of motor cortex that has been associated with overflow DID during movements (Klein et al 2001, Hoy et al 2004), resulted in further increases in overflow DID due to the greater attentional demands associated with tracking a faster target.

6.7.2 Influence of WBM on motor performance

In reference to the influence of DID on the MT performance, DPD patients in the present study were found to have similar ERROR in displacement when compared to NDPD and control groups. The lack of significant difference in ERROR in displacement between DPD patients, NDPD patients and controls, suggests that DID may not have had a direct influence on ERROR in performance. In addition, no differences were found in the increased ERROR in displacement from SLOW to FAST between or within groups, indicating that DPD patients were not at a significant disadvantage when following a faster target. Individual subject performance traces clearly illustrate this relatively good tracking ability in DPD
patients, however, abrupt deviations from the target are present, which are minimal in NDPD patients, and not readily observable in controls. These deviations appear to dramatically increase performance velocity and consequently ERROR in matching the target velocity. In accordance with previous tracking studies that have recorded increases in movement velocity with L-dopa administration (Johnson et al 1996, Hocherman & Giladi 1998; Desmurget et al 2004), the difficulty in matching the velocity of the target in the current study was found to be due to excessive velocity, i.e., DPD patients were consistently moving faster than the target. Examination of individual traces revealed the ERROR in velocity to originate from sudden, fast deviation from target occurring at times where the patient was following the latter accurately. We suggest that ERROR in velocity may therefore be a by-product of the previously mentioned over-excitation of motor cortical areas. A recent study reported similar results, wherein DPD patients exhibited excess force during a grip force task (Wenzelburger et al 2002) Wenzelburder et al (2002) postulated that excess force and DID shared the same pathophysiological mechanisms related to motor fluctuations. In the present study, it is reasonable to assume that the same over-activation of cortical areas, associated with DID (Rascol et al 1998), not only resulted in increased overflow DID during MT, but also resulted in hypermetric voluntary motor outputs, increasing ERROR in velocity. Additionally, this may explain the significant increase in ERROR in velocity from SLOW to FAST, observed in the DPD group. Similar to the increase in WBM with task speed, it can be postulated that increased task speed resulted in increased hypermetric voluntary movement.
Further examination revealed DPD patients to have had significantly greater performance hand velocity when compared to NDPD patients and controls. However, correlation analysis did not indicate a correlation between performance hand velocity and WBM velocity in DPD patients, providing further evidence that ERROR in velocity may in fact be related to hypermetric voluntary movement. It is reasonable to assume that since there is no correlation between performance hand velocity and WBM velocity in DPD patients, WBM is not directly linked to the velocity of performance itself, thus ERROR in velocity could possibly be attributed to other mechanism.

Interestingly, in the NDPD patient groups, a strong correlation was revealed between performance hand velocity and WBM velocity, consistent with results of previous studies indicating motor overflow in PD patients (Marsden 1982; Cincotta et al 2002). Control subjects demonstrated a strong negative correlation between performance hand velocity and WBM velocity, suggesting that control subjects may have restricted movement in the non-performance limbs during the task. This is evident in the lack of significantly increase WBM from SLOW to FAST segments in controls, and is supported by observations that motor overflow is usually only observed in healthy controls under highly effortful conditions and fatiguing voluntary contractions (Armatas et al 1994; Aranyi & Rosler 2002; Hoy et al 2004).

As previously mentioned, Liu et al. (2001) argued that the increased positional mismatches found in their results were due to error correction in summation with DID.
However, DID was not directly quantified in that study. In the present study however, the specific relationship between the positional mismatches and DID was investigated. Based on the individual performance traces, which illustrate purposeful returns to the target after the abrupt deviations from its trajectory, it cannot be disputed that DPD patients are employing error correction. However, the initial deviation from target was surely not a correction since patients were following the target with relatively good accuracy just previous to the deviations, also evident by the lack of significant difference in ERROR displacement between groups. Consequently, we suggest that the source of deviation from the target is the result of hyperkinetic voluntary movement as opposed to a direct influence of the dyskinetic movements themselves. Obviously, DPD patients were able to correct for this deviation using fast corrections that may have had additional influence on the overall ERROR in velocity.

An important factor to consider when reviewing the current findings is that DPD patients differed from NDPD patients significantly in the number of years since diagnosis, DPD patients with a mean number of years since diagnosis of 15 yrs and NDPD patients a mean number of years since diagnosis of 6 yrs. It could be argued that the increased number of years since diagnosis in the DPD group may have caused greater deficits due to underlying disease, resulting in increased ERROR in velocity. However, due to the fact that the ERROR in velocity was the result of DPD patients being faster than the target, it is more reasonable to conclude that ERROR in velocity was the consequence of over-excitation of motor cortical areas, which has been associated with DID (Crossman 1990, De Long 1990, Rascol et al 1998).
Therefore, the current findings suggest that DPD patients with greater number of years since diagnosis were able to perform the MT task with relatively the same ease as NDPD patients and controls, even in the presence of significantly greater WBM. However increased error in matching the velocity of performance with target velocity appeared to have been the result of velocity mismatches due to cortical over-excitation-induced hypermetria. It is possible that DPD patients may in fact benefit from this over-excitation in order to perform motor acts, as they surely would have shown greater deficits in performance in the OFF condition compared to the NDPD group in the ON condition. It can be further suggested that if the L-dopa dose of the DPD patients was to be lowered, thus decreasing DID, motor performance would also suffer. In fact, a small amount of dyskinesia may actually improve performance in these patients. Further studies are needed to determine the neural mechanisms by which these cortical over-excitation-induced hypermetric movements are generated.
References


GENERAL CONCLUSIONS

The goals of the present study were to compare the motor performance and whole-body movement magnitude during a MT task between patients with PD showing mild to moderate DID to those of patients with Parkinson's disease without DID and control subjects, to determine if increased DID was systematically associated with increased error, and finally to assesses the change in amplitude of DID during MT.

It was hypothesized that if magnitude of dyskinesia was systematically associated with increased errors in the tracking performance, dyskinesia could be considered to be the main source of error. However, if there were no relationships between dyskinesia magnitude and error, the source of the latter may indeed originate from a combination of dyskinesia and voluntary error corrections employed by an intact cerebellar system. If fact, dyskinesia could not be considered the main source of ERROR. The current findings suggest that dyskinetic Parkinson's disease patients with longer disease duration were able to perform tracking task with relatively the same accuracy (displacement) as non-dyskinetic patients and controls, and that ERROR in performance was possibly the result of motor cortical over-excitation induced hypermetria during voluntary movement.

It was also hypothesized that whole body movement would increase during manual tracking performance. The current results support this hypothesis. The dyskinetic group of patients demonstrated significantly greater whole body movement during the tracking performance, suggested to be overflow dyskinesia due to over-activation of motor cortical
areas. However, further investigation into the specific mechanisms by which DID influence tracking performance is necessary. A more in-depth analysis of WBM increase from SLOW to FAST tracking in individual limbs that do not present DID, common in very mildly dyskinetic patients, may indicate the specific relationship between over-excitability of the cortex in dyskinetic patients and the influence of the resulting overflow dyskinesia on tracking performance.

In addition, it was originally hypothesized that coherence between frequency of ERROR in performance and frequency of WBM would indicate whether DID was the main source of ERROR. Although coherence was examined, and a difference in coherence between ERROR frequency and WBM frequency was not observed between dyskinetic patients, non-dyskinetic patients and controls, a more in-depth analysis of dyskinesias in individual body segments is necessary. An average coherence between individual coordinates (x, y, or z) with the average frequency of average WBM in each group was not the best method to determine a relationship. Although, the current coherence results may be evidence that other mechanisms play a role in the increased ERROR in tracking performance, a more specific analysis is unquestionably required.

Some important issues to consider when reviewing the current findings are that dyskinetic patients differed from non-dyskinetic patients significantly in the duration of disease, a mean disease duration of 15 yrs in dyskinetic patients and 6 yrs in non-dyskinetic patients. It could be argued that the increased number of years since diagnosis in the dyskinetic
group may have resulted in greater deficits due to underlying disease, resulting in increased error in tracking. However, dyskinetic patient error was the result of increased velocity as opposed to decreased velocity. In addition, it is important to consider that dyskinetic patients were not tested in the OFF condition. A measure of error in the OFF state may help to determine the influence of a greater number of years since diagnosis. Comparison of the tracking traces of the same dyskinetic patients in the OFF state with those recorded during peak-dose drug-induced dyskinesia may indicate whether the deviations observed in the present study are in fact the result of hypermetric voluntary movement.

With over 100,000 Canadians presently diagnosed with Parkinson's disease, the growing need for better medications, clinical assessment, and overall increased quality of life is undeniable. The current methods of DID assessment were extremely effective in the quantification of whole body DID during voluntary movement. The ability to accurately quantify whole body DID during voluntary movement is in itself of major importance. Quantification of the increase in motor overflow with voluntary movement and determination of the relationship between DID and error in performance has many clinical applications. The recorded difference in motor performance between dyskinetic and non-dyskinetic patients may be useful in determining the point at which Parkinson's patients are primed from L-dopa therapy. This information could then be correlated with disease duration, L-dopa dosage, and age, in order to develop more effective medication regiments, also determining the clinical effectiveness of new and existing medications. Methods to assess the severity of DID are
essential in order to further the current understanding of basal ganglia dysfunction in Parkinson’s disease and the altered mechanisms of the basal ganglia after years of L-dopa treatment. The current study may not present definitive answers to these questions, but does present valuable information as to the influence of DID on voluntary motor performance.

Future research may be directed towards characterizing the influence of DID on performance in Parkinson’s disease as compared to the influence of choreic movements in other neurological disease such as Huntington’s disease and Schizophrenia. A better understanding of the influence of choreic-type movements resulting from different neurological dysfunction could be essential in furthering the understanding of the basal ganglia mechanisms underlying the influence of dyskinesia on voluntary motor performance.

In conclusion, it should be noted that the current methods of assessment had not been employed to investigate DID prior to the current study. Although MT has been used extensively to investigate PARKINSON’S DISEASE, the current protocol incorporating magnetic tracking technology was developed specifically for this Masters’ thesis. The programs used for data analysis were also novel programs written expressly for this protocol.
REFERENCES


