THE IMPACT OF DRUG-INDUCED DYSKINESIAS ON RAPID ALTERNATING MOVEMENTS IN PATIENTS WITH PARKINSON'S DISEASE

by

MEHRDAD MARCO GHASSEMI

A thesis submitted in conformity with the requirements
for the degree of Master of Science in Applied Health Sciences

Supervisor: Christian Duval, PhD

Faculty of Applied Health Sciences
Brock University

ABSTRACT

We investigated the likelihood that hypokinesia/bradykinesia coexist with drug-induced dyskinesias (DID) in patients with Parkinson's disease (PD). The influence of dyskinesias on rapid alternating movements (RAM) was investigated in ten dyskinetic patients (DPD). Their motor performance was compared to that of ten age/gender-matched non-dyskinetic patients (NDPD) and ten healthy control subjects. Whole-body magnitude (WBM) and fast pronation-supination at the wrist were recorded using 6-degrees of freedom magnetic motion tracker and forearm rotational sensors, respectively. Subjects were asked to pronate-supinate their dominant hand for 10s. Pre- and post-measures were taken in a neutral position for 20s. RANGE (measure of hypokinesia), DURATION (measure of bradykinesia), VELOCITY (measure of bradykinesia) and IRREGULARITY (measure of fluctuations in movement amplitude) were used to assess RAM performance. Results showed that DPD patients had greater WBM than NDPD and control groups during rest and RAM performance. There were no differences in performance between NDPD and DPD groups for RANGE, DURATION and VELOCITY, despite significant longer disease duration for the DPD group (DPD = 15.5 ± 6.2 years versus NDPD = 6.6 ± 2.6 years). However, both the NDPD and DPD groups showed lower RANGE, longer DURATION, and reduced VELOCITY compared to controls,, suggesting the presence of bradykinesia and hypokinesia. In the case of IRREGULARITY, DPD patients showed clear fluctuations in movement amplitude compared to the NDPD and control groups. However, the lack of correlation between WBM and IRREGULARITY within the DPD group (Spearman's rank order, Rho = 0.31, $p > 0.05$), suggests that DID was not the primary cause of the fluctuating movement

amplitude observed in that group. In conclusion, these findings suggest that DID may coexists with bradykinesia and hypokinesia, but that they are not inevitably accompanied with worsening motor performance.

ACKNOWLEDGMENTS

By and large, I would like to thank everyone who has made this endeavour possible through his or her direct and/or indirect support. There are too many to name and such your individuality will always be appreciated and never forgotten. A special thanks to my colleagues at the movement disorders lab. The last two years have been not only exquisite academically, but also a continuous test of dedication, hard work, teamwork and a relentless effort to excel and aid scientific research in finding answers for people in need of answers. Appropriately, I would like to sincerely thank the men and women who willingly participated in our study, as well as the generous support of Parkinson Society Canada, Canada Foundation for Innovation and Ontario Innovation Trust. This study could not have been possible without your contributions and I feel honoured and privileged to be involved in such cause and calibre of research. Fortunately, my circumstance within this program also allowed a circle of exceptionally talented committee members - Dr. Atkin, Dr. Cadoret and Dr. Jog, who aided me in the development of my dissertation. I thank you for your invaluable time and suggestions. I would also like to truly thank the people who are most dear to me - my family and friends. Mom, Dad, Mahyar and Mehrzad, your continuous love and support can never be repaid or replaced. Julie, I am thankful for your thoughtfulness and encouragement. Last but by no means least, this dissertation could not have been possible without the insight and guidance of Dr. Christian Duval. Dr. Duval not only served passionately, as my supervisor, but also encouraged and challenged me throughout my academic program. I thank you for this opportunity and not accepting anything less than my best efforts.

TABLE OF CONTENTS

INTRODUCTION

Despite revolutionary developments in understanding the pathophysiology and pharmacology, the cause of Parkinson's disease (PD) still remains a mystery with no cure and as yet, no means to even predict or prevent the disease. The prevalence of PD typically increases with age (Bower et al. 1999; [a]Schrag et al. 2000); according to recent Canadian statistics, PD affects nearly 100,000 Canadians. Moreover, due to the aging of the "baby boomers" it is likely that the overall precedence of PD will rise within the near future (Just & Osergaard 2002).

The fundamental neuropathological feature of PD is the result of gradual loss of dopamine-producing neurons in the substantia nigra pars compacta (SNc), located within the basal ganglia (Carlsson 1959; Ehringer & Hornykiewicz 1960). During the early 1960's, this discovery allowed for the development of L-3,4-dihydroxyphenylalanine (levodopa), a precursor of dopamine (DA) that is transformed into DA within the brain. Thus far, the gold standard treatment for PD is levodopa; and secondary to that DA agonist drugs. Specifically, levodopa in combination with a peripheral dopa decarboxylase inhibitor is the most accepted and efficacious agent for the treatment of PD. This treatment combination is effective throughout the course of the illness; however, its use is associated with the occurrence of long-term complications, particularly the appearance of dyskinesias (i.e. involuntary movements) (Bedard et al. 1986; Filion 2000; [a]Obeso et al. 2000). The prevalence of drug-induced dyskinesia (DID) in PD patients has been estimated at approximately 20-30% after five years of levodopa treatment (Ahlskog & Muenter 2001). Although less optimistic estimates propose an increase incidence of 10% per year after

initiating levodopa treatment, and 80-100% after 10 years (Baas 2000). Additionally, dyskinesias are the most common and disabling side effect of levodopa treatment (Rascol et al. 2000). With increasing duration of levodopa therapy, there is also a rise in both frequency and severity of DID. This represents a major source of disability for PD patients (Damiano et al. 2000; Pechevis et al. 2001), as well as limiting the ability of physicians to increase the levodopa dose to provide satisfactory control of parkinsonian symptoms. Although some theories have proposed pharmacodynamic and pharmacokinetic properties of levodopa in accordance with nigrostriatal damage to play a part in DID onset, the cause of DID is still unknown (Bedard et al. 1992; Rascol et al. 1998).

Because of recent improvement in drug therapies as well as drug management, patients with PD are now living longer with the disease. Although in general the mortality rate of PD patients is on a decline, it inevitable that the majority of these patients will experience DID during their course of the disease. Accordingly, it is vital that we improve our understanding of these involuntary movements in order to understand their impact on the quality of life of PD patients.

Given the aforementioned concerns, only a small number of studies have attempted to quantify DID and its affect on voluntary movement in PD patients (Durif et al. 1999). More importantly, no study has provided a three-dimensional (3-D) assessment of the impact of dyskinesias on voluntary movement. Such information would not only be valuable with regard to patient care and quality of life, but would also help in the understanding the origin and nature of dyskinesias, hence providing far-reaching insights into the organization of the basal ganglia and motor systems. This knowledge will consequently add to the development of a robust method for assessing newly emerging

drugs and surgical treatments aimed at improving motor performance and reducing the incidence of DID. Accordingly, the general objective of the proposed research study is to investigate the influence of DID on voluntary motor behaviour in patients with PD.

LITERATURE REVIEW

The literature review section of this paper will discuss current literature regarding PD and DID; specifically examining the basal ganglia circuitry, pathophysiology of bradykinesia, treatments available for PD, pathophysiology and phenomenology of DID. The latter will then lead to the development of the rational for this research study.

2.1 Parkinson's Disease (PD)

In 1817 James Parkinson in his monograph titled, "An essay on the shaking palsy", first described the condition that now bears his name (Parkinson 1817). Yet, it was not until 78 years after Parkinson's monograph that the substantia nigra was proposed to be associated with Parkinson`s disease (PD) (Brissaud 1895). The four cardinal motor features of PD are bradykinesia (slowness of movement), resting tremor, rigidity and postural instability (Kahn & Britton, 2004). During the early stages of the disease (even prior to diagnosis), patients usually notice the resting tremor first, since it is physically observable (Fahn 2003). In some cases bradykinesia will present itself as the first symptom; however, in some patients it is not perceived as a problem, thus delaying diagnosis and treatment. Some clinical signs of bradykinesia could include reduced facial expressions, slower and smaller hand writing, reduced arm swing or leg stride, and softening of the voice (Khan & Britton 2004). With the progression of disease, the gradual loss of dopamine inevitably leads to gradual worsening of symptoms.

2.1.1 Diagnosis

The ability of physicians to distinguish between idiopathic PD (no known aetiology) and other classifications of Parkinsonism is admittedly difficult (considering clinical characteristics are at times similar). This has been well documented, since post-mortem reports account up to 25 percent of the population as misdiagnosed (Khan & Britton 2004). Currently, there is no gold standard diagnostic test for PD patients *in vivo*. A thorough diagnosis can only be made post-mortem (Guttman et al. 2003; Khan & Britton 2004). Presently, the most reliable method for diagnosing PD is by means of clinical examinations, which usually occur over multiple visits.

Since PD is a progressive disease, not all four cardinal symptoms might present themselves at the same time. Nonetheless, it is essential for two of the cardinal symptoms to be present prior to diagnosis, in which one of the cardinal symptoms must be a resting tremor or bradykinesia (Fahn 2003). In addition to clinical examinations, imaging techniques and nuclear medicine studies have been helpful in distinguishing parkinsonism-plus syndromes from Idiopathic PD. However, these techniques are still considered experimental, and further inquiry for their role in PD diagnosis is required (Guttman et al. 2003).

2.1.2 Putative Risk Factors

Currently, it is proposed that PD may be due to a combination of interacting environmental and genetic factors. These multifactorial speculations propose that one or numerous susceptible genes are interacting with one or numerous environmental factors (i.e. occupation, trauma, toxins or infectious diseases) (Lai et al. 2002). Twin studies have played a significant role in attempting to understand these interactions. However, they have

failed to validate genetics as the major cause of PD. For instance, the largest twin study to date, reported the concordance rate of monozygotic twins to be similar to that of dizygotic twins, signifying that genetics does not play a vital role in causing PD (Tanner et al. 1999). Tanner et al. (1999) however, reported a significantly higher concordance rate in 16 monozygotic twin pairs diagnosed before the age of 50 years, an indication that genetics may play a bigger part in young-onset PD.

Epidemiological studies have linked several environmental factors to PD, these include: rural living, farming, exposure to metal, well water, pesticides, diets high in animal fat or carbohydrates, ,head trauma, infectious diseases, and low consumption of anti-oxidant foods rich in vitamin C and E (Lai et al. 2002; Warner & Schapira 2003). Of the numerous risk factors studied, exposure to pesticides has been linked more consistently than any other environmental risk factor (Poirier et al. 1991; Barbeau et al. 1987; Khan & Britton 2004). Despite speculations, no specific environmental agent has been documented.

2.2 The Basal Ganglia

The basal ganglia refer to a collection of nuclei deep within the midbrain of the cerebral hemispheres. One of its main functions is to support the planning and learning of motor movement by means of cortical communication. These nuclei consist of a complex network of parallel loops that receive synaptic information from the entire cortex and return this information via the thalamus to multiple cortical points, including the origin (Alexander et al. 1990; Alexander & Crutcher 1990) (Figure 1). In particular, there are five parallel loops: 1) motor; 2) oculomotor (eye movement); 3) lateral orbitofrontal (personality); 4) dorsal lateral prefrontal (executive functions) and 5) limbic (emotions) (Alexander & Crutcher 1990: Alexander et al. 1990). The pathophysiology of movement

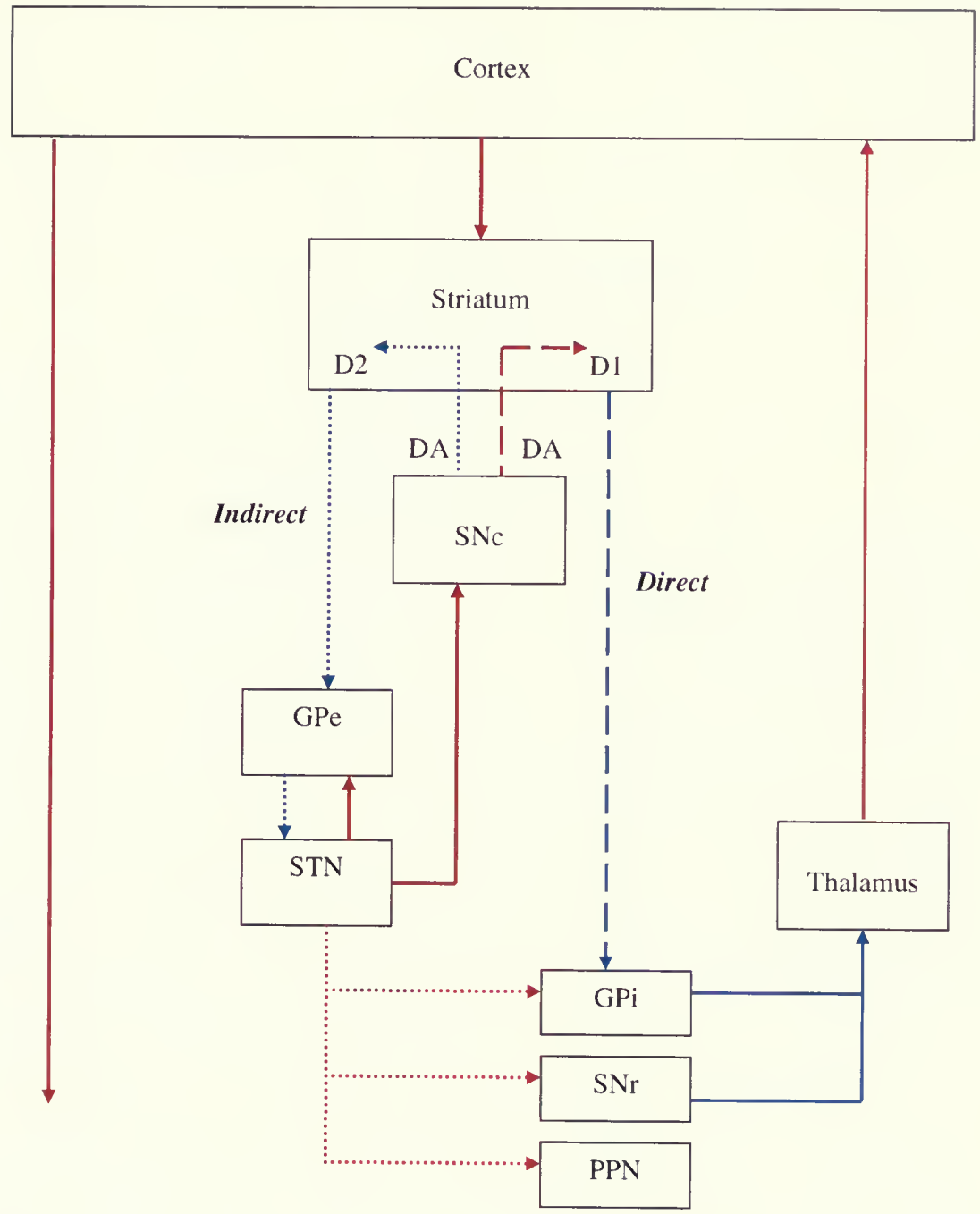
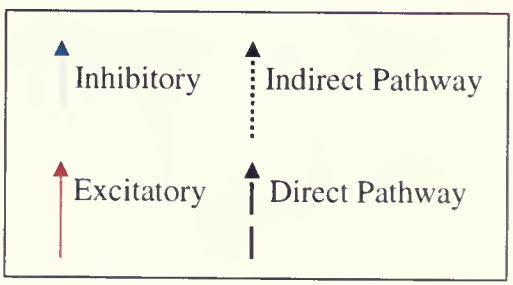


Figure 1.
Normal schematic of the current model of the basal ganglia. Note: The striatum communicates with the output neurons in the GPi and SNr through a direct pathway and with synaptic connections in the GPe and STN through an indirect pathway (inspired by [b]Obeso et al. 2000).



disorders such as PD predominantly involve the motor loop (Figure 1); therefore, for the purpose of this thesis, the other abovementioned loops will not be discussed further.

2.3 Basal Ganglia Circuitry

The basal ganglia are comprised of the striatum (caudate nucleus and putamen), globus pallidus internus (GPi) and externus (GPe), subthalamic nucleus (STN), substantia nigra pars compacta (SNc) and reticulata (SNr) (Figure 1) ([b]Obeso et al., 2000). The striatum represents the 'input' portion of the basal ganglia, since it receives somatotopic organized afferent information from the precentral/supplementary motor areas of the cortex, thalamus and SNc (DeLong 1990; Bezard et al. 2001; Alexander et al. 1990). The GPi and SNr represent the 'output' structures of the basal ganglia, since most of their afferent information projects to the ventral anterior and ventral lateral (VA-VL) thalamus (Alexander et al. 1990; Bezard et al. 2001). The thalamus then projects back to the cortex, where information is then projected to brainstem portions (i.e. pedunculopontine nucleus [PPN]) and subsequently the spinal cord pathways (DeLong 1990). There are also other neural circuits significant to the basal ganglia circuitry, such as direct GPi projections to the PPN; however these will not be discussed in detail.

Precentral/supplementary motor areas of the cortex project to the striatum, specifically to the posterolateral putamen, where they form excitatory glutamate synapses with y-aminobutyric acid (GABA)-containing neurons (Alexander et al. 1990; [b]Obeso et al. 2000). Striatal neurons set apart two efferent pathways that connect the striatum to the basal ganglia output nuclei: the so-called 'direct' and 'indirect' pathways. The direct pathway is comprised of inhibitory GABA-ergic neurons that express mostly dopaminergic D1 receptors, and thus inhibit the GPi/SNr (Figure 2). Direct pathways neurons also use

substance P and opioids derived from the precursor preproenkephalin (PPE)-B (the dynorphins, leucine-enkephalins and α-neoendorphin) as co-transmitters ([b]Obeso et al., 2000; Brotchie, 2000). Striatal neurons in the indirect pathway also possess GABA-ergic neurons and express mostly D2 receptors that connect the putamen with the GPi/SNr via synaptic connections through GPe and STN (Figure 3). Projections from the GPe to the STN are also GABAergic and inhibitory. Neurons of the indirect pathway use enkephalins as co-transmitters (Bezard et al. 2001). Moreover, neurons derived in the STN are glutamergic and therefore excite neurons in the GPi/SNr as well as the pedunculopontine nucleus (PPN) (Alexander et al. 1990; [b]Obeso et al. 2000). In summary, striatal projections from the indirect pathway lead to inhibition of the GPe, disinhibition of the STN and excitation of the GPi/SNr. Activation of the direct pathway inhibits basal ganglia output cells, while activation of the indirect pathway results in their excitation. In other words, activation of the indirect pathway is associated with suppression of movement, while activation of the direct pathway is associated with the facilitation of movement (Alexander et al. 1990; [b]Obeso et al. 2000) (Figure 4).

Dopaminergic projections from the SNc are predominantly directed to GABA-ergic neurons of the striatum. The above model suggests that DA modulates glutamatergic effects on cortico-striatal inputs by applying a binary effect on striatal GABA-ergic neurons: activating D1-receptor-expressing neurons in the direct pathway and inhibiting D2-receptor-expressing neurons in the indirect pathway (Cepeda et al. 1993; Gerfen et al. 1990) (Figure 4). During normal movement, increased nigra-striatal DA projections will increase thalamo-cortical activity (Figure 4), thus creating (in general) facilitation of movement via the direct and indirect pathways.

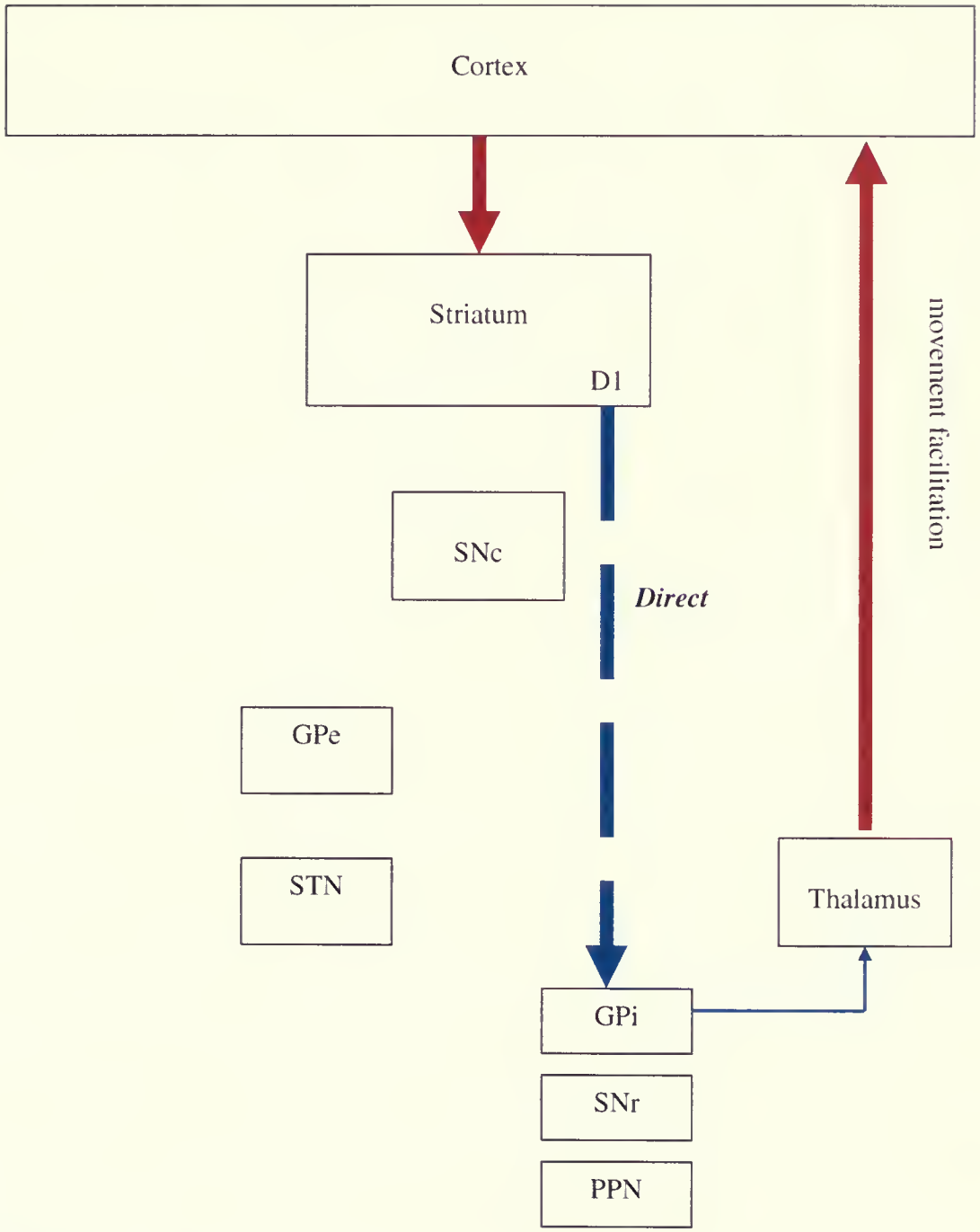
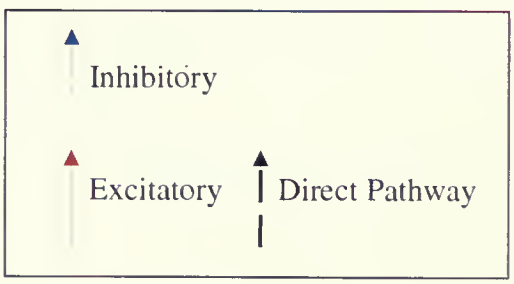


Figure 2.
Normal schematic of the current model of the basal ganglia during movement: Direct pathway. The thickness of the arrows indicates the degree of activation
Note: The direct pathway facilitates desired movements. Increased activity from cortex will provoke increased thalamo-cortical activity (inspired by [b]Obeso et al. 2000).



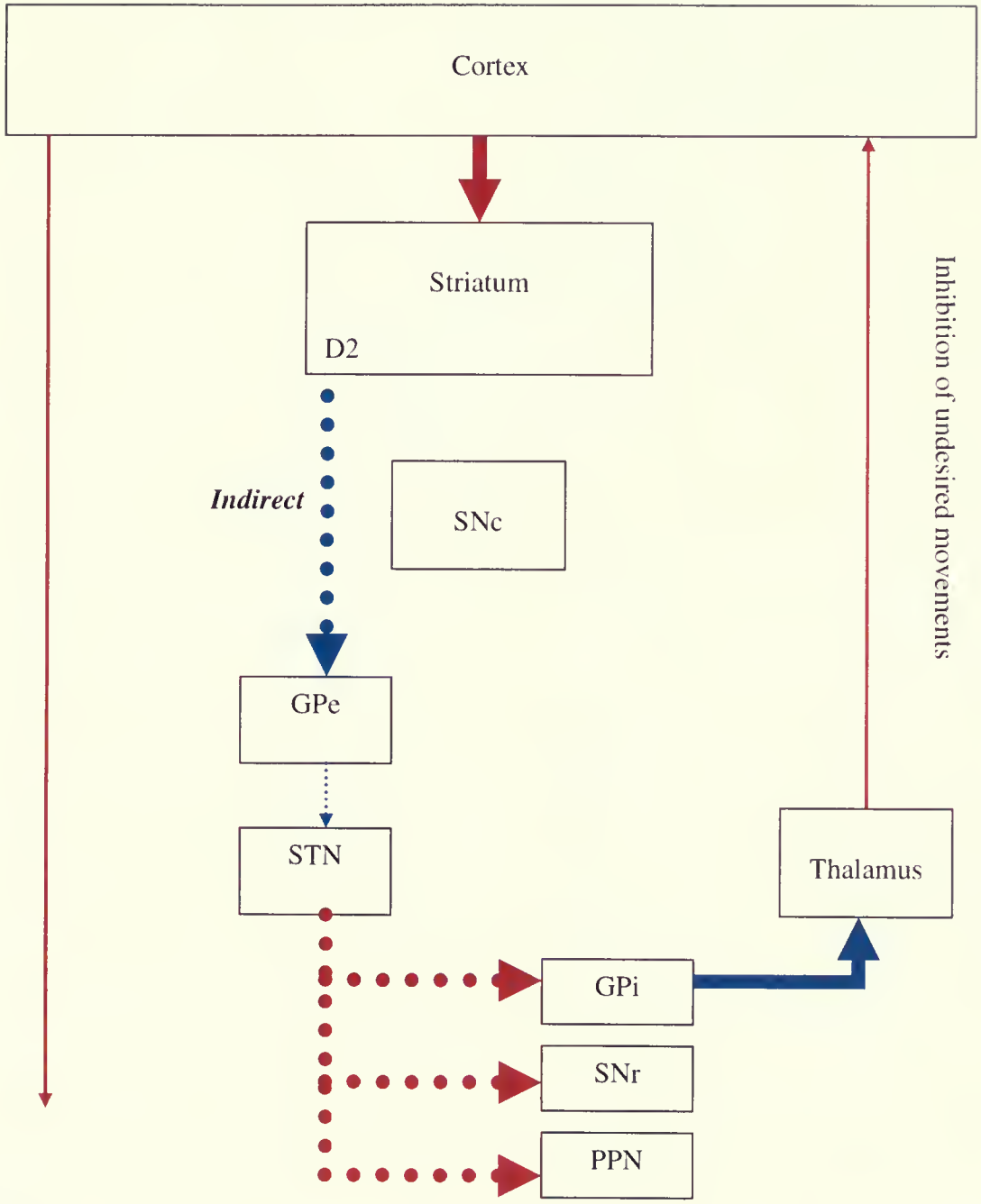
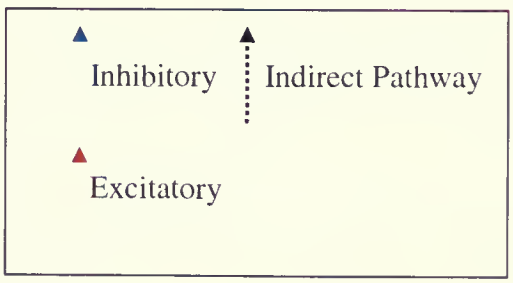


Figure 3.
Normal schematic of the current model of the basal ganglia during movement: Indirect pathway.
The thickness of the arrows indicates the degree of activation of each projection Note: The indirect pathway inhibits undesired movements. Increased input from the cortex will provoke decreased thalamo-cortical activity (inspired by [b]Obeso et al. 2000).



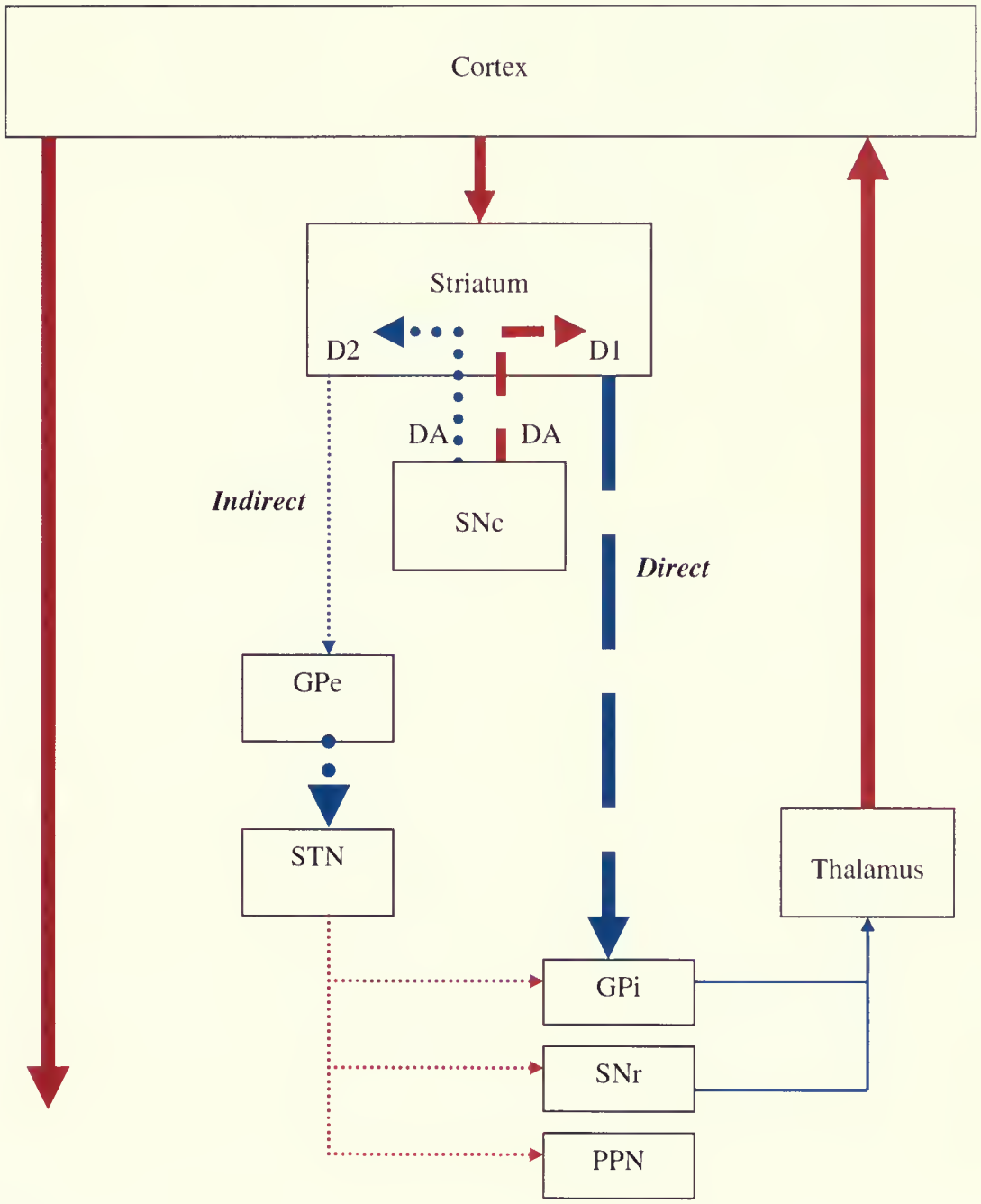
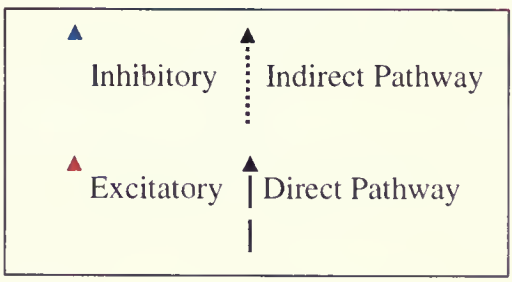


Figure 4.
Normal schematic of the current model of the basal ganglia: Dopamine and movement. The thickness of the arrows indicates the degree of activation of each projection. Note: DA is thought to inhibit neuronal activity in indirect pathway and to excite neurons in the direct pathway. Increased DA in the striatum will increase thalamo-cortical activity (inspired by [b]Obeso et al. 2000).



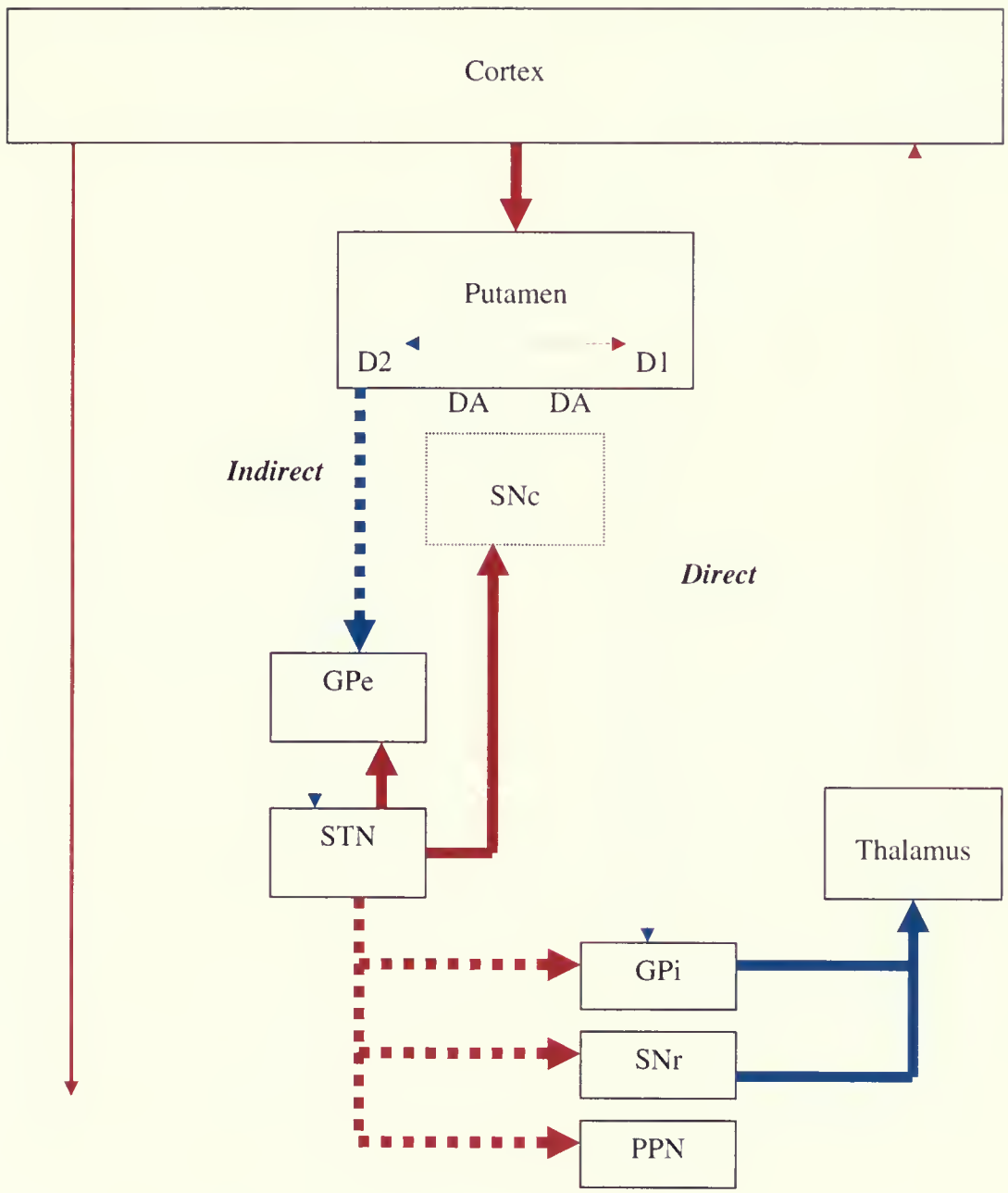
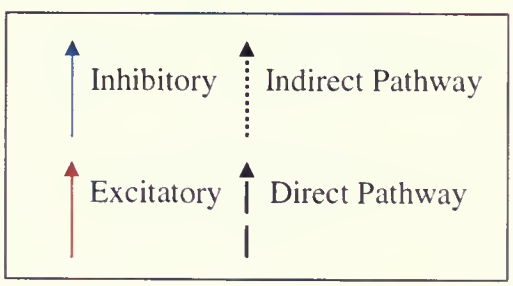


Figure 5.
Parkinsonian state. The thickness of the arrows Indicates the degree of activation of each projection. Note: DA depletion leads to over-activity in STN neurons leading to excess excitation of neurons in the GPi/SNr and overinhibitionof thalmo-cortical and brainstem motor pathways (inspired by [b]Obeso et al. 2000).



2.4 Current Model of the Basal Ganglia in Parkinson's disease

In PD, the progressive death of dopaminergic neurons upsets the symmetry between the direct and indirect pathways, and as a consequence induces hyperactivity of the GPi (Albin et al. 1989; DeLong 1990) (Figure 5). Based on the current model of the basal ganglia, it is evident that DA deficiency leads to a series of functional changes in striato-pallidal circuits (DeLong, 1990; Albin et al. 1989; [b]Obeso et al. 2000). Existing evidence suggests that the loss of dopaminergic neurons decreases the normal inhibition that DA exerts on D2-bearing GABA/enkephalin neurons in the indirect pathway and reduces dopaminergic activation of D1-bearing GABA/substance P/dynorphin neurons in the direct pathway (Penney & Young 1986; DeLong 1990; [b]Obeso et al. 2000) (Figure 5). Diminished dopaminergic inhibition of neurons in the indirect pathway leads to excess inhibition of the GPe, disinhibition of the STN and increased excitatory activation of GPi/SNr neurons (DeLong 1990). The reduced dopaminergic activation of neurons in the direct pathway results in a decreased inhibition of the GPi/SNr ([b]Obeso et al. 2000; DeLong 1990). Therefore, the net result is increased excitation of GPi/SNr neurons via the indirect pathway and decreased inhibition via the direct pathway. This leads to increased output from the GPi/SNr, excessive inhibition of thalamo-cortical and brainstem neurons and the development of parkinsonian features (Albin et al. 1989; DeLong 1990).

Despite the fact that the current basal ganglia model succeeds logically in explaining the motor features of PD, it is admittedly incomplete. It does not account for why tremor, rigidity, bradykinesia, gait dysfunction and postural instability are present in differing degrees in diverse population of patients or why they respond differently to levodopa or surgical procedures (Parent & Cicchetti 1998; [bcd]Obeso et al. 2000). The model

also does not account for why some PD patients develop DID and some do not, specifically among YOPD and LOPD populations. It is evident that the model does not fully address the importance of feedback loops between the STN, GPe and GPi ([b]Obeso et al. 2000) or the role of the PPN, which receives major neural projections from the GPi and STN and provides excitatory innervation to the SNc (Parent & Cicchetti 1998). This might explain why thalamic lesions have not been reported to induce parkinsonian features or why surgery on the output nuclei of the basal ganglia does not lead to deficits in specific motor performances ([c]Obeso et al. 2000).

2.5 Pathophysiology of Bradykinesia

Slowness of movement (bradykinesia) is essentially the main characteristic and most disabling feature of PD. In addition to bradykinesia, the terms "akinesia", poverty of initiating movement and "hypokinesia", smaller movements, are also used in describing slowness of movement. Throughout the early stages of the disease, manifestation of bradykinesia/hypokinesia/akinesia is observed with speaking, walking or standing and sitting in and out of chairs (Fahn 2003). Patients may illustrate reduction in leg stride and arms sway when walking, decreased facial expression and amplitude of voice and slower, smaller handwriting (Fahn 2003). As the disease progresses, there is a steady worsening of bradykinesia, despite levodopa treatment. At its worse, PD patients may become completely akinetic, requiring extreme concentration to initiate and perform the simplest of movements.

Based on the current PD model (Albin et al. 1989; DeLong 1990), the manifestation of bradykinesia/hypokinesia or deficits in rapid voluntary movement is caused by the gradual loss of DA within the SNc. This loss of DA results in excessive and abnormal

inhibitory projections from the basal ganglia output structures to the thalamus (DeLong 1990). It is suggested that these abnormal neural firing patterns within GPi-thalamo-cortical neural circuit produce "neural noise", which is then projected to the cortex (Berardelli et al. 2001). Consequently, it is the projection of this "neural noise" to the motor cortex that is proposed to be the "primary" basis of bradykinesia, which in turn results in the inadequate facilitation of voluntary movements (Berardelli et al. 2001).

2.5.1 Secondary Causes of Bradykinesia

It is also suggested that other factors such as rigidity, muscle weakness and tremor may play a "secondary" role in bradykinesia. Presently, it has been difficult for researchers to accurately measure the effect of rigidity on bradykinesia, although some authors (Tatton & Lee 1975; Johnson et al. 1991) have claimed long-latency stretch reflexes may play a part in slowness of movement; if reflexes are generated in an antagonist muscle during a contraction of an agonist muscle.

Most experiments comparing strength of PD patients with normal subjects have reported mild reductions in strength in different muscle groups (Jordan et al. 1992; Stelmach et al. 1989). The general idea is that patients with PD exhibit weakness in some muscle groups, and this weakness contributes to slowness of movement. Brown et al. (1997) demonstrated that tremor at ~10 Hertz (Hz) in patients OFF therapy prohibits maximum fusion of motor unit contraction, which can be a factor contributing to weakness. The role of tremor in bradykinesia will be discussed in detail in a later section; mainly because tremor represents an interesting model of involuntary motor behaviour that may affect voluntary movements.

2.5.2 Repetitive Movements

Characteristically, the extent of bradykinesia is persistent throughout simple movements (i.e. flexion/extension), however if PD patients are asked to perform complex tasks (movements), either by repeating the task or by combining it with other movements, bradykinesia becomes more prominent. In particular, this phenomenon is brought about when PD patients perform rapid alternating movements (RAM), such as wrist pronation-supination (Agostino et al. 1998; Johnson et al. 1998; Duval et al. In Print). Hence, RAM is often used as a direct measure of slowness of movement (Okada & Okada 1983; Beuter et al. 1999; Duval et al. 2005 In Print). As a result of this phenomenon, patients typically display hypokinesia and fatigue. In more severe cases, patients may also exhibit hesitation in initiating movements or arrests in ongoing movement.

2.6 Treatment of PD

Symptomatic relief through DA replacement therapy still remains as the main medical approach for treating PD. Presently, levodopa in combination with carbidopa (to prevent DA from metabolizing peripherally) is the most powerful and efficacious pharmacological treatment for PD patients. Recently, the use of catechol-O-methyltransferase (COMT) (to prevent metabolization of DA) inhibitor in combination with levodopa has shown to extend the plasma half-life of levodopa (Kaakkola 2000). Next to levodopa, the second most efficacious drugs in treating PD are DA agonists. In comparison to levodopa, DA agonists have been shown to bring about psychosis, hallucinations, and confusion, especially in the elderly. Conversely, DA agonist therapy has shown to reduce motor fluctuations and DID more so than levodopa (Rascol et al. 2000; Parkinson Study

Group 2000). Despite this improvement, the same studies reported levodopa to produce greater symptomatic relief than DA agonists.

Because a better understanding of the basal ganglia has been achieved, surgical procedures, such as stereotaxic deep brain stimulation (DBS) are increasingly becoming more available for the treatment of PD. The reason for this popularity is due to the fact that previous lesioned-based procedures such as thalamotomy or pallidotomy involve greater risk in causing neurological deficits (Fahn 2003). With DBS however, the stimulation can be adjusted and electrodes from their respective sites can be removed if needed (Fahn 2003). In particular, DBS of the STN has been shown to be the most efficacious site for reducing bradykinesia (Fahn 2003). This reduction in bradykinesia also allows for a reduction in levodopa treatment, as a result decreasing the severity of DID in PD patients.

2.7 Drug-Induced Dyskinesia (DID)

During the early stages of PD, patient- response to levodopa is excellent and its benefits endure even if a single dose is neglected. However, as the disease progresses, most patients begin to experience motor fluctuations in which levodopa does not adequately treat the Parkinsonian symptoms ([a]Obeso et al. 2000). As a result, it becomes increasingly difficult to deliver a dose of levodopa that provides both an anti-parkinsonian effect and prevent side effects such as DID.

2.7.1 Putative Risk Factors of DID

Reports from epidemiological studies have indicated variables such as age, age of onset of PD, and time from onset to start of drug therapy to be correlated with the incidence of dyskinesias (Blin et al. 1988; de Jong et al. 1987; Pederzoli et al. 1983; Lyons et al.

1998; Kostic et al. 1991). Schrag and Quinn (2000) suggested that dosage levels of levodopa as well as duration of treatment and disease were associated with a higher incidence of dyskinesias. Dyskinesias also appeared sooner in YOPD than LOPD (Schrag & Quinn 2000). These results support a similar study conducted by Grandas et al. (1999), where the age of onset of PD and the initial levodopa dose were the main independent predictors of DID using levodopa. Additionally, YOPD patients had a higher risk of developing DID during the first two years of drug therapy. Other studies have also confirmed this notion (Schrag, & Quinn 2000; Bass 2000), however, the underlying principle behind this observation is still not clear.

2.8 Phenomenology of DID

Abnormal movements caused by DID can be classified into 4 distinct motor patterns: Chorea; Dystonia; Ballism and Myoclonus.

2.8.1 Chorea

Chorea refers to purposeless, swift, unsustained movements that occur during "on" periods (Vidailhet et al. 1999; Hoff et al. 1999). This type of abnormal movement is the most common form of DID and occurs in both peak-dose (peak plasma level of levodopa or agonist drugs) and biphasic dyskinesia (occurring both before the onset of maximal levodopa benefit and as the levodopa effect is wearing off) (Fahn 2000). A characteristic feature of chorea is that the movements are unpredictable in timing, direction, and distribution (i.e. random). The mildest forms of choreic movements are distinguished as "overflow chorea". These movements usually occur during active voluntary movements and are not present at rest (Hoff et al. 1999; Fahn 2000). For instance, if the individual is

able to perform rapid repetitive movements of the wrist, choreic dyskinesias might arise elsewhere in the body (i.e. non-performing limbs).

2.8.2 Dystonia

After chorea, dystonia is the second most common form of DID (Fahn 2000). These movements are characterized by sustained muscle contraction and they can occur either during peak-dose dystonia, beginning or end-off-dose dystonia, or "off" dystonia (Ilson et al. 1984). Dystonic movements are more severe than choreic movements and therefore can cause further interference during activities of daily living.

Peak dose dystonia often occurs in a restricted body part. Some examples include sustained, fixed contractions of the trapezius muscle, an arm or leg muscle, or facial muscles (Ilson et al. 1984; Fahn 2000). Moreover, "off" dystonia is most commonly observed in the early morning affecting one foot, but can occur at any time of the day when the patient is "off". The contractions are usually sustained and long lasting in a restricted body part, often causing extreme pain (Ilson et al. 1984).

2.8.3 Ballism

Ballism refers to large (amplitude) choreic movements of the proximal parts of the limbs, causing flinging and flailing movements (Vidailhet et al. 1999). This type of extreme chorea is not common in DPD patients. Although, when it does occur, it can be either unilateral (hemiballism) on the more severe side of Parkinsonism or bilateral (biballism) if PD is bilaterally severe (Fahn 2000).

2.8.4 Myoclonus

Myoclonic jerks refer to sudden, brief, shock-like involuntary movements (Fahn 2000). In PD, the jerks are caused by muscular contractions, usually due to an overdose of levodopa. These types of movements can occur unilaterally or bilaterally in the extremities, typically during sleep, although they may also occur during the day (Fahn 2000). The presence of myoclonus is usually ominous, indicating the presence of cognitive complications from levodopa and often representing either toxicity to levodopa in PD or the development of some other form of Parkinsonism, such as diffuse Lewy-body disease (Fahn 2000).

2.9 Role of Dopamine in DID

Levodopa "honeymoon" period generally lasts 3-5 years, in which symptomatic relief is at its best. Subsequent to this period, most patients eventually experience DID. The development of DID usually require daily treatment of levodopa over several months ([b]Obeso et al. 2000). The same application pertains to the MPTP primate model of Parkinsonism, where doses between 50 mg and 100 mg of levodopa must be administered daily or twice daily for weeks before dyskinesias develop (Calon et al. 1995). Once the manifestation of dyskinesia has taken place, even if therapy is discontinued completely for several weeks, the next initial dose of levodopa will still set off the same dyskinesia in humans and MPTP monkeys (priming phenomenon) ([a]Calon et al. 2000; Pearce et al. 1998). It is suggested that this "priming" effect instigated by levodopa may cause a long lasting permanent change in the brain, resulting in modification of the response of the basal ganglia to exogenous DA ([ab]Calon et al. 2000). Interestingly, there have been recent reports of normal monkeys developing dyskinesias after chronic high doses of levodopa (80 mg)

(Pearce 1999). Accordingly, no conclusions have been made with respect to the precise mechanism responsible for this "priming" effect.

2.10 Current Model of DID: Revisiting the Basal Ganglia Model in PD

According to the current basal ganglia model of PD, dyskinesias occur due to excessive inhibition of neurons in the putamen-GPe projection, and as a result disinhibiting the GPe (Crossman 1987). Consequently, this disinhibition of the GPe results in excessive inhibition of the STN, which in turn decreases the STN excitatory drive and subsequent hypoactivity of GPi/SNr projections (Figure 6) (Crossman 1990; Crossman 1987; DeLong 1990). This reduction in GPi/SNr output leads to decreased inhibition of thalamo-cortical neurons and over-excitation of cortical motor areas, in turn leading to the manifestation of dyskinesias (Crossman 1990; Crossman 1987; DeLong 1990; [b]Obeso et al. 2000). This notion has been supported by experiments on both MPTP animal models (Filion et al. 1991) and PD patients, which show increases in neural activity in the GPe and reduced neural activation in the GPi during DID (Lozano 2000). Despite these observations, the basic cellular mechanisms underlying DID are still unclear. Although the goal of the present study is not to

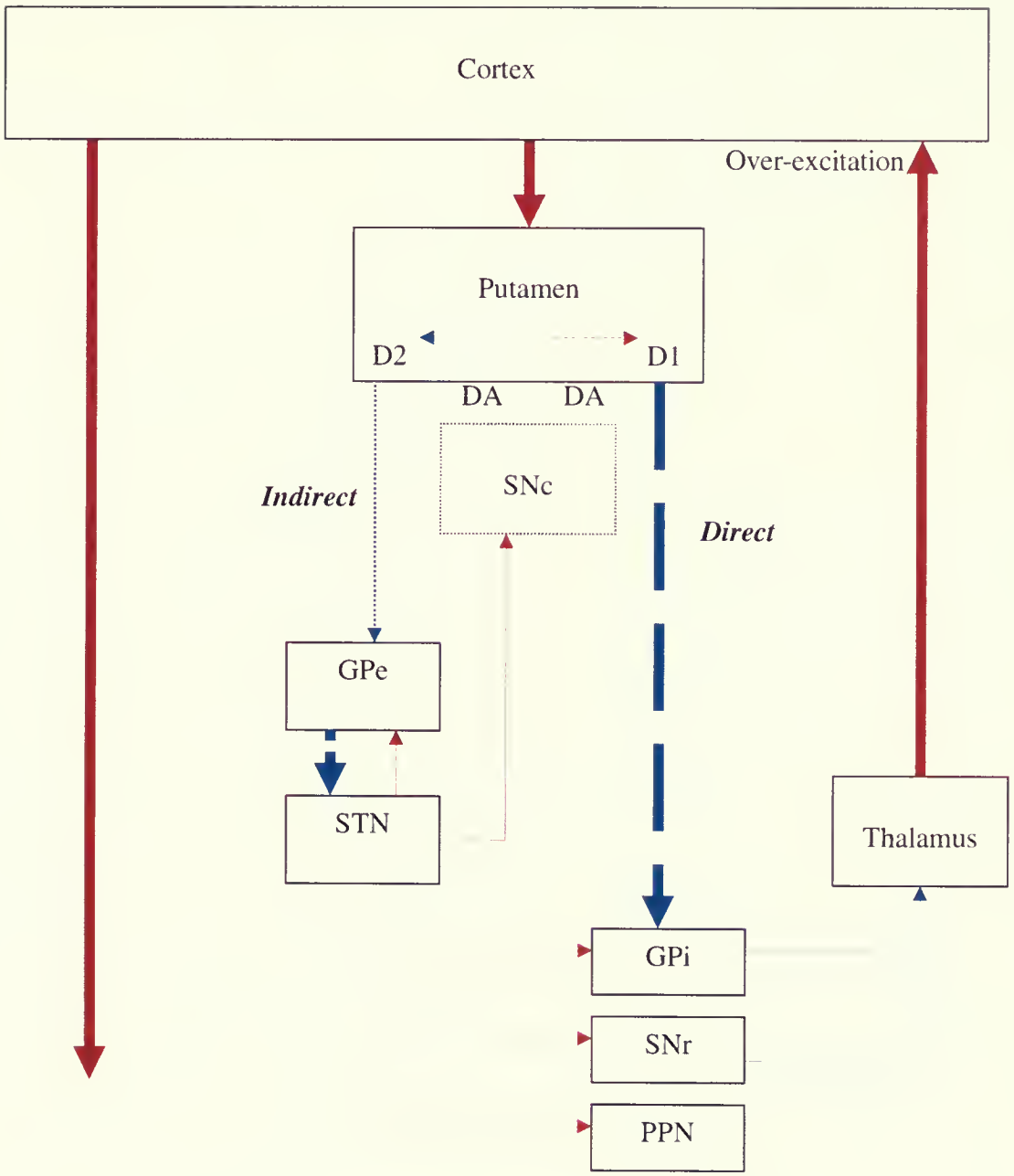
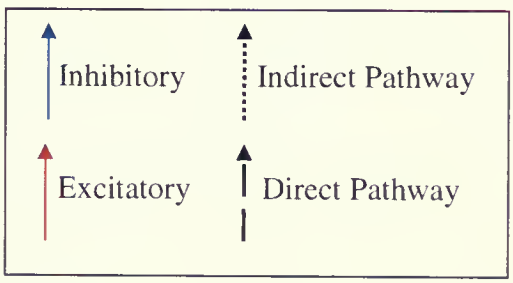


Figure 6.
Dyskinetic state. The thickness of the arrows indicates the degree of activation of each projection. Note: DID is characterized by reduced activity in the STN leading to reduced activation of the GPi/SNr. This results in reduced inhibition of thalamo-cortical neurons and over-excitation of cortical areas (inspired by [b]Obeso et al. 2000).



determine the origin of DID, it is important that we review the basic mechanisms theorised to be responsible for this involuntary release of movement.

2.10.1 DA receptor supersensitivity

Denervation-induced supersensitivity of DA receptors has been generally acknowledged as the most probable mechanism of DID (Bedard et al. 1999; Jenner 2000). According to this hypothesis, supersensitive receptors respond exaggeratedly to DA produced from levodopa, thus leading to dyskinetic movements. This theory proposes that functional alteration at this level may change the equilibrium between the direct and indirect pathways and between the excitatory and inhibitory projections of the cortico-basal ganglia-thalamo-cortical motor loop (Jenner 2000). This assumption is compatible with some valuable clinical observations. For instance, post mortem reports indicate an increase in D2 DA receptor binding sites in untreated PD patients (Lee et al. 1978) and MPTP treated monkeys (Creese et al. 1977). Yet, dyskinesias are virtually never observed after the first initial dose of levodopa, especially since this is period at which the supersensitivity is expected to be present ([a]Obeso et al. 2000). In fact, DID may take several weeks or months to appear (Cotzias et al. 1969; Graybiel et al. 2000). The supersensitivity theory also does not account for why normal monkeys present dyskinesias after being exposed to high oral doses of levodopa (Pearce et al. 1995). Furthermore, data from animal models of PD have indicated that upregulation of D2 receptors is temporary (Murata & Kanazawa 1993; Alexander et al. 1993). Given these discrepancies, it is suggested that DID may appear as a result of pharmacological changes induced by non-physiological levels of exogenous levodopa, instead of DA receptor hypersensitivity (Olanow et al. 2000).

2.10.2 Temporal Profile of Receptor Stimulation

Because levodopa possesses a short pharmacokinetic plasma elimination half-life (60-90 minutes), it is currently suggested that intermittent oral administration of levodopa causes an *abnormal pulsatile stimulation of DA receptors*, which distinctly differs from the more continuous physiologic release of DA (Grace 1991; Olanow & Obeso 2000). This pulsatility caused by exogenous DA can be responsible for a receptor (or a post-receptor) dysregulation and consequent alterations in neural firing patterns (Olanow & Obeso 2000). Moreover, it is plausible that abnormal DA receptor stimulation may be responsible for the activation of different intracellular signalling pathways than those that arise in the normal condition (Sealfon & Olanow 2000). Although several of these molecular changes have been identified (Olanow et al. 2000), the precise location and signals responsible for inducing DID is not known. This theory might explain why DA agonists (drugs that mimic dopamine) which usually have a longer elimination half-life than levodopa, induce less dyskinesia (Bedard et al. 1986; Pearce et al. 1998), or why short-acting DA agonists almost never induce dyskinesias when administered continuously, but do so when administered intermittently (Blanchet et al. 1995).

2.11 Proposed Model of DID

Based on the recent literature, [d]Obeso et al. (2000) have attempted to provide a new model in explaining the manifestation of DID in PD (Figure 7). The model suggests that reduced rate of neural firing in the GPi is not the only factor responsible for the development of DID. Rather, the pulsatile effects of exogenous DA on the striatum triggers abnormal neural firing and in turn affect the temporal and spatial firing patterns in addition

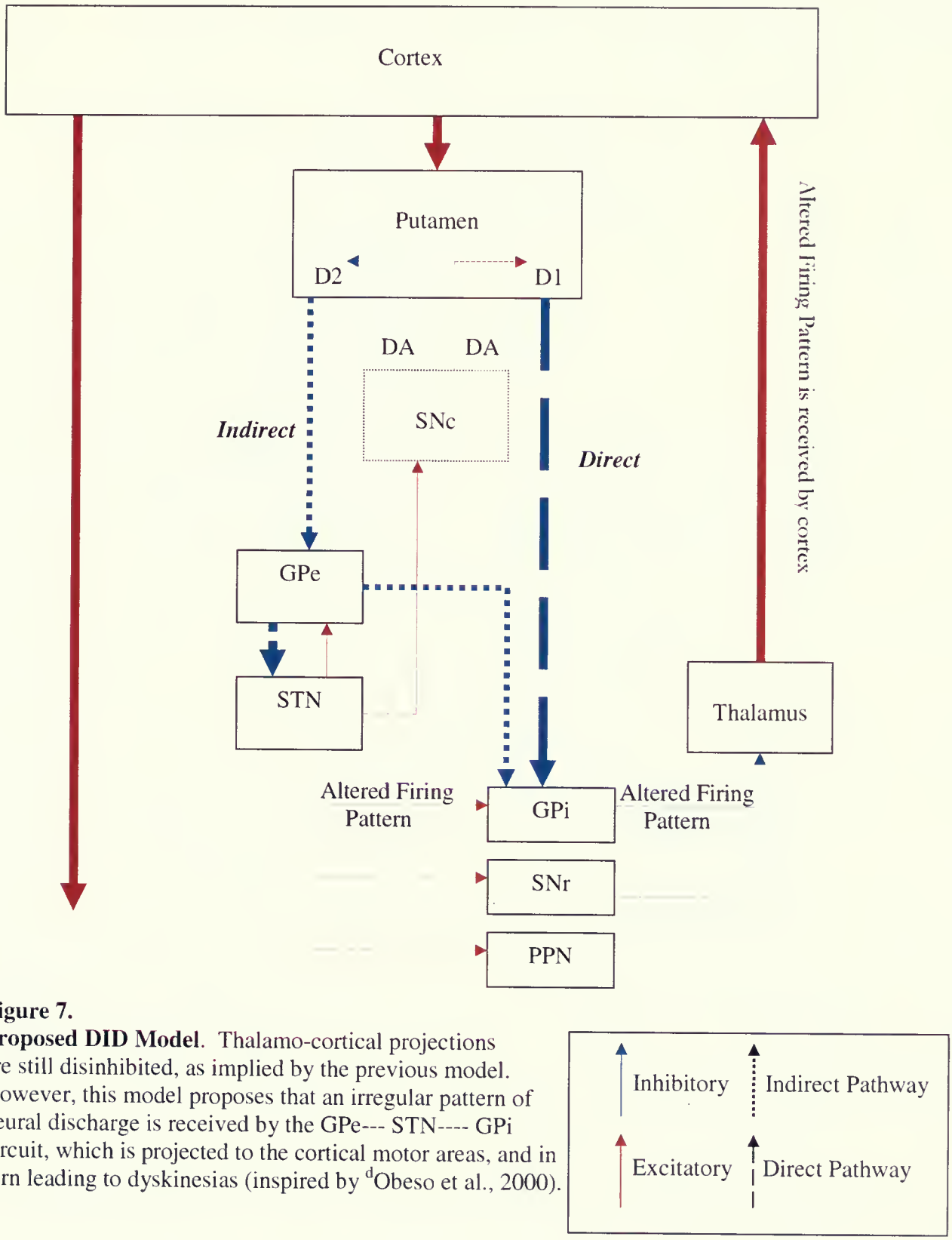


Figure 7.
Proposed DID Model. Thalamo-cortical projections are still disinhibited, as implied by the previous model. However, this model proposes that an irregular pattern of neural discharge is received by the GPe--- STN---- GPi circuit, which is projected to the cortical motor areas, and in turn leading to dyskinesias (inspired by [d]Obeso et al., 2000).

to rate of neural frequency ([d]Obeso et al. 2000). Therefore, it would be elusive to attribute the development of dyskinesias solely on the premise of reduced neural firing in the GPi, as suggested by the above model. In fact, alterations in temporal and spatial firing of the GPi can account for why pallidotomy and DBS reduced or abolished DID, while at the same time improving bradykinesia in PD patients ([d]Obeso et al. 2000). Accordingly, it would be the communication of these abnormal neural patterns from the basal ganglia en route for cortical motor areas that would create dyskinesias in PD patients. Therefore, it can be assumed that hypoactivity of the GPi cannot be solely responsible or even the most significant factor in manifestation of dyskinesias ([d]Obeso et al. 2000). In fact, the same assumption can pertain to the pathophysiology of bradykinesia, tremor and rigidity, since hyperactivity of the GPi does not fully validate the basis of these motor characteristics ([d]Obeso et al. 2000).

2. 12 Rationale

As previously stated. the pathophysiology of bradykinesia is presumed to be the result of excessive abnormal neural firing patterns from the basal ganglia output structures to the cortex (via the thalamus) (DeLong 1990). On the other hand, dyskinesias may be the consequence of reduction in the basal ganglia output structures, leading to decreased inhibition of thalamo-cortical neurons and over-excitation of cortical motor areas (Crossman 1990; Crossman 1987; DeLong 1990; [b]Obeso et al. 2000). Whether these two phenomena can coexist, or are present independently in patients remains to be determined.

As it is the case for tremor, DlD may be considered as an involuntary release of movement. Subsequently, it may be reasonable to assume that DlD may affect the speed at which voluntary movements are performed, as previously suggested for tremor. Here, we

review the possible mechanisms by which tremor may affect voluntary movement in order to make a parallel between how tremor and DID may participate in bradykinesia/hypokinesia.

Although the precise pathways where tremor might be generated is not fully understood, data from PD animal models (Filion 1979; Filion & Tremblay 1988; Lamarre et al. 1975) has lead to the theory that changes in oscillatory activity within the basal ganglia and/or thalamus (specifically the anterior segment of the ventral lateral thalamus [VLa] where GP projections are processed) may participate in the generation or propagation of oscillations causing tremor (Pare et al. 1990). Additionally, since the VLa of the thalamus is reciprocally and topographically connected to other sections within the thalamic nuclei (i.e. posterior VL [VLp]) (Deschenes et al. 1984; Steriade et al. 1984), these interactions may result in additional synchronization between neighbouring thalamic nuclei, which are not necessarily GP recipient sectors. The idea is that, these oscillations (tremor discharge) can consequently alter voluntary motor commands in the cortex via thalamo-cortical circuits. Thus, for these reasons we feel that it is important to discuss the role of tremor because it represents a central model of involuntary movement superimposed over voluntary motor behaviour. In fact, Alberts (1972) hypothesized that tremor may possibly be the result of involuntary release of a motor program used for RAM. Recent studies have supported this theory by being able to show that brain structures involved in RAM are similar to that implicated during tremor (Parker et al. 1992; Duffau et al. 1996). Indeed, Volkmann et al. (1996) was able to show in PD patients that the motor cortex is part of a network of brain segments that show tremor-related oscillatory activity. Accordingly, the authors suggested that these central motor circuit oscillations could act as "noise" that may

interfere with voluntary motor activity. Ventral-lateral thalamotomy, a surgical procedure that is effective for alleviating tremor (Ohye et al. 1982; Nagaseki et al. 1986; Duval et al. 2000; Duval et al. In Print), has been shown to improve fine movement accuracy (Perret 1968; Duval et al. 2005 In Press). Moreover, Logigian et al. (1991) demonstrated that large amplitude finger tremor influenced the timing at which voluntary muscle contraction is performed. Carboncini et al. (2001) supported this observation by demonstrating that tremor caused an increase in movement time during an upper-arm extension task. Therefore, tremor may play a role in bradykinesia.

Data from metabolic imaging (PET and *f*MRI) studies have revealed decreased activation of basal ganglia and cortical areas (involved in movement) in PD patients than normal subjects (Jahanshahi et al. 1995). Interestingly, treatment-using apomorphine seems to reverse this phenomenon, while at the same time improving bradykinesia scores (Rascol et al. 1992). Conversely, there seems to be overactivity of the SMA and primary motor areas in dyskinetic patients (Rascol et al. 1998). The assumption is that the mechanism responsible for dyskinetic messages differs from that of bradykinesia/hypokinesia (Berardelli et al. 2001; Krack et al. 1998). Since neural mechanisms responsible for bradykinesia (hypo-activity of cortical areas) are opposite of the ones responsible for dyskinesia (hyper-activity of cortical areas), bradykinesia should not be present while patients are experiencing dyskinesias. Although the current basal ganglia model of bradykinesia/hypokinesia and DID suggest opposite neural imbalance, clinical evidence propose that dyskinesias can occur at the same time as bradykinesia/hypokinesia (Berardelli et al. 2001). To our knowledge however, no studies have quantified motor performance simultaneously with DID magnitude. Yet, such as the case for tremor, it is possible that

DID may act as noise superposed over the voluntary motor command, impeding performance. Accordingly, it is possible that the presence of DID will result in slowness of movement due to the conflicting involuntary and voluntary motor commands.

2.13 Hypothesis

According to the aforementioned evidence presented, we hypothesize that bradykinesia/hypokinesia will be present during choreic DID, hindering RAM performance in PD patients. If RAM is not hindered by DID, then it could be assumed that bradykinesia/hypokinesia are indeed opposite neural disturbances.

2.14 Quantifying Dyskinesias

Despite the increasing prevalence of DID, few studies have investigated the influence of DID on voluntary motor behaviour. Presently, the most popular procedures used to clinically assess dyskinesias are subjective clinical rating scales and self-report diaries by patients, scales being the most dependent (Burkhard, et al. 1999). However, subjective scales were developed primarily to rate the severity of dyskinesias, body segments involved and/or type of dyskinesia present (Goetz et al. 1994; Marconi et al. 1994; Lozano et al. 2000). Moreover, recent attempts to objectively assess dyskinesias using rotation-sensitive movement monitors (Burkhard et al. 1999), accelerometers (Hoff et al. 2001; Keijsers et al. 2000), electromyography (Yanagisawa & Nezu 1987) and Doppler radars (Vitek & Giroux 2000) have not provided a 3-D assessment of DID and its impact on voluntary movement. In fact, only one study has investigated possible interaction between DID and motor behaviour; Durif et al. (1999) found that both motor and mental tasks may increase the quantity of DID in patients. Accordingly, the present study intends to quantify whole-body choreic DID by using a 3-D representation and determine its impact on

voluntary movements in patients with PD. DID and involuntary movements will be quantified by using a magnetic motion tracker system. This system is capable of interpreting 3-D whole-body kinematics, measuring both position and orientation of body movements.

METHODS

3.1 Participants

Whole-body magnitude (WBM) and motor performance will be quantified in thirty participants at the Brock University motor disorders lab. Ten idiopathic DPD participants (aged 56-76 years old, mean 67.5 $\pm$ 6.3 years) who demonstrate mild to moderate peak-dose choreic dyskinesias following their levodopa treatment will be recruited from the Movement Disorder Clinic at the London Health Science Centre, Ontario. Reports from the neurologist will be assessed to determine DID characteristics for all patients. Participants will be excluded from the study if they suffered from dementia or psychiatric disorders (or if they used neuroleptic drugs), presented dystonia as their predominant form of dyskinesia, possessed high amplitude tremors, or had surgical procedures related to their Parkinson's. Also, ten age/gender-match non-DPD (NDPD) participants, who will also meet the aforementioned basic criteria, but who have not yet experienced DID in their lifetime (this was assessed by self-report diaries and the patient's nurse [aged 47-78 years old, mean 67.9 $\pm$ 9.3 years]) and ten age/gender-match healthy control subjects (aged 47-79 years old, mean 66.5 $\pm$ 10.9 years) will be tested. The Brock University and University of Western Ontario Ethics Review Board will approve the experimental design and subjects will provide signed consent prior to testing. The PD groups will be tested during the *ON* condition; 20-40 minutes following their afternoon L-dopa dose (session one) and again

approximately 1.5-2 hours following their L-dopa dose (session two). The third section of the unified Parkinson's disease rating scale (UPDRS) will be used to measure parkinsonian motor disability (maximal score 108) between testing sessions and once again following the second testing session to distinguish best *ON* condition. Testing will take place in the afternoon, since clinical evidence has suggested that PD patients experience DID more prominently after a build up of successive doses of levodopa/carbidopa (Joseph et al. 1995) and also because DID possess a diurnal motor pattern, which is described as an increase in severity of DID in the evenings (Marsden 1980; Merello et al. 1997; Nutt 2001; Joseph et al. 1995).

3.2 Apparatus

WBM will be quantified using the *flock of birds magnetic motion tracker system* (Innovative Sports Training, Chicago, IL). This system uses 15 sensors that provide the displacement (x, y and z) and orientation (pitch, yaw and roll) of movement in each body segment relative to a fixed transmitter. By using the "grid" method within a twelve feet radius, the system is capable of providing resolution of 0.1 deg rotational and 0.08 cm translational; and accuracy of 0.5 deg rotational and 0.25 cm translational (Innovative Sports Training, Chicago, IL; Eckhouse et al. 1996; Milne et al. 1996). This method requires that a series of readings be taken at known locations, which are equally spaced throughout the measurement grid (x, y and z). Upon completion of all recorded readings, the system computes the correction polynomials using a regression equation; thus adjusting the mapped space for any distortions within the magnetic field. However, we will reduce the abovementioned grid and calibrate a smaller testing space. In total, 100 readings will be taken at every 30.5 cm intervals throughout the space in the x, y and z by means of an

anthropometer. Upon completion, the calibrated space will consist of a 3 feet (x) by 4 feet (y) by 4 feet (z) grid, yielding an accuracy of 0.04 cm and resolution of 0.04 cm (Figure 8). It is worthy to note that the working space will only be calibrated once, where all participants will be tested.

Sensors will be placed bilaterally on the following body segments: superior spinae of the scapula, mid-lateral upper-arm, mid-lateral forearm, dorsal hand, lateral shank and dorsal foot. Sensors will also be attached to the posterior head (transverse plane running through the eyes), thorax (T1) and sacrum (between S1 and S2), respectively. Patients will be positioned (within the middle of the working space) approximately one meter away from the magnetic transmitter facing the positive y-axes.

Subsequent to patient sensor set-up, body segments will be digitized (using a stylus) based on pre-determined anatomical landmarks, in order for the system to assign each sensor the centre of mass of local segment axes. The system calculates these anatomical landmarks based on the manual entry of subjects height and weight, where then the system uses anthropometric tables to calculate centre of mass for each body segment axes ("centroid" method). By distinguishing joint centers, the long axes of body segments are established.

3.3 Experimental Procedure

Following digitization, participants will be instructed to sit on an armless-wooden chair and hold the two handballs attached to the potentiometer while keeping their elbows approximately three inches away from their body (approximately 120^0) in a neutral

position (Figure 8). Participants will be instructed to pronate-supinate their dominant hand (the non-dominant hand will hold the other handball during RAM performance but

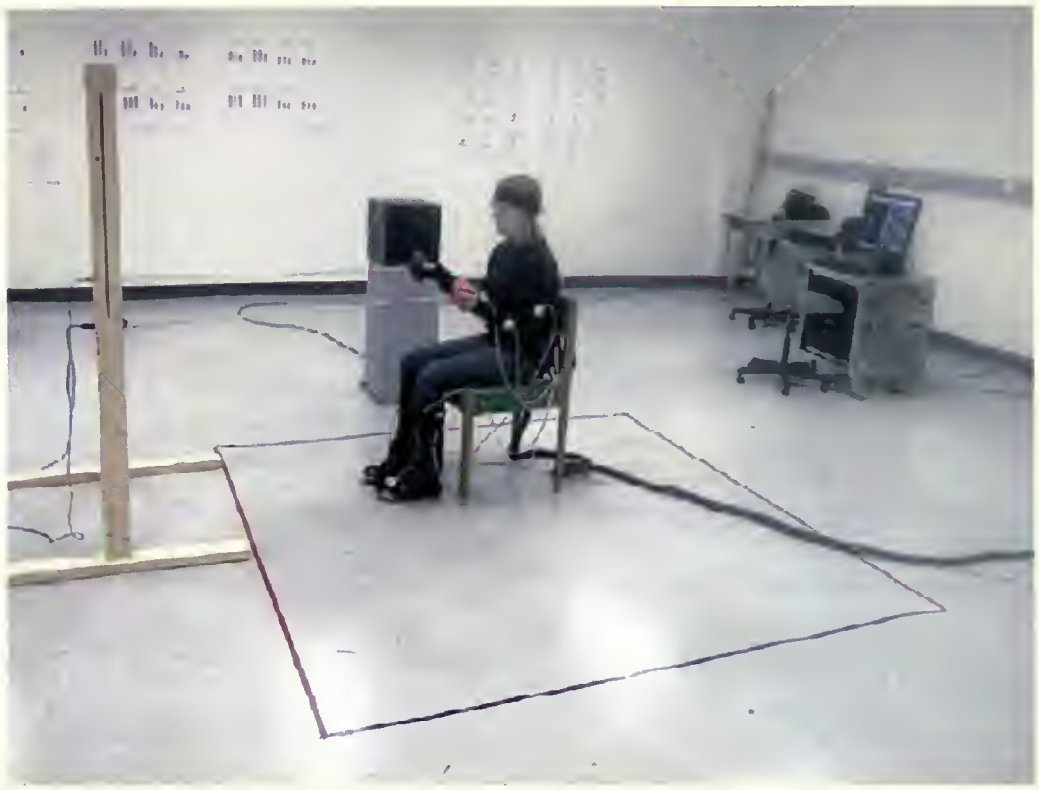


Figure 8. Experimental setup for DID and RAM assessment.

will not perform the RAM task) and to abstain from any voluntary movements other than the one requested for the pronation-supination task, while at same time not suppressing any involuntary movements (hand dominance was determined by the subjects themselves). Additionally, it is important to note that subjects will be instructed to perform the RAM task with maximal rotational excursion and as fast as possible.

An auditory cue will signal the starting point of the recording session. First, the participants will be instructed hold their neutral position as stated above for a period of 20 seconds, then they will be instructed to pronate-supinate their dominant hand for ten

seconds, however only seven seconds from the beginning of movement will be used for analysis. Upon RAM completion, another 20 sec without movement (in neutral condition) will be recorded. This cycle will be repeated three consecutive times, with a one-minute rest period between each trial.

To identify peak dose dyskinesias (dyskinetic group), two sessions will be recorded for all participants, abiding by the following guidelines throughout the testing procedure: participants will be continuously monitored and asked to provide feedback with respect to their dyskinesia severity; additionally, movement magnitude displayed by the magnetic tracker system will be compared between sessions to indicate the session with most DID. Thus, the session that shows more DID according to these guidelines will be ultimately used for analysis. In almost all cases (except for two subjects) the second session confirmed the best "ON" condition.

3.4 Movement Analysis

The amplitude of displacement for each sensor will be computed by calculating the overall mean magnitude of x, y and z. The x, y and z epochs for each sensor will be divided into seven second data epochs. Then the mean position of x, y and z of the seven seconds will be subtracted for each sensor. Subsequently, we will calculate the RMS for x, y and z. Then square all RMS values for x, y and z and calculate the mean. Finally, we will compute the square root of the mean and sum the magnitude, thus yielding WBM (i.e. three-dimensional vectorial average). WBM will be determined by computing the sum of all sensors, except for the performance hand, forearm and upper arm, in addition to the sacrum.

RAM will be quantified by first using an automated algorithm to identify each peak and trough (Figure 9.a). Subsequently, four RAM characteristics will be computed ([Figure 9.b-10] Duval et al. 2001; Duval et al. In Print): 1) range or mean angular displacement over a full cycle of pronation-supination in degrees (a lower value indicates the presence of hypokinesia); 2) mean duration of full cycle of pronation-supination in seconds (a high value denotes the presence of bradykinesia); 3) maximal instantaneous velocity over a full cycle of pronation-supination in degrees per second (a lower value indicates bradykinesia) and 4) signal smoothness or RAM cycle amplitude irregularity. The latter is obtained by computing the standard deviation (SD) of the linear envelope (low pass filter at 1 Hz) from the normalized pronation-supination trace (mean = 0 and SD = 1). A high value indicates more variability in RAM amplitude, hence a more irregular performance (Duval et al. 2001; Duval et al. In Press). Thus, we believe that this may be a measure to investigate the influence of DID on RAM. For analysis and results, the three trials for the "Peak-dose session" were averaged for rest and performance WBM, as well as for RAM quantification measures.

3.5 Statistical Analysis

Recently, a study was conducted using RAM range, duration and irregularity for comparing two groups: patients with PD and healthy controls (Duval et al. In Print). Based on the results of the latter study, to maintain a power of 0.8 in the present sample a minimum prerequisite of four subjects for duration, range and ten subjects for irregularity are required (Rosner 1995 method for power calculation). In the Duval et al (In Press) study, PD patients were tested during the "OFF" condition (twelve hours post L-dopa dose) when compared to healthy controls. Thus, any lack of significance revealed between PD

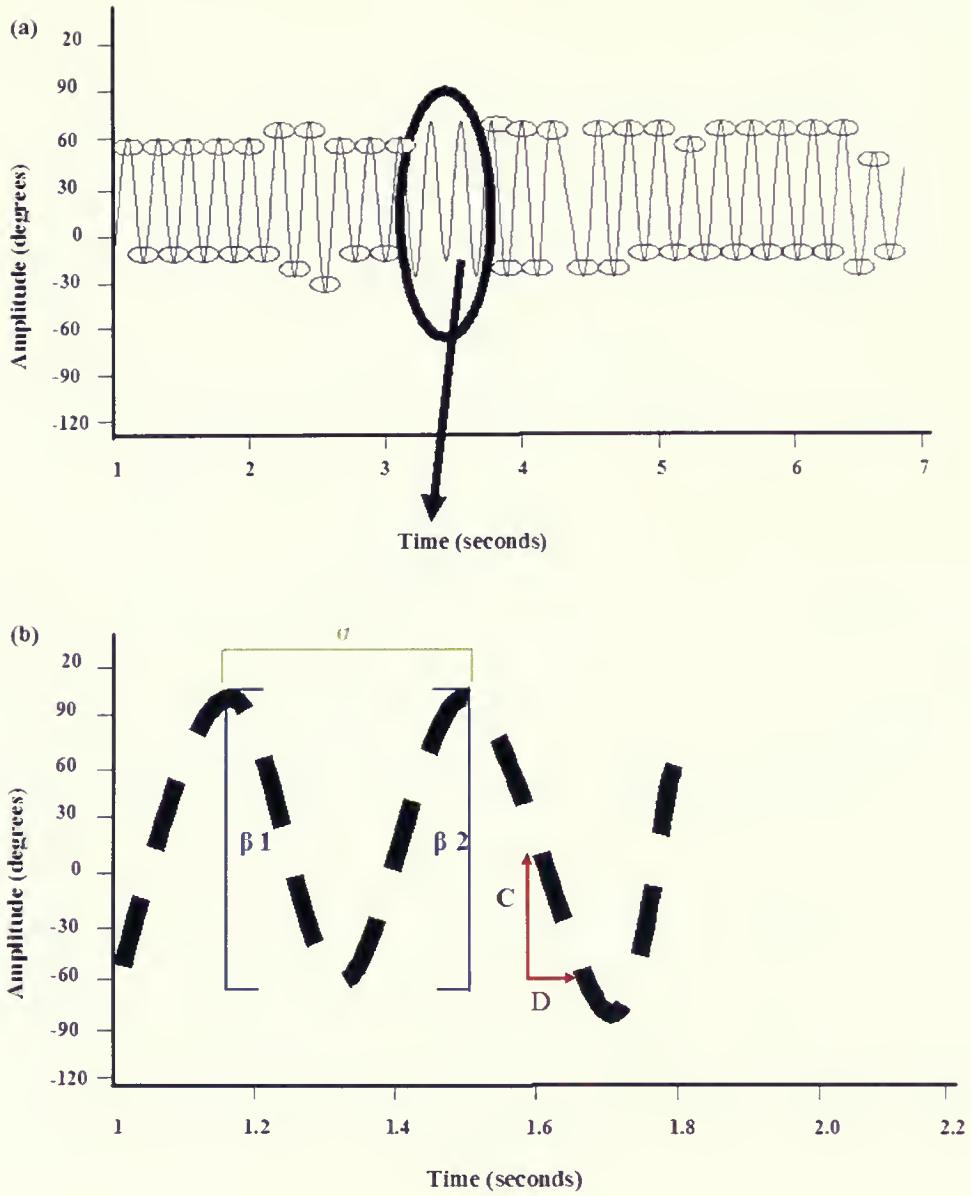


Figure 9. Analysis of RAM range, duration and velocity: The first step of the RAM analysis is to use an automated algorithm that will detect each peak and trough (represented by oval circles) of the RAM signal (a). RAM range represents the total length of one pronation-supination cycle (β 1 + β 2). RAM duration for one cycle of pronation-supination represents the time period between peaks (α). Maximal instantaneous velocity represents C / D (degrees per sec) between two data points (b).

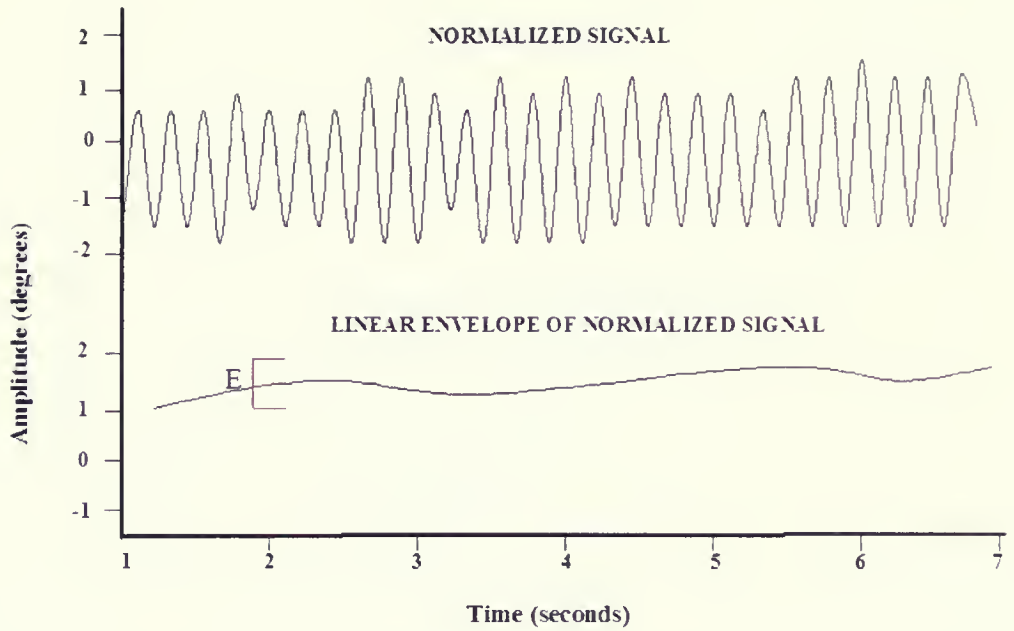


Figure 10. Analysis of RAM irregularity. Irregularity is the standard deviation of the linear envelope (low pass filter at 1 Hz) from a normalized signal (E).

patients and controls in the present study must then be considered as a consequence of dopaminergic medication (i.e. PD patients are in the "ON" condition), meaning that patients might be able to perform similar to that of healthy controls due to DA replenishment via levodopa.

WBM during rest and performance for all groups will be compared using a two-way analysis of variance (*ANOVA*) (*Group x Condition*) with repeated measures on the last factor (*Condition*). Significance will be declared at $p< 0.05$. *Post hoc* multiple comparisons of means will be performed using the Student Newman-Keuls test to indicate which group comparisons yield statistical significance. Kruskal-Wallis one-way *ANOVA* on ranks will be used to determine statistical difference between groups for RAM range, duration, velocity and irregularity, respectively. Additionally, all patients with PD will be pooled and a

Spearman rank order correlation will determine whether a relationship existed between RAM performance AND the following clinical characteristics: age, years since diagnosis, daily levodopa dose, and UPDRS motor score.

The impact of drug-induced dyskinesias on rapid alternating movements in patients with Parkinson's disease

Marco Ghassemi*.....

1- Faculty of Applied Health Sciences, Brock University, Ontario, Canada, L2S 3A1.

2-Movement Disorder Clinic, Department of Clinical Neurology, London Health Sciences Centre, London Ontario.

Corresponding author:
Christian Duval
500 Glendridge Avenue
St.Catharines, Ontario
L2S 3A1
Tel: 905-688-5550 ext. 4496
Email: cduval@brocku.ca

Key words: Parkinson's disease, dyskinesia, pronation-supination, bradykinesia,

MANUSCRIPT

4.1 Abstract

We investigated the likelihood that hypokinesia/bradykinesia coexist with drug-induced dyskinesias (DID) in patients with Parkinson's disease (PD). The influence of dyskinesias on rapid alternating movements (RAM) was investigated in ten dyskinetic patients (DPD). Their motor performance was compared to that of ten age/gender-matched non-dyskinetic patients (NDPD) and ten healthy control subjects. Whole-body magnitude (WBM) and fast pronation-supination at the wrist were recorded using 6-degrees of freedom magnetic motion tracker and forearm rotational sensors, respectively. Subjects were asked to pronate and supinate their dominant hand for 10s. Pre- and post-measures were taken in a neutral position for 20s. RANGE (measure of hypokinesia), DURATION (measure of bradykinesia), VELOCITY (measure of bradykinesia) and IRREGULARITY (measure of fluctuations in movement amplitude) were used to assess RAM performance. Results showed that DPD patients had greater WBM than NDPD and control groups during rest and RAM performance. There were no differences in performance between NDPD and DPD groups for RANGE, DURATION and VELOCITY, despite significant longer disease duration for the DPD group (DPD = 15.5 ± 6.2 years versus NDPD = 6.6 ± 2.6 years). However, both the NDPD and DPD groups showed lower RANGE, longer DURATION, and reduced VELOCITY compared to controls, suggesting the presence of bradykinesia and hypokinesia. In the case of IRREGULARITY, DPD patients showed clear fluctuations in movement amplitude compared to the NDPD and control groups. However, the lack of correlation between WBM and IRREGULARITY within the DPD group (Spearman's rank order, Rho = 0.31, $p > 0.05$), suggests that DID was not the primary cause of the fluctuating

movement amplitude observed in that group. In conclusion, these findings suggest that DID may coexists with bradykinesia and hypokinesia, but that they are not inevitably accompanied with worsening motor performance.

4.2 Introduction

The debilitating motor functions observed in Parkinson's patients are instigated by the progressive loss of dopaminergic neurons in the substantia nigra pars compacta. Levodopa (L-dopa) remains one of the most efficacious pharmacological agents available for the symptomatic relief of idiopathic Parkinson's disease (PD). However, its use is associated with long term complications; the most common and disabling being drug-induced dyskinesias (DID) (Bedard et al. 1986; Rascol et al 2000). Although the pathophysiological origin of DID is not well understood, it has been suggested that that changes in temporal and spatial patterns of neural firing within the basal ganglia motor circuits may account for DID manifestation (Agid et al 1985; Blanchet et al 1995; Vitek and Giroux 2000; [b]Obeso et al 2000). There is also clear evidence of abnormal over-activation of motor cortical and prefrontal areas in dyskinetic patients (Rascol et al 1998; Brooks et al 2000). Current models of bradykinesia and hypokinesia however suggest that the latter symptoms are the result of decreased abnormal neural firing patterns from the basal ganglia output structures to the cortex, via the thalamus (DeLong 1990; Berardelli et al 2001).

According to the aforementioned studies, bradykinesia/hypokinesia and DID may result from opposite neural disturbances. Interestingly, it has been suggested that bradykinesia may be clinically present simultaneously with DID (Berardelli et al. 2001). Another possibility is that DID itself may impact upon the motor performance of patients

during rapid alternating movements (RAM). DID would then represent noise that may affect the speed at which voluntary movements are performed. In fact, this latter hypothesis has been suggested for PD tremor, another involuntary movement superimposed over voluntary motor behaviour. Volkmann et al. (1996) was able to show in PD patients that the motor cortex is part of a network of brain segments that show tremor-related oscillatory activity. The authors suggested that these central motor circuit oscillations (or "noise") could interfere with voluntary motor activity. Moreover, Logigian et al. (1991) demonstrated that large amplitude finger tremor influenced the timing at which voluntary muscle contraction is performed. Imaging studies have also shown that tremor possesses similar neural networks as RAM (Parker et al. 1992; Duffau et al. 1996). Carboncini et al. (2001) supported this observation by demonstrating that tremor caused an increase in movement time during an upper-arm extension task. Therefore, tremor may play a role in bradykinesia. In fact, ventral-lateral thalamotomy, a surgical procedure that is effective for alleviating tremor (Ohye et al. 1982; Nagaseki et al. 1986; Duval et al. 2000; Duval et al. In Print), has been shown to improve fine movement accuracy (Perret 1968, 1970; Duval et al. In Press). Whether DID has a similar influence on voluntary motor behaviour in PD patients is yet to be determined.

In keeping with the aforementioned evidence presented, we hypothesize that bradykinesia/hypokinesia may be present during choreic DID, hindering RAM performance in PD patients. If RAM is not hindered by DID, then it could be assumed that bradykinesia/hypokinesia are indeed opposite neural disturbances. Accordingly, the goal of the present study was to investigate the impact of peak-dose choreic DID on RAM in patients with PD.

4.3 Methods

4.3.1 Participants

Whole-body magnitude (WBM) and motor performance were quantified in thirty participants at the Brock University motor disorders lab. Ten idiopathic DPD (DPD) participants (aged 56-76 years old, mean 67.5 $\pm$ 6.3 years) who demonstrated mild to moderate peak-dose choreic dyskinesias following their levodopa treatment were recruited from the Movement Disorder Clinic at the London Health Science Centre, Ontario. Participants were excluded from the study if they suffered from dementia or psychiatric disorders (or if they used neuroleptic drugs), presented dystonia as their predominant form of dyskinesia, possessed high amplitude tremors, or had surgical procedures related to their Parkinson's. Also tested, ten age/gender-match non-DPD (NDPD) participants, who also met the aforementioned basic criteria, but had not yet experience DID in their lifetime (aged 47-78 years old, mean 67.9 $\pm$ 9.3 years) and ten age/gender-match healthy control subjects (aged 47-79 years old, mean 66.5 $\pm$ 10.9 years). The Brock University and University of Western Ontario Ethics Review Board approved the experimental design and subjects provided signed consent prior to testing. Patients were tested during the *ON* condition; 20-40 minutes following their afternoon L-dopa dose (session one) and again approximately 1.5-2 hours following their L-dopa dose (session two). The third section of the unified Parkinson's disease rating scale (UPDRS) was used to measure parkinsonian motor disability (maximal score 108) between testing sessions and once again following the second testing session to distinguish best *ON* condition. Testing took place in the afternoon, since clinical evidence has suggested that PD patients experience DID more prominently after a build up of successive doses of levodopa/carbidopa (Joseph et al. 1995) and also

because DID possess a diurnal motor pattern, which is described as an increase in severity of DID in the evenings (Marsden 1980; Merello et al. 1997; Nutt 2001; Joseph et al. 1995).

4.3.2 Apparatus

WBM was quantified using the *flock of birds magnetic motion tracker system* (Innovative Sports Training, Chicago, IL). This system uses 15 sensors that provide the displacement (x, y and z) and orientation (pitch, yaw and roll) of movement in each body segment relative to a fixed transmitter. By using the "grid" method within a twelve feet radius, the system was capable of providing resolution of 0.1 deg rotational and 0.08 cm translational; and accuracy of 0.5 deg rotational and 0.25 cm translational (Innovative Sports Training, Chicago, IL; Eckhouse et al. 1996; Milne et al. 1996). This method requires that a series of readings be taken at known locations, which are equally spaced throughout the measurement grid (x, y and z). Upon completion of all recorded readings, the system computes the correction polynomials using a regression equation; thus adjusting the mapped space for any distortions within the magnetic field. However, in order to improve the accuracy and resolution, we reduced the abovementioned grid and calibrated a smaller testing space. In total, 100 readings were taken at every 30.5 cm intervals throughout the space in the x, y and z by means of an anthropometer. Upon completion, the calibrated space consisted of 3 feet (x) by 4 feet (y) by 4 feet (z) grid, yielding an accuracy of 0.04 cm and resolution of 0.04 cm. It is worthy to note that the working space was only calibrated once, where all participants were tested.

Sensors were placed bilaterally on each of the following body segments: superior spinae of the scapula, mid-lateral upper-arm, mid-lateral forearm, dorsal hand, lateral shank and dorsal foot. Sensors were also attached to the posterior head (transverse plane running

through the eyes), thorax (T1) and sacrum (between S1 and S2), respectively. Patients were positioned (within the middle of the working space) approximately one meter away from the magnetic transmitter facing the positive y-axes.

Subsequent to patient sensor set-up, body segments were digitized (using a stylus) based on pre-determined anatomical landmarks, in order for the system to assign each sensor the centre of mass of local segment axes. The system calculates these anatomical landmarks based on the manual entry of subjects height and weight, where then the system uses anthropometric tables ("centroid" method) to calculate centre of mass for each body segment axes. By distinguishing joint centers, the long axes of body segments are established. All patients were digitized prior to testing and data was sampled at 100 Hz, per sensor.

RAM was quantified using a consecutive pronation-supination of the wrist while holding a forearm rotational sensor. The system includes two handballs located at one end of a light 1.2-m wooden dowel; attached to the other end of each dowel is a potentiometer fixed inside a plastic box that detects rotation as subjects rotate the ball. The forearm rotational sensor has a resolution of 0.3 degrees. Analog outputs from the potentiometer were sampled at 200 Hz and stored for analysis.

4.3.3 Experimental Procedure

Following digitization, participants were instructed to sit on an armless-wooden chair and hold the two handballs attached to the potentiometer while keeping their elbows approximately three inches away from their body (approximately 120^0) in a neutral position. Participants were instructed to pronate-supinate their dominant hand (the non-

dominant hand held the other handball during RAM performance but did not perform the RAM task) and to abstain from any voluntary movements other than the one requested for the pronation-supination task, while at same time not suppressing any involuntary movements. Additionally, it is important to note that subjects were instructed to perform the RAM task with maximal rotational excursion and as fast as possible.

An auditory cue signalled the starting of the recording session. First, the participants were instructed to hold their neutral position as stated above for a period of 20 seconds, then they were instructed to pronate-supinate their dominant forearm for ten seconds, however only seven seconds from the beginning of movement was used for analysis. Upon RAM completion, another 20 sec without movement (in neutral condition) was recorded. This cycle was repeated three consecutive times, with a one-minute rest period between each trial.

To identify peak dose dyskinesias (dyskinetic group), two sessions were recorded for all participants and we abided by the following guidelines throughout the testing procedure: participants were continuously monitored and asked to provide feedback with respect to their dyskinesia severity; additionally, movement magnitude displayed by the magnetic tracker system was compared between sessions to indicate the session with most DID. Thus, the session that showed more DID base on these guidelines was ultimately used for analysis. In almost all cases (except for two subjects) the second session confirmed the best "ON" condition.

4.3.4 Movement Analysis

The amplitude of each sensor was computed by calculating the mean magnitude of x, y and z. The x, y and z epochs for each sensor were divided into seven second data epochs. Then the mean position of x, y and z of the seven seconds were subtracted for each sensor. Subsequently, we calculated the RMS for all sensors. We then squared all RMS values for x, y and z and calculated the mean. Finally, we computed the square root of the mean and summed the magnitude, thus yielding three-dimensional vectorial amplitude. WBM was determined by computing the sum of all sensors, except for the performance hand, forearm and upper arm, in addition to the sacrum.

RAM was quantified by first using an automated algorithm to identify each peak and trough. Subsequently, four RAM characteristics were computed (Duval et al. 2001; Duval et al. In Print): 1) range or mean angular displacement over a full cycle of pronation-supination in degrees (a lower value indicates the presence of hypokinesia); 2) mean duration of full cycle of pronation-supination in seconds (a high value denotes the presence of bradykinesia); 3) maximal instantaneous velocity over a full cycle of pronation-supination in degrees per second (a lower value indicates bradykinesia) and 4) signal smoothness or RAM cycle amplitude irregularity. The latter was obtained by computing the standard deviation (SD) of the linear envelope from the normalized pronation-supination trace (mean = 0 and SD = 1). A high value indicates more variability in RAM amplitude, hence a more irregular performance (Duval et al. 2001; Duval et al. In Press). Thus, we believe that this may be a measure to investigate the influence of DID on RAM.

4.3.5 Statistical Analysis

Recently, a study was conducted using RAM range, duration, and irregularity for comparing two groups; patients with PD and healthy controls (Duval et al. 2005 In Print). Based on the results of the latter study, to maintain a power of 0.8 in the present sample a minimum prerequisite of four subjects for duration and range and ten subjects for irregularity are required (Rosner 1995 method for power calculation). In the Duval et al (2005 In Print) study PD patients were tested during the "OFF" condition (twelve hours post L-dopa dose) when compared to healthy controls. Thus, any lack of significance revealed between PD patients and controls in the present study must then be considered as a consequence of dopaminergic medication (i.e. PD patients are in the "ON" condition).

WBM during rest and performance condition for all groups were compared using two-way analysis of variance (*ANOVA*) (*Group x Condition*) with repeated measures on the last factor (*Condition*). Significance was declared at $p < 0.05$. *Post hoc* multiple comparisons of means were performed using the Student Newman-Keuls test to indicate which group comparisons yield statistical significance. Kruskal-Wallis one-way ANOVA on ranks were performed to determine statistical difference between groups for RAM range, duration, velocity and irregularity, respectively. Additionally, all patients with PD were pooled and a Spearman rank order correlation was used to determine whether a relationship existed between RAM performance AND the following clinical characteristics: age, years since diagnosis, daily levodopa dose, and UPDRS motor score.

4.4. Results

The results includes the average section is Participant characteristics are illustrated in Table 1. It is important to note that within the pooled PD group, age, age of onset and

daily levodopa dose were not correlated with RAM characteristics since all correlations were found to be below 0.35 (Spearman's Rho, $p > 0.05$ in all cases), thus indicating that these factors did not influence RAM performance.

Table 1. Participants' clinical characteristics for best "ON" session (PD Parkinson's disease, UPDRS unified Parkinson's disease rating scale). Age/gender match Controls (aged 47 -79 years old, mean 66.5+10.9 years).**Note:** a significant difference existed for disease duration (Mann-Whitney rank sum-test: $t = 148$, $p < 0.05$) and age of onset ($t = 72$, $p < 0.05$, DPD = 51.6 years old vs. NDPD = 61.3 years old), but not for age, L-dopa daily dose and motor score between DPD and NDPD ($p < 0.05$).

	#	Age	Years Since Diagnosis (years)	Motor Score (UPDRS)	L-dopa daily dose (mg)
	1	66	17	18	400
	2	70	12	2	1000
	3	75	20	14	800
	4	68	8	24	400
DPD	5	56	11	17	2100
	6	59	6	19.5	600
	7	65	21	36	900
	8	76	21	53	300
	9	70	19	12	400
	10	70	24	25	300
Mean		*67.5*	*15.9*	*22.05*	*720*
SD		*6.3*	*6.2*	*14.1*	*547.3*
	1	68	10	41.5	500
	2	72	3	14.4	300
	3	75	5	19.5	300
Age/Gender	4	68	6	46.5	800
Match NDPD	5	47	10	16	3600
	6	58	5	29.5	1000
	7	66	6	27.5	400
	8	78	5	21	750
	9	72	10	24.5	300
	10	75	4	40	600
Mean		*67.9*	*6.4*	*28.0*	*855*
SD		*9.3*	*2.6*	*11.2*	*994.0*

.

4.4.1 Whole-Body Magnitude

WBM for all groups is illustrated in Figure 11. For WBM, ANOVA revealed there were *Group* ($F = 15.34$, $df = 2$, $p < 0.05$), *Condition* ($F = 154.22$, $df = 1$, $p < 0.05$) and *Group x Condition* interaction ($F = 22.3$, $df = 2$, $p < 0.05$). *Post hoc* analysis revealed that during the *rest* condition, NDPD patients and controls showed similar WBM ($p > 0.05$), however the DPD group showed significantly greater WBM than other groups ($p < 0.05$, in all cases), as expected. During motor performance, NDPD patients and controls demonstrated similar WBM ($p > 0.05$); and again the DPD group demonstrated significantly greater WBM than other groups ($p < 0.05$, in all cases). All groups showed a significant increase in WBM from rest to performance ($p < 0.05$), however, this increase was greater for the DPD group.

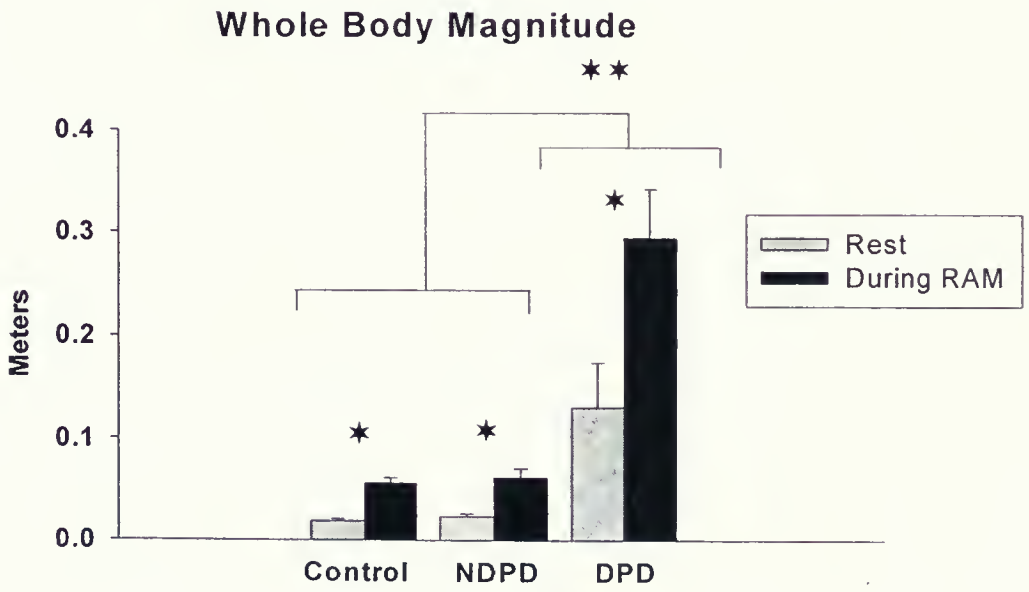


Figure 11. Whole-body magnitude. Collective results for all groups. Two stars (✶✶) indicates significant difference between groups, one star (✶) indicates significant difference within group. Note that there were no significant differences between NDPD and controls ($p > 0.05$).

In addition to WBM, the movement amplitude of the *non-performing hand* for all groups was measured: Figure 12 illustrates this comparison. ANOVA (Kruskall-Wallis) on ranks revealed a significant group effect ($H = 11.2$, $p < 0.05$). Post-hoc analysis (Student-Knewman-Keuls) revealed that both NDPD patients and controls showed similar lower hand movement amplitude during motor performance ($p < 0.05$). However, The DPD group showed significantly larger hand movement than both the NDPD and control groups ($p < 0.05$).

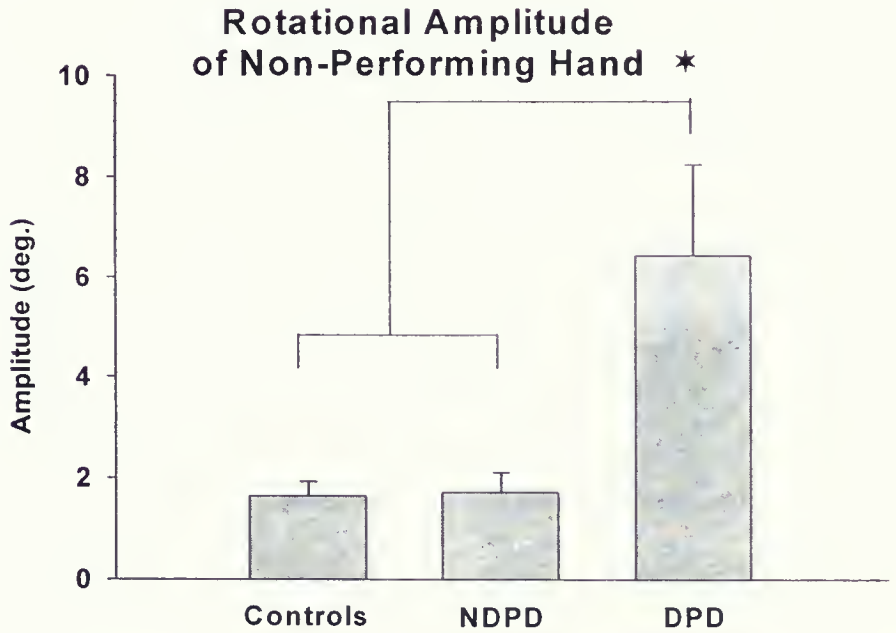


Figure 12. Rotational amplitude of the non-performing hand during motor performance. One star (✶) indicates a significant difference between groups. The NDPD group and controls showed similar movement amplitude in the opposite hand during motor performance. However, the DPD group showed significantly greater hand amplitude than other groups.

4.4.2 RAM Performance

Figure 13 illustrates the results for RAM range, duration, velocity and irregularity. For range, ANOVA showed a significant group effect ($H = 6.8$, $p < 0.05$). Post-hoc analysis revealed that both DPD and NDPD groups showed similar lower range ($p > 0.05$), despite longer disease duration [DPD = 15 years versus NDPD = 6.6 years, Mann-Whitney rank sum-test: $t = 148$, $p < 0.05$]). However both patient groups showed significantly lower range compared to controls ($p < 0.05$), indicating the presence of hypokinesia. No correlations existed between range and WBM within the DPD group ($Rho = 0.2$, $p > 0.05$), meaning the level of WBM was not associated with decreased range. For duration, ANOVA revealed no significant group effect ($p > 0.05$). Thus, movement duration for the DPD group was similar the NDPD ($p > 0.05$) and control groups ($p > 0.05$). No correlation existed between duration and WBM within DPD ($Rho = 0.47$, $p > 0.05$). For Velocity, ANOVA showed a significant group effect ($H = 7.9$, $p < 0.05$). Post-hoc analysis revealed that both DPD and NDPD groups showed similar slower velocity ($p > 0.05$). However, both PD groups showed significantly slower velocity than controls ($p < 0.05$), suggesting the presence of bradykinesia. No correlation existed between velocity and WBM within the DPD group ($Rho = -0.08$, $p > 0.05$). For irregularity, ANOVA showed a significant group effect ($H = 6.7$, $p < 0.05$). Post-hoc analysis revealed that both the NDPD group and controls showed similar lower irregularity score ($p > 0.05$). On the other hand, DPD patients showed a higher irregularity during movement than NDPD patients and controls ($p < 0.05$). No correlations existed between irregularity and WBM within the DPD group ($Rho = 0.31$, $p > 0.05$). Figure 14 illustrates an example of RAM performance from a patient with DID and his or her age/gender match NDPD patient and control.

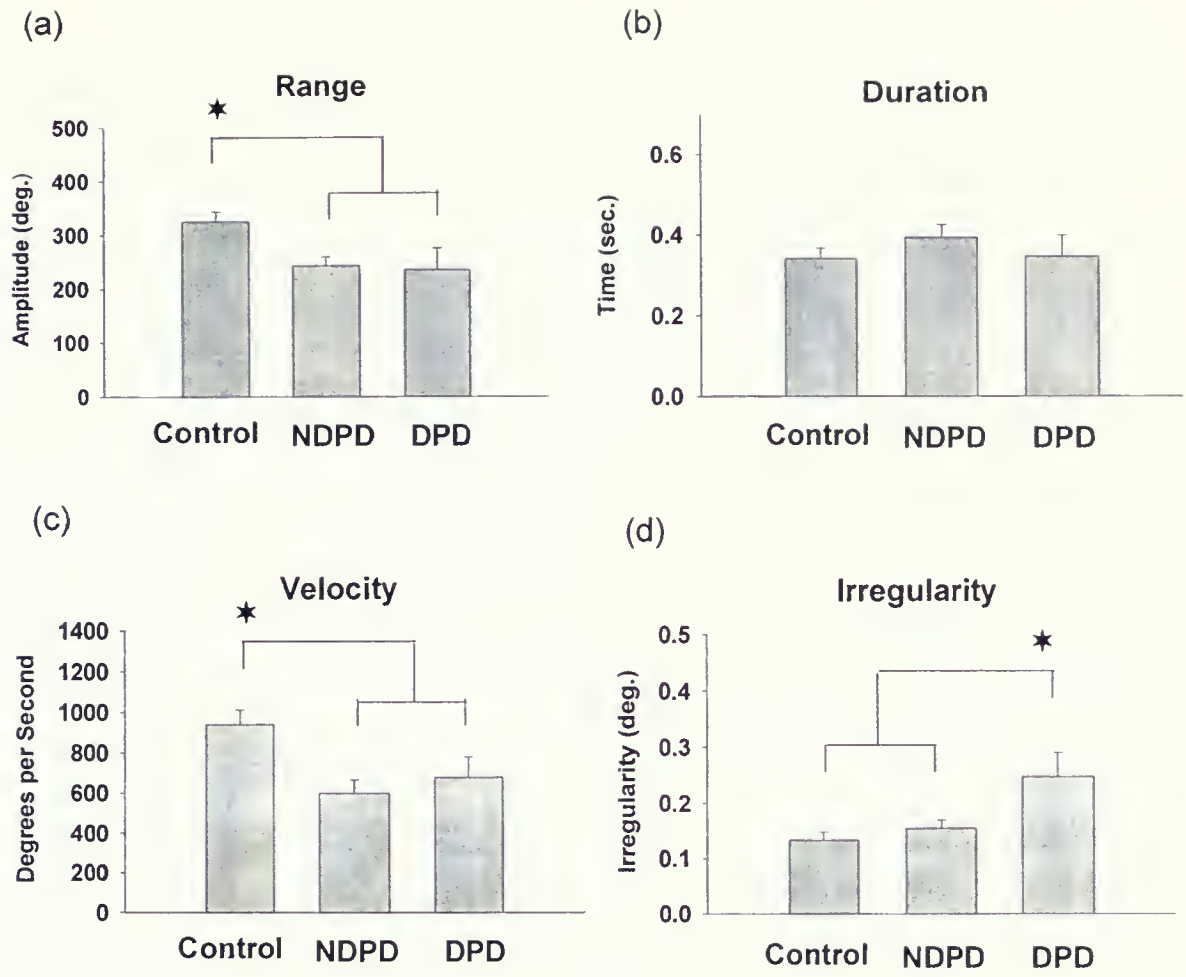


Figure 13. RAM task. Collective results for all groups for range (a), duration (b), velocity (c) and irregularity (d). One star (✶) indicates a significant difference between groups. For range, controls showed greater movement amplitude than DPD and NDPD patients. For duration, all groups showed a similar performance. For peak velocity, controls performed faster than DPD and NDPD patients. Irregularity was greater in DPD than NDPD patients and controls.

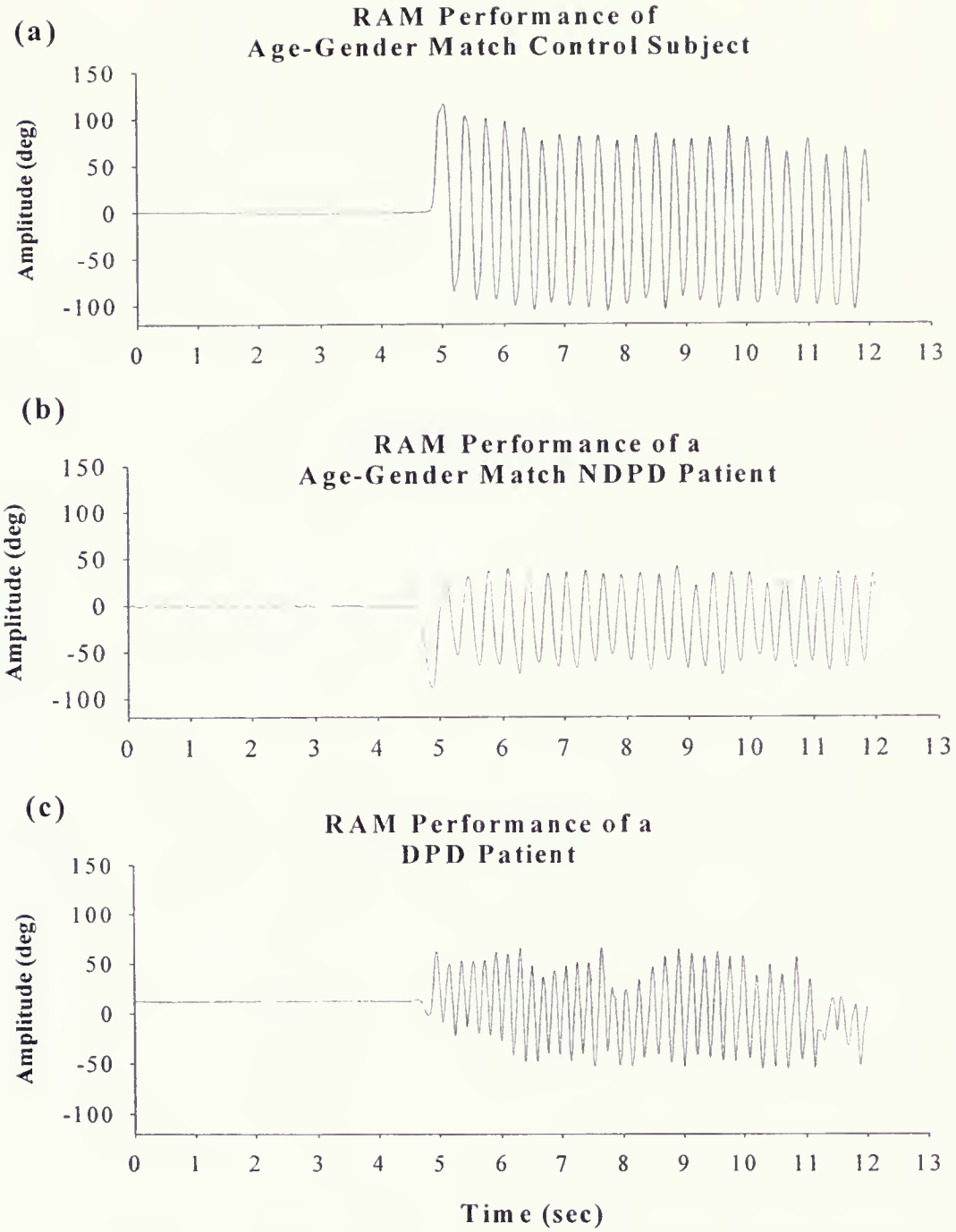


Figure 14. RAM performance of a PD patient (c) and his age/gender match NDPD patient (b) and control (a). Note that the DPD and NDPD patients show similar lower movement amplitude compared to the control subject. However, the number of pronation/supination movement was higher for the DPD group compared to controls and NDPD. Fluctuations in movement amplitude was higher in the DPD patient than NDPD patient and control.

To further support our results, a separate but similar analysis (as stated above) between the same subject groups was performed for the *motor performance* condition (Figure 15). In this case, the ten DPD patients were categorized into two groups of five: 1) a *high* WBM group (i.e. DPD patients with greater DID magnitude) and *low* WBM group (i.e. DPD patients with smaller DID magnitude). Age/gender match NDPD patients and controls were also categorized in the aforementioned manner according to their matched DPD patient. Subsequently, WBM *during motor performance* was compared between groups using a Kruskal-Wallis one-way ANOVA on ranks. The latter test was also employed to compare RAM range, duration, velocity and irregularity between groups, respectively. Figure 15 illustrates the results for WBM and RAM characteristics for *low* and *high* groups. WBM during RAM was significantly greater in the *DPD hi* group than *DPD low* group ($p < 0.05$). WBM in both *low* and *high DPD* groups were also significantly greater than all other groups ($p < 0.05$, in all cases), as expected. As for RAM range, duration, velocity, or irregularity, no significant differences were found between groups ($p > 0.05$). However, careful interpretation of these results is needed since there is a clear trend for NDPD patients to perform worse than controls. Interestingly, Figure 15 illustrates that in some circumstances, DPD patients with low levels of DID performed much better than their counterparts in the NDPD group. Irregularity had a tendency to be present only in the DPD groups, irrespective of their DID magnitude.

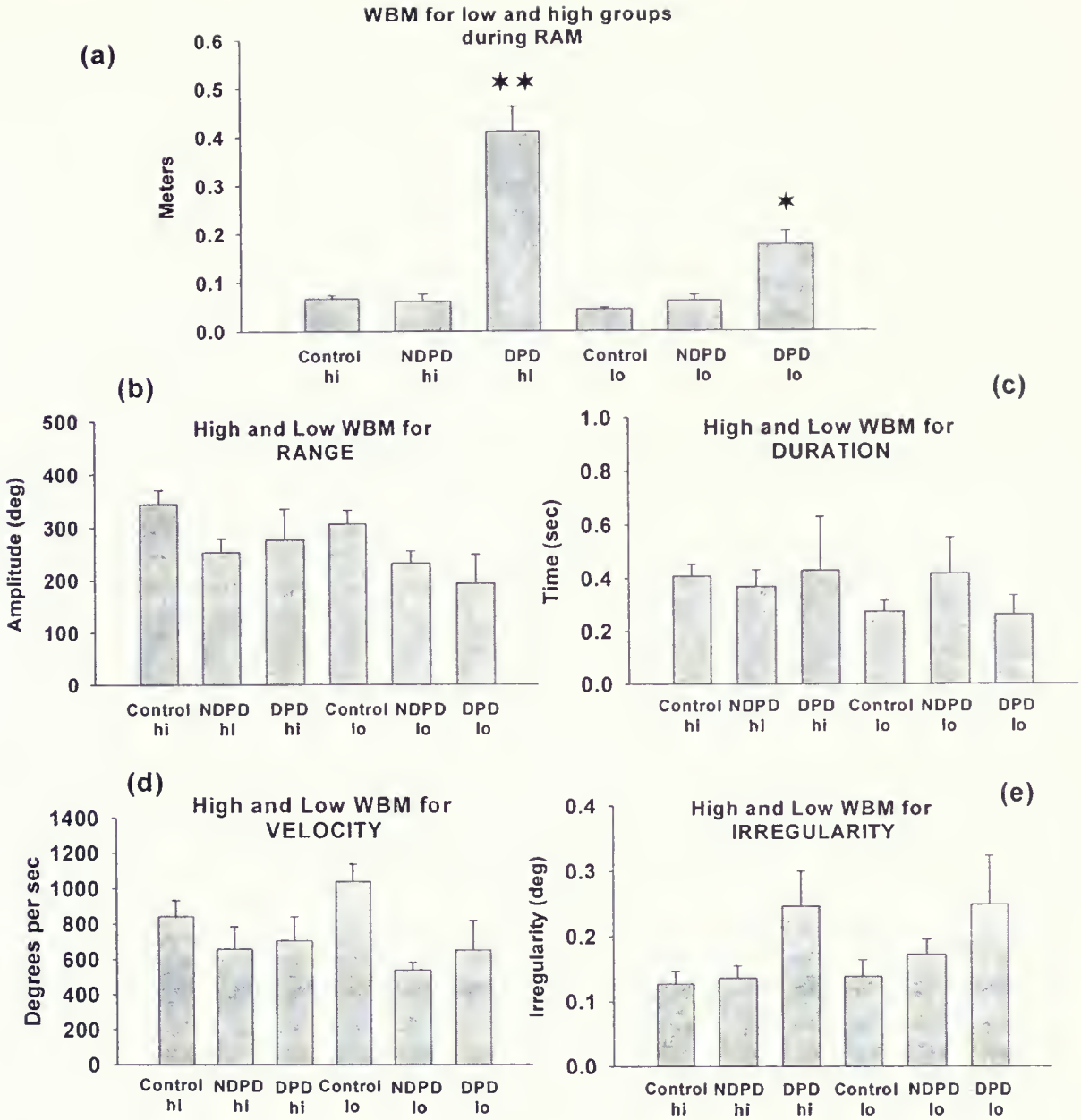


Figure 15. WBM and RAM characteristics during motor performance. Collective results for *high* and *low* groups: WBM (a), range (b), duration (c), velocity (d) and irregularity (e). *high* and *Low* WBM was significantly greater in the DPD groups than all other groups. There were no significant differences between groups for range, duration, velocity and irregularity, respectively ($p > 0.05$, in all cases). Despite this lack of significance, there was clear a tendency such that the *low DPD* group performed RAM at similar amplitude, but in a shorter duration than their age/gender match NDPD patients. In fact, duration was similar to controls. *Low DPD* patients also appeared to perform at a faster peak velocity than their NDPD counterparts. For irregularity, there was a tendency for DPD groups to perform more irregularly than NDPD and control groups.

4.5 Discussion

4.5.1 Whole-Body Magnitude and the impact of RAM

The results revealed that at rest, DPD patients had higher WBM than NDPD and controls, as expected. During motor performance, NDPD patients and controls demonstrated a similarly low increase in WBM, but the DPD group demonstrated significantly greater WBM during performance, and a greater increase from rest to active than other groups. The relatively small augmented movements observed in NDPD and control groups during motor performance is probably the result of motor-overflow, a phenomenon known to occur in patients with PD (van den Berg et al. 2000; Hoy et al. 2004) and healthy individuals (Armatas et al. 1994, 1996; Daffertshofer et al. 1999). However, in DPD patients this augmentation in WBM is referred to as "overflow dyskinesia". A phenomenon consistent with clinical observations from other studies, which report marked aggravation of DID in patients with PD during voluntary motor behaviour (Nutt 1990; Durif et al. 1999). Furthermore, during motor performance, the NDPD and control groups demonstrated similar hand amplitude in the non-performing hand, while the DPD group showed significantly larger hand amplitude than other groups. In this case, it is reasonable to assume while DPD patients were performing RAM in one hand, they were simultaneously experiencing significantly greater *mirror movements* (MM) in the non-performing hand (involuntary movements occurring in analogous muscles contralateral to the voluntary movements). Although MM have been reported in healthy adults (Armatas et al. 1994, 1996; Daffertshofer et al. 1999) it is most often more pronounced in movement disorders (i.e. PD, Armatas et al 1996; van den Berg et al. 2000). However, in the present study DPD patients showed significantly greater MM than NDPD patients, possibly

suggesting that MM are more pronounced in patients with DID. Although it is difficult to interpret this observation, it is possible that cortical-overactivation, a phenomenon observed in DPD patients (Rascol et al 1998; Brooks et al 2000), may play a secondary role in augmenting these movements. Since DPD patients are already experiencing overflow dyskinesias in non-performing limbs, it is logical to assume that MM would also facilitate motor activation in the non-performing hand.

4.5.2 RAM Performance

During RAM performance, DPD and NDPD groups showed similar lower range (despite longer disease duration) than controls, indicating the presence of hypokinesia. Duration for the DPD group was similar to the NDPD and controls. For peak velocity, both DPD and NDPD groups showed similar slower velocity than controls, suggesting the presence of bradykinesia. RAM irregularity was significantly greater in DPD patients than NDPD and controls. Moreover, within each PD group no correlations existed between range, duration, velocity and irregularity and WBM, respectively, indicating that an increase in WBM in the DPD group (or pooled patients with PD) was not systematically associated with decreased RAM performance.

Based on our aforementioned hypothesis, DPD patients should demonstrate smaller amplitude and longer duration and shorter velocity scores during RAM than NDPD patients. The rationale behind this assumption is that neural noise output associated with DID would conflict with voluntary cortical motor commands, thus leading to an aggravated bradykinesia/hypokinesia. Evidently, this was not the case; DPD patients in fact showed similar range, duration and velocity compared to NDPD patients, despite DPD patients

having longer disease duration than NDPD patients. Therefore, it is clear that neural noise generated by dyskinesias in the cortex seems to have no hindering effect on motor circuits used to generate fast repetitive alternating movements. In fact, the presence of dyskinesias appears to be accompanied with neither a positive or negative effect on bradykinesia. Accordingly, it is reasonable to suggest that the presence of DID may be accompanied with cortical overactivity that may facilitate neural circuits responsible for RAM generation, thus representing a source of compensatory mechanism.

For RAM irregularity, it was expected that DPD patients would have a higher score. Indeed, RAM irregularity was greater in DPD patients than other groups. However, no correlation was found between WBM and RAM irregularity, suggesting that the latter was not influenced by the former. Although it is difficult to interpret the direct cause of this relationship, this increase could be a matter of scaling a fast paced movement. Therefore, while attempting to meet this scale, DPD patients simultaneously generated or displayed a more irregular RAM performance. The cortical overactivation associated with DID may alter the way patients scale repetitive movements. An alternative explanation could be that this increase in irregularity may be due to the progressive nature of the disease, as seen in patients with longer disease duration (i.e. DPD patients in the present study). In fact, within the pooled PD groups there was a weak positive correlation between disease duration and irregularity (Rho = 0.53, $p < 0.05$), suggesting that patients with longer disease duration performed at a more irregular movement.

4.5.3 The relationship between dyskinesias and bradykinesia/hypokinesia

The present results revealed that patients with DID did not perform worse than patients in the NDPD group, thus suggesting that dyskinesias did not have direct influence

on voluntary motor behaviour. However, we propose that the induction of DID, at a certain level, may compensate for some of the bradykinetic and hypokinetic processes. The latter argument can be supported by the fact that DPD patients had significantly longer disease duration than their age/gender match NDPD patients but still performed at a similar capacity. For instance, if the L-dopa dose of the DPD group was reduced enough to eliminate DID, the level of performance of the DPD group would most likely fall well below that of the NDPD group, supporting the counterbalancing of longer disease duration effect. Although our second analysis failed to reach significance, there was a clear tendency in certain cases (i.e. PD patients with *low* WBM) where DPD patients actually performed better than NDPD patients. To attempt to rationalise this concept, it is useful to review the literature on cortical- overactivity observed in dyskinetic patients.

It is thought that the cause of augmented DID by motor tasks may be a cause of abnormal facilitation of attentional processes (Durif et al. 1999). Indeed, there is evidence of overactivity in pre-motor, supplementary motor, primary motor, basal ganglia and prefrontal projections in DPD patients compared to NDPD patients at rest and during voluntary motor tasks (Rascol et al 1998; Brooks et al 2000). It could be that over-activation of motor sensory areas caused by dyskinesias are spawning other areas of the CNS to adapt to basal ganglia dysfunction. Thus, a possible by-product of this process is better RAM performance. Although this study does not clearly confirm such neural mechanisms to be responsible for the above findings, this may be perceived as a compensatory mechanism initiated by the priming effect of DID. If this is the case, abnormal excitation of the limbic and motor structures projecting to the cortex may in turn enhance other processing mechanisms by recruiting additional neural circuits for the

execution of motor commands. Consequently, in some cases this may allow patients with DID to perform better than NDPD patients.

Therefore, there are two possible mechanisms that may be occurring in the dyskinetic brain: on the one hand the overactivation of thalamocortical excitatory projections are somehow alleviating some of the interaction between the primary deficit responsible for bradykinesia and hypokinesia; or DID may in fact be facilitating neural circuits responsible for the generation of RAM.

Additionally, it is also probable that overactivation of one part of the cortex may alter the balance between reciprocal inhibition and excitation in other areas of cortex, hence changing the neural firing patterns within the motor sensory system. Accordingly, DlD may be associated with the compensating characteristics of the basal ganglia, a mechanism manifested due to dopaminergic loss and alteration (pulsatile stimulation of exogenous DA).

Results from chronic high frequency DBS of the GPi can also be of great interest, since Krack et al (1998) discovered that by stimulating the ventral zone of the Gpi, they were able to decrease DID, while at the same time eliminating the anti-akinetic effects of levodopa treatment; patients became severely akinetic after DBS. Interestingly, stimulation of the Gpi at a more dorsal location (located inside the GPe or dorsal border of the GPi) improved OFF-drug bradykinesia but simultaneously induced dyskinesias in some PD patients. This may further support that that the priming of dyskinesias in particular segments of the cortex may be accompanied with releasing some of the deficit responsible for the underlying bradykinesia. Accordingly, there is no consistent evidence indicating that

alleviation of DID is purely accompanied with improved bradykinesia, or vice versa. In fact, pallidotomy, a successful intervention that alleviates DID, only has mild effects (30% improvement) on bradykinesia scores in OFF PD patients and no benefits in the ON condition (Samuel et al 1998).

It is plausible that dyskinesia, hypokinesia and bradykinesia are marked from three separate or distinct patterns of neural firing, allowing dyskinesia to occur at the same time as bradykinesia and hypokinesia. Indeed, the present study supports this possible coexistence, since DPD patients showed similar bradykinesia and hypokinesia severity to that of NDPD patients. In the context of this coexistence, it is plausible that neural circuits generated by dyskinesias could aid or alleviate, from the bradykinesia, one component of an encoded cortical motor command, such as cortical encoding for duration or amplitude of muscle movement. Based on the new dyskinesia model proposed by [b]Obeso et al (2000), this would be logical, since they suggest that overactivation of thalamocortical projections is not confined to purely an increase in firing frequency, but rather this increase in neural activation is also accompanied with changes in the quantity and duration of firing bursts, degree of neural synchrony and degree of lateral inhibition. Mink et al. (1996) suggests that the temporal and spatial pattern of the normal basal ganglia may assist the cortex in activating programs that are responsible for desired movements and suppression of undesired movements.

Therefore, it is also plausible that dyskinesia, hypokinesia and bradykinesia are marked from three separate or distinct neural pathways. For instance, cortical overactivation may originate from hypoactivity of the GPI-thalamo-cortical pathway, while bradykinesia and hypokinesia originate from the GP projections to brainstem segments that

receive somatotopic neural input from the basal ganglia output nuclei and STN (i.e. PPN) (Parent & Cicchetti 1998; [ab]Obeso et al. 2000). Thus, because it is not fully confirmed where bradykinesia and hypokinesia are generated, it is possible that their functions may be associated with brain stem segments such as the PPN, which in addition to receiving major neural projections from the GPi and STN, also provides excitatory innervation to the SNc (Parent & Cicchetti 1998; [ab]Obeso et al. 2000). Therefore, cortical-overactivity, in combination with a lack of remodulation in the brainstem pathways, may attribute to this alleviation or bypass of bradykinesia and hypokinesia. Accordingly, this may support the coexistence between bradykinesia, hypokinesia and DID.

4.5.4 Clinical implications of the present results.

Despite the fact that severe motor complications such as DID can ultimately be disabling at some point during the course of PD, mild to moderate DID may not have a negative effect on voluntary motor behaviour during the initial phases of the appearance of DID. Interestingly, previous studies who investigated the impact of DID on quality of life in PD patients have produced conflicting results; from no effect to a negative effect on quality of life of PD patients (Karlsen et al. 2000; [b]Schrag et al. 2000; Siderowf et al. 2002; Damiano et al. 2000; Pechevis et al. 2001). However, in a recent study, Marras et al (2004) investigated the impact of DID on quality of life of 182 early PD patients over a four year period. The results confirmed that within the four years of dopaminergic treatment, dyskinesias did not have a negative impact on the quality of life of PD patients. In fact, dyskinetic patients showed better quality of life scores than non-dyskinetic patients over the first two years of treatment after the appearance of DID. Finally, no association existed during the following two years. The authors suggested that the latter may have been due to

increased severity of DID or that PD at more advanced stages may diminish the impact of DID relative to other aspects of motor function (Marras et al. 2004). Accordingly, since DPD patients in the present study had longer disease duration than NDPD patients but showed similarities in RAM performance, it is reasonable to suggest that DID may not have negative impact on motor performance, but rather may play a positive role. Of course, the present implications may apply only for fast repetitive movements, as slower or more fine movements may still be affected by DID. In that case, there would be a strong relationship between the amplitude of DID and motor performance. Although further investigation in this matter is admittedly needed, our results nevertheless may have useful therapeutic implications; possibly supporting the use of levodopa even in the early stages of the appearance of DID.

4.6 References

Agid Y, Bonnet AM, Ruberg M, Javoy-Agid F (1985) Pathophysiology of L-dopa-induced abnormal involuntary movements. *Psychopharmacology* 2 (suppl): 145-159.

Armatas, CA, Summers JJ, Bradshaw JL (1994) Mirror movements in normal adult subjects. *J Clin Exp Neuropsychol* 16: 405-413.

Armatas CA, Summers JJ, Bradshaw JL (1996) Handedness and performance variability as factors influencing mirror movement occurrence. *J Clin Exp Neuropsychol* 18: 823-835.

Bedard PJ, et al (1986) Chronic treatment with levodopa, but not bromocriptine induces dyskinesia in MPTP-treated parkinsonian monkeys: Correlation with [^{3}H]spiperone binding. *Brain Res* 379: 294-299.

Berardelli A, Rothwell JC, Thompson PD, Hallet M (2001) Pathophysiology of bradykinesia in parkisnon's disease. *Brain* 124: 2131-2146.

Blanchet PJ, et al (1995) Continuous administration decreases and pulsatile administration increases behavioural sensitivity to a novel dopamine D2 agonist (U-91356A)in MPTP-exposed monkeys. *J Pharmacol Ex* 272: 854-859.

Brooks DJ, Piccini P, Turjanski N, Samuel M (2000) Neuroimaging of dyskinesia. *Ann Neurol* 47 (suppl 1): S154-S159.

Carboncini MC, Manzoni D, Strambi S, Bonuccelli U, Pavese N, Andre P, Rossi B (2001) The relation between EMG activity and kinematic parameters strongly supports a role of the action tremor in parkinsonian bradykinesia. *Movement Disorders* 61 (1): 47-57.

Daffertshofer A, Berg C van den, Beek PJ (1999) A dynamical model for mirror movements. *Physica D* 132: 243-266.

Damiano AM, McGarth MM, Willian MK, Snyder CF, LeWitt PA, Richter RR (2000). Evaluation of a measurement strategy for Parkinson's disease: Patient health-related quality of life. *Qual Life Res* 9: 87-100.

DeLong MR (1990) Primate models of movements disorders of basal ganglia origin. *Trends in Neurosciences* 13: 281-285.

Duffau H, Tzourio N, Caparros-Lefebvre D, Parker F, Mazoyer B (1996) Tremor and voluntary repetitive movement in Parkinson' disease: comparison before and after L-dopa with positron emission tomography. *Exp Brain Res* 107 (3): 453-462.

Durif F, Vidailhet M, Debilly B, Agid Y (1999) Worsening of levodopa-induced dyskinesias by motor and mental tasks. *Movement Disorders* 14 (2): 242-245.

Duval C, Panisset M, Bertrand, G, Sadikot AF (2000) Evidence that ventrolateral thalamotomy may eliminate the supraspinal component of both pathological and normal physiological tremors. *Exp Brain Res* 132 (2): 216-222.

Duval C, Panisset M, Sadikot AF (2001) The relationship between physiological tremor and the performance of rapid alternating movements in healthy elderly subjects. *Exp Brain Res* 139: 412-418.

Duval C, Panisset M, Strafella AP, Sadikot AF (2005) The impact of ventrolateral thalamotomy on tremor and bradykinesia in patients with Parkinson's disease. *Exp Brain Res*. In print.

Eckhouse RH, Penny MA, Maulucci R (1996) A comparison of kinematic recording instruments. *Journal of Medical Systems* 20 (6): 439-456.

Hoy KE, Fitzgerald PB, Bradshaw JL, Armatas CA, Georgiou-Karistianis N (2004) Investigating the cortical origins of motor overlow. *Brain Research Reviews* 46: 315-327.

Joseph CL, Jolene Siple J, McWhorter JK, Camicioli R (1995) Adverse reactions to controlled release levodopa/carbidopa in older persons: Case control. *Journal of American Geriatric Society* 43 (No 1): 47-50.

Karlsen KH, Tandleberg E, Aersland D, Larsen JP (2000). Health related quality of life in Parkinson's disease: A progressive longitudinal study. *J Neurol Neurosurg Psychiatry* 69: 584-589.

Krack P, Pollack P, Limousin P, Hoffmann D, Benazzouz A, Le Bas JF, et al. (1998) Opposite motor effects of pallidal stimulation in Parkinson's disease. *Ann Neurol* 43: 180-192.

Logigian E, Hefter H, Reiners K, Freund H (1991) Does tremor pace repetitive voluntary motor behaviour in Parkinson's disease? *Annual Neurology* 30: 172-179.

Marras C, Lang A, Krahn M, Tomlinson G, Naglie G and Parkinson Study Group (2004). Quality of life in early Parkinson's disease: Impact of dyskinesias and motor fluctuations. *Movement Disorders* 19 (1): 22-28.

Marsden CD (1980) "On-Off" phenomenon in Parkinson's disease. In: Rinne UK, Klinger M, Stamm G, editors. *Parkinson's disease: Current progress, problems and management* Amsterdam/New York: Elsevier/North-Holland Biomedical Press, 241-254.

Merello M, Hughes A, Colosimo C, Hoffman M, Starkstein S, Leiguarda R (1997) Sleep benefit in Parkinson's disease. *Movement Disorders* 12: 506-508.

Milne AD, Chess DG, Johnson JA, King GJW (1996) Accuracy of an electromagnetic tracking device: A study of the optimal operating range and metal inteference. *Journal of Biomechanics* 29 (6): 791-793.

Mink JW (1996) The basal ganglia: focused selection and inhibition of competing motor programs [Review]. *Prog Neurobiol* 50: 381-425.

Negaseki Y, Shibazaki T, hirai T, Kawashima Y, Hirato M, Wada H, Miyazaki M, Ohye C (1986) Long-term follow-up results of selective VlM-thalamotomy. *J Neurosurgery* 65: 296-302.

Nutt JG (2001) Fluctuations in response to treatment for parkinson's disease. *Adv Neurol* 86: 361-366.

Nutt JG (1990) Levodopa-induced dyskinesias: review, observations and speculations. *Neurology* 40: 340-345.

[a]Obeso JA, Rodriguez-Oroz MC, Rodriuez M, Lanciego JL, Artieda J, Gonzalo N, Olanow CW (2000) Pathophysiology of the basal ganglia in Parkinson's disease. *Trends in Neurosciences* 23 (suppl. 1) S8-S19.

[b]Obeso JA, Rodriguez-Oroz MC, Rodriguez M, DeLong MR, Olanow CW (2000) Pathophysiology of levodopa-induced dyskinesias in parkinson's disease: Problem with the current model. *Annual Neurology* 47 (suppl. 1): S22-S34.

Ohye C, Hirai T, Miyazaki M, Shibazaki T, Nakajima H (1982) VIM thalamotomy for the treatment of various kinds of tremor. *Appl Neurophysiol* 45: 275-280.

Parent A, Cicchetti F (1998) The current model of the basal ganglia organization under scrutiny. *Movement Disorders* 13: 199-203.

Parker F, Tzourio N, Blond S, Petit H, Mazoyer B (1992) Evidence for a common network of brain tructures involved in parkinsonian tremor and voluntary repetitive movement. *Brain Res* 584 (1-20): 11-17.

Pechevis M, Clarke CE, Vieregge P, et al (2001). Direct and indirect costs of Parkinson's disease and L-dopa induced dyskinesias: A prospective European study. *Parkinsonism Relat Disord* 7(suppl.): 106.

Perret E (1968) Simple motor performance of patients with Parkinson's disease before and after surgical lesion in the thalamus. *J Neurol Neurosurg psychiatry* 31: 284-290.

Rascol O, Brooks DJ, Korczyn AD, et al (2000) A five year study of the incidence of dyskinesias in patients with early Parkinson's disease who were treated with ropinirole or levodopa. *New England Journal of Medicine* 342: 1484-1491.

Rascol O, Sabatini U, Brefel C, Fabre N, Rai S, Senard JM, Celsis P, Viallard G, Montastruc JL, Chollet F (1998) Cortical motor overactivation in parkinsonian patients with L-dopa-induced peak-dose dyskinesia. *Brain* 121: 527-533.

Rosner B (1995) Fundamentals of biostatistics. 4th ed. Belmont (CA): Wadworth Publishing Company, p 511–514.

Samuel M, Caputo E, Brooks DJ, Schrag A, Scaravalli T, Branston NM et al. (1998) A study of medial pallidotomy for Parkinson's disease: Clinical outcome, MRI location and complications. *Brain* 121: 59-75.

Schrag A, Selai C, Jahanshahi M, Quin NP (2000). The EQ-5D---a generic quality of life measure---is a useful instrument to measure quality of life in patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry* 69: 67-73.

Siderowf A, Ravina B, Glick HA (2002). Preference-based quality of life in patients with Parkinson's disease. *Neurology* 59: 103-108.

van den Berg C, Beck PJ, Wagenaar RC, van Wieringen PCW (2000) Coordination disorders in patients with Parkinson's disease: A study of paced rhythmic forearm movements. *Exp Brian Res* 134: 174-186.

Vitek JL, Giroux M (2000) Physiology of hypokinetic and hyperkinetic movement disorders: Model for dyskinesia. *Annual Neurology* 47 (suppl. 1): S131-S140.

Volkman J, Joliot M, Mogilner A, Ioannides AA, Lado F, Fazzini E, Ribary U, Llinas R (1996) Central motor loop ocilations in parkinsonian resting tremor revealed by magnetoencephalography. *Neurology* 46 (5): 1359-1370.

GENERAL CONCLUSION

Results from the present study showed that DID seem to have no hindering effect on motor circuits used to generate fast repetitive movements. In fact, the presence of dyskinesias appears to be accompanied with neither a positive or negative effect on neural processes responsible for bradykinetic and hypokinetic processes, despite DPD patients having longer disease duration than NDPD patients. Accordingly, the presence of DID may be accompanied with cortical overactivity that may facilitate or alleviate neural circuits responsible for RAM generation, thus representing a source of compensatory mechanism. Although our results may have significant and useful therapeutic implications, further investigation in this matter is admittedly needed.

5.1 Limitations/Future Applications

Considering that the present findings are recent to this field of study, it is vital for future studies to quantify patients with DID in the "OFF" condition. This will further substantiate the impact of DID on voluntary motor behaviour and confirm whether or not the initial phases of the appearance of DID in fact plays a positive role in generating fast repetitive movements. Future studies should also lay emphasis on incorporating a larger sample size (including young-onset and late-onset PD patients) as well as assessing a broader spectrum of dyskinesias. This will further augment any trends as well as generalize outcomes to PD populations. Ultimately, the present findings of this study are a valuable addition to further understanding the role as well as the impact of involuntary movements on the quality life of PD patients. Accordingly, one of the most important features of this study is that previous methods in assessing DID have not integrated a 3-D whole-body

assessment of involuntary movements and their impact on voluntary motor behaviour. Finally, this is an essential step in developing a dynamic approach for the accurate evaluation of pharmacological and surgical interventions aimed at improving motor function, while keeping involuntary movements at a level that may be proposed as beneficial in PD patients.

BIBLIOGRAPHY

Alberts WW (1972) A simple view of parkinsonian tremor. Electrical stimulation of cortex adjacent to the rolandic fissure in awake man. *Brain Res* 44: 357-369.

Albin RL, Young AB, Penney JB (1989). The functional anatomy of basal ganglia disorders. *Trends in Neurosciences* 12: 366-375.

Alexander GE, Crutcher MD, DeLong MR (1990) Basal ganglia-thalamocortical circuits: Parallel substrates for motor, oculomotor, "prefrontal" and "limbic" functions. *Prog Brain Res* 85: 119-146.

Alexander GE, Crutcher MD (1990) Functional architecture of basal ganglia circuits: neural substrates of parallel processing. *Trends in Neurosciences* 13: 266-271.

Agid Y, Bonnet AM, Ruberg M, Javoy-Agid F (1985) Pathophysiology of L-dopa-induced abnormal involuntary movements. *Psychopharmacology* 2 (suppl): 145-159.

Agostino R, Berardelli A, Curra A, Accornero N, Manfredi M (1998) Clinical impairment of sequential finger improvements in Parkinson's disease. *Movement Disorders* 13: 418-421.

Ahlskog JE, Muenter MD (2001) Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. *Mov Disord* 16(3): 448-58.

Alexander GM et al. (1993) Changes in brain dopamine-receptors in MPTP parkinsonian monkeys following L-dopa treatment. *Brain Res* 625: 276-282.

Armatas, CA, Summers JJ, Bradshaw JL (1994) Mirror movements in normal adult subjects. *J Clin Exp Neuropsychol* 16: 405-413.

Armatas CA, Summers JJ, Bradshaw JL (1996) Handedness and performance variability as factors influencing mirror movement occurrence. *J Clin Exp Neuropsychol* 18: 823-835.

Barbeau A, Roy M, Bernier G, et al (1987) Ecogenetics of Parkinson's disease: Prevalence and environmental aspects of rural areas. *Canadian Journal of Neurol Science* 14: 36-41.

Bass H (2000) Dyskinesia in parkinson's disease: Pathophysiology and clinical risk factors. *Journal of Neurology* 247 (suppl. 4): IV/12-IV/16.

Bedard PJ, Mancilla BG, Blanchette P, Gagnon C, Di Paolo T (1992). Levodopa-induced dyskinesias: Facts or fancy. What does the MPTP monkey model tell us? *Canadian Journal of Neural Science* 19 (suppl. 1): 134-137.

Bedard PJ, Blanchet PJ, Levesque D, Soghomonian JJ, Grondin R, Morissette M, Goulet M, Calon F, Falardeau P, Mancilla BG, Doucet JP, Robertson GS, DiPaolo T (1999) Pathophysiology of l-dopa-induced dyskinesias. *Movement Disorders* 14 (suppl. 1): 4-8.

Bedard PJ, et al (1986) Chronic treatment with levodopa, but not bromocriptine induces dyskinesia in MPTP-treated parkinsonian monkeys: Correlation with [^{3}H]spiperone binding. *Brain Res* 379: 294-299.

Berardelli A, Rothwell JC, Thompson PD, Hallet M (2001) Pathophysiology of bradykinesia in parkisnon's disease. *Brain* 124: 2131-2146.

Beuter A, Geoffroy A, Edwards R (1999) Analysis of rapid alternating movements in Cree subjects exposed to methylmercury and in subjects with neurological deficits. *Environmental Research* 80: 64-79.

Bezard E, Brotchie JM, Gross CE (2001) Pathophysiology of levodopa-induced dyskinesia: Potential for new therapies. *Nature Reviews* 2: 577-588.

Blanchet PJ, et al (1995) Continuous administration decreases and pulsatile administration increases behavioural sensitivity to a novel dopamine D2 agonist (U-91356A)in MPTP-exposed monkeys. *J Pharmacol Ex* 272: 854-859.

Blin J, Bonnet AM, Agid Y (1988) Does levodopa aggravate Parkinson's disease?. *Neurology* 38: 1410-1416.

Bower JH, Maraganore DM, McDonnell SK, Rocca WA (1999) Incidence and distribution of Parkinsonism in Olmsted county, Minnesota, 1976-1990. *Neurology* 52 (6): 1214-1220.

Brissaude E (1895) Lecons sur les maladies nerveuses. *Masson et Cie Paris.*

Brooks DJ, Piccini P, Turjanski N, Samuel M (2000) Neuroimaging of dyskinesia. *Ann Neurol* 47 (suppl 1): S154-S159.

Brotchie JM (2000) The neural mechanisms underlying levodopa-induced dyskinesia in Parkinson's disease. *Annual Neurology* 47 (suppl. 1): S105-S114.

Brown RG, Marsden CD (1991). Dual task performance and processing resources in normal subjects and patients with Parkinson's disease. *Brain* 114: 215-231.

Brown P, Corcos DM, Rothwell JC (1997) Does Parkinsonian action tremor contribute to muscle weakness in Parkinson's disease? *Brain* 120: 401-408.

Burkhard PR, Shale H, Langston JW, Tetrud JW (1999) Quantification of dyskinesias in Parkinson's disease: Validation of a novel instrumental method. *Movement Disorders* 14 (5): 754-763.

[a]Calon F, Pharm B, Grondin R, Morissette M. Goulet M, Blanchet PJ, Di-Paolo T, Bedard PJ (2000) Molecular basis of levodopa-induced dyskinesias. *Annual Neurolog* 47 (suppl. 1): S70-S78.

[b]Calon F, Tahar AH, Blanchet PJ, Morissette M, Grondin R., Goulet M, Doucet JP, Robertson GS, Nestler E, Di-Paolo T, Bedard PJ (2000) Dopamine-receptor stimulation: Biobehavioural biochemical consequences. *Trends in Neurosciences* 23 (suppl.): S92-S100.

Calon F et al (1995) L-dopa or D2 agonist induced dyskinesia in MPTP monkeys: Correlation with changes in dopamine and $GABA_A$ receptors in the striaopallidal complex. *Brain Res* 680: 43-52.

Carboncini MC, Manzoni D, Strambi S, Bonuccelli U, Pavese N, Andre P, Rossi B (2001) The relation between EMG activity and kinematic parameters strongly supports a role of the action tremor in parkinsonian bradykinesia. *Movement Disorders* 61 (1): 47-57.

Carlsson A (1959) The occurrence, distribution and physiological role of catecholamines in the nervous system. *Pharmacology Rev* 11: 490-493.

Cepeda C, et al (1993) Neuromudulatory actions of dopamine in the neostraitum are dependent upon the excitatory amino acid receptor subtypes activated. *Proc Natl Acad Sci U.S.A* 90: 9576-9580.

Cotzias GC, Papavasilious PS, Gellene R (1969) Modification of Parkinsonism – chronic treatment with L-dopa. *New England Journal of Medicine* 280: 337-345.

Creese I, Burt DR, Snyder SH (1977) Dopamine receptor binding enhancement accompanies lesion-induced behavioural supersensitivity. *Science* 197: 596-598.

Crossman AR (1987) Primate models of dyskinesia: The experimental approach to the study of basal ganglia-related involuntary disorders. *Neuroscience* 21: 1-40.

Crossman AR (1990) A hypothesis of the pathophysiological mechanism the underlie levodopa or dopamine agonist-induced dyskinesia in Parkinson's disease. *Movement Disorders* 5: 100-108.

Daffertshofer A, Berg C van den, Beek PJ (1999) A dynamical model for mirror movements. *Physica D* 132: 243-266.

Damiano AM, McGarth MM, Willian MK, Snyder CF, LeWitt PA, Richter RR (2000). Evaluation of a measurement strategy for Parkinson's disease: Patient health-related quality of life. *Qual Life Res* 9: 87-100.

De Jong GJ, Meerwaldt JD, Schmitz PI (1987) Factors that influence the occurrence of response variations in Parkinson's disease. *Annal Neurology* 22: 4-7.

DeLong MR (1990) Primate models of movements disorders of basal ganglia origin. *Trends in Neurosciences* 13: 281-285.

Deschenes M, Paradis M, Roy JP, Steriade M (1984) Electrophysiology of neurons of lateral thalamic nuclei in cat: resting properties and burst discharges. *Journal of Neurophysiology* 51: 1196-1219.

Duffau H, Tzourio N, Caparros-Lefebvre D, Parker F, Mazoyer B (1996) Tremor and voluntary repetitive movement in Parkinson' disease: comparison before and after L-dopa with positron emission tomography. *Exp Brain Res* 107 (3): 453-462.

Durif F, Vidailhet M, Debilly B, Agid Y (1999) Worsening of levodopa-induced dyskinesias by motor and mental tasks. *Movement Disorders* 14 (2): 242-245.

Duval C, Panisset M, Sadikot AF (2001) The relationship between physiological tremor and the performance of rapid alternating movements in healthy elderly subjects. *Exp Brain Res* 139: 412-418.

Duval C, Panisset M, Strafella AP, Sadikot AF (2005) The impact of ventrolateral thalamotomy on tremor and bradykinesia in patients with Parkinson's disease. *Exp Brain Res*. In print.

Duval C, Panisset M, Bertrand, G, Sadikot AF (2000) Evidence that ventrolateral thalamotomy may eliminate the supraspinal component of both pathological and normal physiological tremors. *Exp Brain Res* 132 (2): 216-222.

Eckhouse RH, Penny MA, Maulucci R (1996) A comparison of kinematic recording instruments. *Journal of Medical Systems* 20 (6): 439-456.

Ehringer H, Hornykiewics O (1960) Verteilung von noradrenalin und dopamin (3-hydroxytyramin) im gehirn des menschen und ihr verhalten bei erkrankungen der extrapyramidalen systems. *Klin Wochenschr* 38: 1236-1239.

Fahn S (2000) The spectrum of levodopa-induced dyskinesias. *Annal Neurology* 47 (suppl. 1): S2-S11.

Fahn S (2003) Description of Parkinson's disease as a clinical syndrome. *Annals New York Academy of Sciences* 991: 1-14.

Filion M (1979) Effects of interruption of nigrastriatal pathway and of dopaminergic agents on the spontaneous activity of globus pallidus neurons in the awake monkey. *Brain Res* 178: 425-441.

Filion M, Tremblay L (1988) Abnormal spontaneous activity of the globus pallidus neurons in monkeys with MPTP-induced parkinsonism. *Brain Res* 547: 142-151.

Filion M et al (1991) Effects of dopamine agonists on the spontaneous activity of the globus pallidus neurons in monkeys with MPTP-induced parkinsonism. *Brain Res* 547: 152-161.

Filion M (2000). Physiologic basis of dyskinesia. Annal *Neurology* 47 (suppl. 1): S35-S41.

Friedman A (1994) Old-onset Parkinson's disease compared with young-onset disease: Clinical differences and similarities. *ACTA Neurologica Scandinavica* 89: 258-261.

Gerfen CR, et al (1990) D1 and D2 dopamine receptor-regulated gene expression of striatonigral and striatopallidal neurons. *Science* 250: 1429-1432.

Goetz CG, Stebbins GT, Shale HM, Lang AE, Chernik DA, Chmura TA, Ahlskog JE, Dorflinger EE (1994) Utility of an objective dyskinesia rating scale for Parkinson's disease: inter- and intrarater reliability assessment. *Movement Disorders* 9 (4): 390-394.

Grace AA (1991) Phasic versus tonic dopamine release and the modulation of dopamine system responsivity: A hypothesis for the etiology of schizophrenia. *Neuroscience* 41: 1-24.

Graybiel AM, Canales JJ, Capper-Loup C (2000) Levodopa-induced dyskinesias and dopamine-dependent stereotypies: A new hypothesis. *Trends in Neurosciences* 23 (Suppl.): S71-S77.

Grandas F, Galiano ML, Tabernero C (1999) Risk factors for levodopa-induced dyskinesias in Parkinson's disease. *Journal of Neurology* 246: 1127-1133.

Guttman M, Kish SJ, Furukawa Y (2003) Current concepts in the diagnosis and management of Parkinson's disease. *Canadian Medical Association Journal* 168 (3): 293-301.

Hoff JI, van Hilten BJ, Roos RAC (1999) A review of the assessment of dyskinesias. *Movement Disorders* 14 (5): 737-743.

Hoff JJ, Plas AA, Wagemans EAH, van Hilten JJ (2001) Accelerometric assessment of levodopa-induced dyskinesias in Parkinson's disease. *Movement Disorders* 16 (1): 58-61.

Hoy KE, Fitzgerald PB, Bradshaw JL, Armatas CA, Georgiou-Karistianis N (2004) Investigating the cortical origins of motor overlow. *Brain Research Reviews* 46: 315-327.

Ilson J, Fahn S, Cote L (1984) Painful dystonic spasms in Parkinson's disease. *Advances in Neurology* 40: 395-398.

Jahanshani M, Jenkins IH, Brown RG, Marsden CD, Pissingham RE, Brooks DJ (1995) Self-initiated versus externally triggered movements: An investigation using measurement of regional blood flow with PET and movement-related potentials in normal and Parkinson's disease subjects. *Brain* 118: 913-933.

Jenner P (2000) Pathophysiology and biochemistry of dyskinesia: Clues for the development of non-dopaminergic treatments. *Journal of Neurology* 247 (suppl. 2): II/43-II/50.

Johnson TV, Kipnis AN, Lee MC, Loewenson RB, Ebner TJ (1991) Modulation of the stretch reflexdruing volitional sinusoidal tracking in Parkinson's disease. *Brain* 114: 443-460.

Johnson KA, Cunnington R, Bradshaw JL, Philips JG, Iansek R, Rogers MA (1998) Bimanual co-ordination in Parkinson's disease. *Brain* 121 743-753.

Jordan N, Sagar HJ, Cooper, JA (1992) A component analysis of the generation and release of isometric force in Parkinson's disease. *Journal of neurol Neurosurgery Psychiatry* 55: 572-576.

Joseph CL, Jolene Siple J, McWhorter JK, Camicioli R (1995) Adverse reactions to controlled release levodopa/carbidopa in older persons: Case control. *Journal of American Geriatric Society* 43 (No 1): 47-50.

Just H, Ostergaard K (2002) Health related quality of life in patients with advanced Parkinson's disease treated with deep brain stimulation of the subthalamic nuclei. *Movement Disorders* 17 (1): 539-545.

Kaakkola S (2000) Clinical pharmacology, therapeutic use and potency of COMT inhibitors in Parkinson's disease. *Drugs* 59 (6): 1233-1250.

Keijsers NL W, Horstink MWIM, van Hilten JJ, Hoff JI, Gielen CCAM (2000) Detection and assessement of the severity of levodopa-induced dyskinesias in patients with Parkinson's disease by neural networks. *Movement Disorders* 15 (6): 1104-1111.

Karlsen KH, Tandleberg E, Aersland D, Larsen JP (2000). Health related quality of life in Parkinson's disease: A progressive longitudinal study. *J Neurol Neurosurg Psychiatry* 69: 584-589.

Khan NL, Britton T (2004) Parkinson's disease: Clinical features, pathophysiology and genetic. *Hospital Pharmacist* 11: 9-15.

Kostic V, Przedborski S, Flaster E, Sternic N (1991) Early development of levodopa-induced dyskinesias and response fluctuations in young-onset Parkinson's Disease. *Neurology* 41: 202-205.

Krack P, Pollak P, Limousin O, Hoffman D, Benazzouz A, Le Bas JF, et al (1998) Opposite motor effects of pallidal stimulation in Parkinson's disease. *Annual Neurology* 43: 180-192.

Lai BCL, Marion SA, Teschke K, Tsui JKC (2002) Occupational and environmental risk factors for Parkinson's disease. *Parkinsonism and Related Disorders* 8 (5): 297-310.

Lamaare Y, Joffoy AJ, Dumont M, De Montigny C, Grou F, Lund JP (1975) Central mechanism of tremor in some feline and primate models. *Can J Neurol Sci* 2: 227-233.

Lee T, Seeman P, Raiput A, Farley IJ, Hornykiewics O (1978) Receptor basis for dopaminergic supersensitivity in Parkinson's disease. *Nature* 273: 150-151.

Logigian E, Hefter H, Reiners K, Freund H (1991) Does tremor pace repetitive voluntary motor behaviour in Parkinson's disease? *Annual Neurology* 30: 172-179.

Lozano AM (2000) Neural recordings in Parkinson's disease patients with dyskinesias induced by apomorphine. *Annual Neurology* 47 (suppl. 1): 141-146.

Lyons KE, Hubble JP, Troster AI, Pahwa R, Koller WC (1998) Gender differences in Parkinson's disease. *Clinical Neuropharmacology* 21: 118-121.

Marconi R, Lefebvre-Caparros D, Bonnet AM, Vidailhet M, Dubois B, Agid Y (1994) Levodopa-induced dyskinesias in Parkinson's disease phenomenology and pathophysiology. *Movement Disorders* 9 (1): 2-12.

Marras C, Lang A, Krahn M, Tomlinson G, Naglie G and Parkinson Study Group (2004). Quality of life in early Parkinson's disease: Impact of dyskinesias and motor fluctuations. *Movement Disorders* 19 (1): 22-28

Marsden CD (1980) "On-Off" phenomenon in Parkinson's disease. In: Rinne UK, Klinger M, Stamm G, editors. *Parkinson's disease: Current progress, problems and management* Amsterdam/New York: Elsevier/North-Holland Biomedical Press, 241-254.

Merello M, Hughes A, Colosimo C, Hoffman M, Starkstein S, Leiguarda R (1997) Sleep benefit in Parkinson's disease. *Movement Disorders* 12: 506-508.

Milne AD, Chess DG, Johnson JA, King GJW (1996) Accuracy of an electromagnetic tracking device: A study of the optimal operating range and metal inteference. *Journal of Biomechanics* 29 (6): 791-793.

Mink JW (1996) The basal ganglia: focused selection and inhibition of competing motor programs [Review]. *Prog Neurobiol* 50: 381-425.

Murata M, Kanazawa I (1993) Repeated L-dopa administration reduces the ability of dopamine storage and abolishes the supersensitivity of dopamine receptors in the striatum on intact rat. *Neuroscience Res Commun* 16: 15-23.

Negaseki Y, Shibazaki T, hirai T, Kawashima Y, Hirato M, Wada H, Miyazaki M, Ohye C (1986) Long-term follow-up results of selective VIM-thalamotomy. *J Neurosurgery* 65: 296-302.

Nutt JG (2001) Fluctuations in response to treatment for parkinson's disease. *Adv Neurol* 86: 361-366.

Nutt JG (1990) Levodopa-induced dyskinesias: review, observations and speculations. *Neurology* 40: 340-345.

[a]Obeso JA, Olanow CW, Nutt JG (2000) Levodopa motor complications in parkinson's disease. *Trends in Neurosciences* 23 (suppl.): S2-S7.

[b]Obeso JA, Rodriguez-Oroz MC, Rodriuez M, Lanciego JL, Artieda J, Gonzalo N, Olanow CW (2000) Pathophysiology of the basal ganglia in Parkinson's disease. *Trends in Neurosciences* 23 (suppl. 1) S8-S19.

[c]Obeso JA, Rodriguez-Oroz MC, Macias R, Alvarez L, Guridi J, Vitek J, DeLong MR (2000) Pathophysiological basis of surgery for parkinson's disease. *Neurology* 55 (suppl. 6): S7-S12.

[d]Obeso JA, Rodriguez-Oroz MC, Rodriguez M, DeLong MR, Olanow CW (2000) Pathophysiology of levodopa-induced dyskinesias in parkinson's disease: Problem with the current model. *Annl Neurology* 47 (suppl. 1): S22-S34.

Ohye C, Hirai T, Miyazaki M, Shibazaki T, Nakajima H (1982) VIM thalamotomy for the treatment of various kinds of tremor. *Appl Neurophysiol* 45: 275-280.

Okada M, Okada M (1983) A method for quantification of alternate pronation and supination of forearms. *Comput Biomed Res* 16 (1): 59-78.

Olanow CW, Schapira AHV, Rascol O (2000) Continuous dopamine-receptor stimulation in early parkinson's disease. *Trends in Neurosciences* 23 (suppl.): S117-S126.

Olanow CW, Obeso JA (2000) Pulsatile stimulation of dopamine receptors and L-dopa-induced motor complications in Parkinson's disease: implications for early use of COMT inhibitors. *Neurology* 55 (suppl. 4): 572-577.

Pan HS, Penney JB, Young, AB (1985) Gamma-aminobutyric acid and benzodiazepine receptor changes induced by unilateral 6-hydroxydopamine lesions of the medial forebrain bundle. *Journal of Neurochemistry* 45: 1396-1404.

Pare D, Curro'Dossi R, Steriade M (1990) neural basis of the parkinsonian resting tremor: a hypothesis and its implications for treatment. *Neurosceince* 35: 217-226.

Parent A, Cicchetti F (1998) The current model of the basal ganglia organization under scrutiny. *Movement Disorders* 13: 199-203.

Parker F, Tzourio N, Blond S, Petit H, Mazoyer B (1992) Evidence for a common network of brain tructures involved in parkinsonian tremor and voluntary repetitive movement. *Brain Res* 584 (1-20): 11-17.

Parkinson J (1817) *An essay on the shaking palsy.* London: Sherwood, Neely and Jones.

Parkinson Study Group (2000) Pramipexole vs levodopa as initial treatment for Parkinson's disease: A randomized controlled trial. *Journal of American Medical Association* 284: 1931-1938.

Pearce RK, et al (1995) Altered striatal preproenkephalin mRNA levels in normal macaque monkeys with dyskinesias induced by chronic L-dopa administration. *British Journal of Pharmacology* 116: 78-95.

Pearce RK (1999) L-dopa and dyskinesias in normal monkeys. *Movement Disorder* 14 (suppl. 1): 9-12.

Pearce RK, Banerji T, Jenner P, Marsden CD (1998) De novo administration of ropinirole and bromocriptine induces less dyskinesia than L-dopa in MPTP-treated marmoset. *Movement Disorders* 13: 234-241.

Pechevis M, Clarke CE, Vieregge P, et al (2001). Direct and indirect costs of Parkinson's disease and L-dopa induced dyskinesias: A prospective European study. *Parkinsonism Relat Disord* 7(suppl.): 106.

Penney J, Young AM (1986) Striatal inhomogeneities and basal ganglia function. Movement Disorders 1: 3-15.

Perret E (1968) Simple motor performance of patients with Parkinson's disease before and after surgical lesion in the thalamus. *J Neurol Neurosurg psychiatry* 31: 284-290.

Perret E, eggenberger E, Siegfried J (1970) Simple and complex finger movement performance of patients with Parkinsonism before and after a unilateral stereotaxic thalamotomy. *J Neurol Neurosurg psychiatry* 33 (1): 16-21.

Pederzoli M, Girotti F, Scigliano G, Aiello G, Carella F, Caraceni T (1983) L-dopa long term treatment in Parkinson's disease: age-related side effects. *Neurology* 33: 1518-1522.

Poirier J, Kogan S, Gauthier S (1991) Environment, genetics and idiopathic Parkinson's disease. *Canadian Journal of Neurol Science* 18 (1): 70-76.

Rascol O, Sabatini U, Chollet F, Celsis P, Monatastruc JL, Marc-Vergnes JP, et al (1992) Supplementary and primary sensory motor area activity in Parkinson's disease: regional cerebral blood flow changes during finger movements and effects of apomorphine. *Arc Neurology* 49: 144-148.

Rascol O, Sabitini U, Brefel C, Fabre N, Rai S, Senard JM, et al (1998) Cortical motor overactivation in parkinsonian patients with l-dopa-induced peak-dose dyskinesia. *Brain* 121: 527-533.

Rascol O, Brooks DJ, Korczyn AD, et al (2000) A five year study of the incidence of dyskinesias in patients with early Parkinson's disease who were treated with ropinirole or levodopa. *New England Journal of Medicine* 342: 1484-1491.

Rosner B (1995) Fundamentals of biostatistics. 4th ed. Belmont (CA): Wadworth Publishing Company, p 511–514.

Samuel M, Caputo E, Brooks DJ, Schrag A, Scaravalli T, Branston NM et al. (1998) A study of medial pallidotomy for Parkinson's disease: Clinical outcome, MRI location and complications. *Brain* 121: 59-75.

[a]Schrag A, Ben-Shlomo Y, Quinn NP (2000) Cross sectional prevalence survey of idiopathic parkinson's disease and parkinsonism in London. *British Medical Journal* 321: 21-22.

[b]Schrag A, Selai C, Jahanshahi M, Quin NP (2000). The EQ-5D---a generic quality of life measure---is a useful instrument to measure quality of life in patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry* 69: 67-73.

Schrag A, Quinn N (2000) Dyskinesias and motor fluctuations in Parkinson's disease: A community-based study. *Brain* 123: 2297-2305.

Schultz W, Apicella P, Ljungberg T (1993) Responses of monkey dopamine neurons to reward and conditional stimuli during successive steps of learning a delayed response task. *J Neurosci* 13 (3): 900-913.

Sealfon SC, Olanow CW (2000) Dopamine receptors: from structure to behaviour. *Trends Neurosciences* 23 (suppl. Basal Ganglia, Parkinson's disease and levodopa therapy): S34-S40.

Stelmach GE, Teasdale N, Philips J, Worringham CJ (1989) Force production characteristics in Parkinson's disease in Parkinson's disease. *Exp Brain Res* 76: 165-172.

Siderowf A, Ravina B, Glick HA (2002). Preference-based quality of life in patients with Parkinson's disease. *Neurology* 59: 103-108.

Steriade M, parent A, Hada J (1984) Thalamic projections of nucleus reticularis thalami of cat: a study by using retrogade transport of HRP and fluorescent tracers. *Journal of Neurophysiology* 229: 531-547.

Tanner CM, Goldman SM (1996) Epidemiology of Parkinson's disease. (Neurol. Clin.) 2: 317-335.

Tanner CM, Ottman R, Goldman SM, Ellenberg J, Chan P, Mayeux R, Langston JW (1999) Parkinson's disease in twins: an etiological study. *Journal of American Medical Association* 27: 341-346.

Tatton WG, Lee RG (1975) Evidence of abnormal long-loop reflexes in rigid parkinsonian patients. *Brain Res* 100: 671-676.

van den Berg C, Beck PJ, Wagenaar RC, van Wieringen PCW (2000) Coordination disorders in patients with Parkinson's disease: A study of paced rhythmic forearm movements. *Exp Brian Res* 134: 174-186.

Vidailhet M, Bonnet AM, Marconi R, Durif F, Agid Y (1999) The phenomenology of l-dopa-induced dyskinesias in Parkinson's disease. *Movement Disorders* 14 (suppl. 1): 13-18.

Vitek JL, Giroux M (2000) Physiology of hypokinetic and hyperkinetic movement disorders: Model for dyskinesia. *Annual Neurology* 47 (suppl. 1): S131-S140.

Volkman J, Joliot M, Mogilner A, Ioannides AA, Lado F, Fazzini E, Ribary U, Llinas R (1996) Central motor loop ocilations in parkinsonian resting tremor revealed by magnetoencephalography. *Neurology* 46 (5): 1359-1370.

Warner TT, Schapira AH (2003) Genetic and environmental factors in the cause of Parkinson's disease. *Annals of Neurology* 53 (Suppl. 3): S16-S23.

Yanagisawa N, Nezu A (1987) *European Neurology* 26 (suppl. 1): 30-40.