UNIVERSITÉ DU QUÉBEC À MONTRÉAL

L'IMPACT DE LA CHORÉE SUR LES MOUVEMENTS ALTERNÉS RAPIDES DES PATIENTS AYANT LA MALADIE DE HUNTINGTON

(THE IMPACT OF CHOREA ON RAPID ALTERNATING MOVEMENTS IN PATIENTS WITH HUNTINGTON'S DISEASE)

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PAR
ALISON L. FENNEY

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DEDICATION

This thesis is dedicated to my parents
who taught me it is never to late to learn something new,
and to my sister, without whom I would never have known that
nothing is impossible!

I would also like to dedicate this thesis to the patients with Huntington's disease who shared their time and lives with me, educating me in the human side of the disease equation. Their generosity, courage and interest in research were a constant inspiration to me, and without which this experience would not have been complete.

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List of Abbreviations

ANOVA	Analysis of variance
BDNF	Brain derived neurotrophic factor
BG	Basal Ganglia
BOSH	Behaviour observation scale Huntington
CAG	Glutamine
CAPIT	Core Assessment Program for intra-cerebral Transplantations
DBS	Deep brain stimulation
DOPA	Dopamine
DRPLA	Dentato-rubral-pallidolysian atrophy
EMG	Electromyography
fMRI	Functional magnetic resonance imaging
GABA	Gamma-aminobutyric acid
Gpe	Globus Pallidus externus
Gpi	Globus Pallidus internus
HD	Huntington's Disease
HTT	Huntinton Protein
MT	Manual tracking
NMDA	N-methyl-D-aspartic acid
PD	Parkinson's disease
PET	Positron emission tomography
RAM	Rapid alternating movement
SD	Standard deviation
SEP	Sensory Evoked Potential
SNr	Substantia Nigra pars reticulate
STN	Subthalamic nucleus
TFC	Total Functional Capacity Scale
UHDRS	Unified Huntington's disease rating scale
UPS	Ubiquitin Protease System
VA	Ventral Anterior
VL	Ventral Lateral
WBIM	Whole body involuntary movement

ABSTRACT

The goal of this study was to isolate the impact of chorea on voluntary movements, in order to better assess the role of involuntary movement in motor disturbances observed in patients with Huntington's disease. Whole-body involuntary movements (WBIM) and voluntary motor acts were recorded simultaneously, using a magnetic tracker system, in fifteen choreic HD patients and fifteen healthy age-, gender-matched control subjects. Participants were asked to perform two distinct tasks, a rapid alternating movement (RAM) task, yielding measures of bradykinesia and hypokinesia, and a manual-tracking (MT) task yielding a measure of chorea intrusion during accurate movements.

Patients with HD had better RAM performance than healthy controls, this finding ruling out the presence of core bradykinesia in these patients. During the manual tracking task patients with HD showed deviations from the target that significantly hindered their ability to match target velocity. In addition, error in performance was correlated with the amplitude of whole-body chorea, illustrating the deleterious effect of chorea during accurate movements. These results clearly show that core bradykinesia is not a symptom of HD when chorea is predominant, but that chorea is the main cause of error in performance during accurate movements. Accordingly, patients with HD would greatly benefit from therapeutic treatment aimed at reducing chorea while maintaining proper motor function.

RESUME

Le but de cette étude était d'isoler l'impact de la chorée sur les mouvements volontaires, pour mieux évaluer le rôle des mouvements involontaires sur les perturbations motrices observées chez les patients ayant la maladie de Huntington. Les mouvements involontaires du corps ainsi que les actions motrices volontaires furent enregistrés simultanément, à l'aide d'un système de pistage magnétique, chez quinze patients choréiques ayant la maladie de Huntington ainsi que chez quinze sujets contrôle en bonne santé de même âge et sexe. Il a été demandé aux participants d'accomplir deux tâches distinctes; une de mouvements alternés rapides (RAM) qui permettra de quantifier l'hypokinésie et la bradykinésie, et une tâche de poursuite manuelle (MT) qui fournira une mesure quant à l'intrusion des chorées lors de mouvements précis.
Les patients ayant la maladie de Huntington ont obtenu de meilleurs résultats comparativement aux sujets contrôles lors de la tâche RAM, démontrant ainsi l'absence de bradykinésie chez ces sujets. Lors de la tâche MT, les patients ayant la maladie de Huntington ont démontré une déviation par rapport à l'emplacement de la cible réduisant ainsi leur habileté à reproduire sa vitesse. De plus, une corrélation fût établie entre l'erreur au niveau des performances et l'amplitude des chorées du corps, illustrant l'effet néfaste des chorées lors de mouvements précis. Ces résultats démontrent clairement que la bradykinésie n'est pas un symptôme de la maladie de Huntington lorsque des chorées sont présentes, mais que les chorées sont la principale cause d'erreur de performance lors de mouvements précis. Donc, les patients atteints de la maladie de Huntington bénéficieraient grandement de traitements visant à réduire les chorées tout en maintenant une fonction motrice adéquate.

Mot clefs Huntington, bradykinesia, chorée, quantification, Parkinson

1. INTRODUCTION

One in every 10,000 Canadians suffers from Huntington's Disease (HD) (Huntington Society of Canada 2005) a statistic that places Canada at the high end of world prevalence rates, 4-10 per 100,000 (Qin et al. 2005; Reddy et al. 1999). HD is a genetically inherited neurodegenerative condition caused by the unstable expansion of the CAG trinucleotide repeat (Myers 2004; Berardelli et al. 1999; Canals et al. 2004). The repeat results from a mutation of the gene that encodes the protein huntingtin, located on chromosome 4p16.3 (Myers 2004; Huntington's Disease Collaborative Research Group 1993). Huntingtin protein is thought to be necessary for developing and sustaining normal brain function (Menalled et al. 2002; Young 2003). HD is characterized by disordered voluntary and involuntary movement (Carella et al. 2003; Bilney et al. 2005; Berardelli et al. 1999; van Vugt et al. 2004), cognitive deficit and psychiatric symptoms (Gardien et al. 2004; Naarding et al. 2001; Young 2003).

Although the genetic cause of the disease has been isolated, there are no existing therapies to delay or prevent onset (Bhidayasiri & Truong 2004), and treatment is aimed at the alleviation of symptoms (Bilney et al. 2003).

The pathophysiology of HD is marked by a progression from hyperkinetic to hypokinetic movements in typical adult onset (Berardelli et al. 1999), although there is extensive variability in motor symptom expression. HD is the most common cause of chorea (Bhidayasiri & Truong 2004), the presence of which often decreases as disease progresses to later stages (Berardelli et al. 1999). There is evidence to suggest that chorea and other involuntary movements in HD negatively affect motor function, specifically accuracy (Phillips et al. 1996; Bilney et al. 2003) and gait regulation (Bilney et al. 2005). The motor symptoms of Huntington's disease have been researched for many years but very little work has been dedicated to the specific movement characteristics of choreic patients. Due to the lack of therapeutic options currently available to effectively treat chorea in HD it is essential to establish a greater

understanding of this involuntary movement, its characteristics and the neural networks involved in its expression.

The first general aim of this study is to quantify the mutual influence of chorea and voluntary movement in patients with adult onset Huntington's disease. Quantification of chorea during voluntary movement will enable a greater understanding of the mutual influence of chorea and voluntary movement, and it's application to therapies aimed at improving performance of daily living activities and the maintenance of quality of life in choreic patients.

Treatment of motor symptoms, specifically chorea, is not suggested unless the condition becomes debilitating, as therapies used have extensive negative side effects and may aggravate psychiatric symptoms (Bhidayasiri & Truong 2004). Adverse side-effects associated with anti-choreic medication include parkinsonism, sedation, insomnia, depression, anxiety and akathesia (Bonelli et al 2004). It has been suggested that chorea may not be the only, or most influential source of motor disability in HD (Thompson et al. 1988). The coexistence of hyperkinetic and hypokinetic motor behaviour in patients with HD (Thompson et al. 1988; Joel 2001) makes it increasingly difficult to isolate the main source of error in movement, as well as the effects of each condition on performance (Hanajima et al. 1999). The lack of data on un-medicated HD patients calls into question whether the hypokinetic features of movement, e.g bradykinesia, are a natural symptom of the disease or a condition brought on, or aggravated, by drug therapy. It is imperative to isolate and quantify the existence of hyperkinetic and hypokinetic characteristics in HD in order to determine which is the more influential source of disability.

The second general aim of this study is to determine if bradykinesia co-exists with chorea in patients with adult-onset Huntington's disease. Quantification of hyperkinetic and hypokinetic features of motor behaviour in patients will enable a baseline understanding of motor symptoms in the disease and their interaction with one another during performance. This information will enable more accurate and efficient tailoring of drug therapy to alleviate negative motor symptoms without introducing any

new impairment such as those adverse side effects previously experienced with drug treatment.

2. REVIEW OF LITERATURE

The following review of literature will outline current information regarding the types, prevalence, progression, aetiology and pathophysiology of Huntington's disease, with specific focus on the motor behavior and abnormalities associated with this disease. This review is designed to establish a foundation of information regarding HD in order to form an understanding of those aspects of the condition that are widely accepted, controversial, or yet unknown. The rational of this study will then be discussed based on these findings.

2.1 Huntington's Disease (HD)

The cardinal pathological feature of HD is loss of medium spiny neurons in the striatum (Backman & Farde 2001), specifically those with GABAergic projections to the external pallidum and SNr (Weeks et al. 1997; Reiner et al. 1988). Striatal degeneration in HD progresses along mediolateral and dorsoventral gradients affecting the dorsomedial caudate and dorsal putamen (Joel 2001; Quinn & Schrag 1998). Currently there is no known method to halt or reverse the striatal damage caused by HD.

HD, occurring at a rate of 10 per 10,000 among Caucasian populations, with no gender preference (Bhidayasiri & Truong, 2004), has a mean age at onset of 32-42 years with a mean disease duration of 15-17 years (Quinn et al. 1998). The condition is autosomal dominant and 90% of cases are inherited from the father (Quinn et al. 1998), offspring of an effected family member have a 50% chance of having inherited the fully penetrant mutated gene (Myers 2004; Bhidayasiri & Truong, 2004). Age of onset has been inversely correlated with CAG repeat length in HD (Saft et al. 2003; Reddy et al. 1999; Young 2003), although repeat length accounts for only 50% of variance in age at onset (Albin et al. 1995). HD is associated with repeat instability (Ross et al. 1997) and genetic anticipation (Young 2003; Reddy et al. 1999). Instability in HD increases with

the transmission of longer repeats, paternal transmission can expand more then 1-2 triplets in length (Ross et al. 1997; Mangiarini et al. 1997). Anticipation, increasing disease severity and decreasing age of onset, occurs most commonly through paternal transmission (Ross et al. 1997). Approximately 28% of cases are late onset, 50 years and older, and only 6% juvenile onset (Quinn & Schrag 1998). The Westphal variant, also known as the rigid akinetic type and clinically associated with early/juvenile onset is very rare and presents with seizures, action tremor, bradykinesia, eye movement abnormalities, cerebellar ataxia and dystonia (Magnet et al. 2004). Pathophysiologic characteristics of Westphal variant include atrophy of the direct striatal pathway to GPi, globus pallidus internus, and atrophy of enkephalin striatal projections to the GPe, globus pallidus externus (Albin et al. 1990; Magnet et al. 2004). Adult onset is the predominant form of HD, responsible for approximately 68% of cases (Quinn & Schrag 1998). This form presents initially with motor 'clumsiness' due to abnormal voluntary movement, bradykinesia (Sanchez-Pernaute et al. 2000) and involuntary movement, such as motor tics and chorea (Ross et al. 1997). Predictive genetic testing is available for individuals with a family history of the condition (Evers-Kiebooms et al. 1998), testing predicts whether asymptomatic individuals will be affected by the condition later in life.

Although the onset of Huntington's disease has long been associated with the presentation of motor symptoms (Georgeou et al. 2003), recent research has shown that cognitive and emotional disturbances may pre date motor signs (Lawrence et al. 1998; Snowden et al. 2002).

Stage or progression of HD is measured using clinical scales such as the total functional capacity (TFC) scale and the Unified Huntington disease rating scale (UHDRS) (Shoulson 1979; Huntington Disease Study Group 1996). The total functional capacity (TFC) scale is a standardized measure of capacity to participate in activities in the workplace and home, on a scale from 13 (normal) to 0 (severe disability). According to the TFC scale there are five stages of progression in adult-onset Huntington's disease (Shoulson 1979). Stages encompass a wide range of years from diagnosis due to the

variance in progression and expression of symptoms and degeneration in HD. The first stage encompasses diagnosis up to eight years into the disease, engagement in the individuals occupation is normal, ability to handle financial affairs and domestic responsibilities remains in-tact, as well as full ability to perform activities of daily living independently. The second stage occurs 3-13 years from diagnosis, engagement in work and financial affairs is diminished but household responsibilities and daily activities can be completed independently. The third stage, occurring anywhere from 5-16 years from diagnosis, all activities are impaired and assistance is required, either home or institutional care. The fourth and fifth stage, 9-21 and 11-26 years from diagnosis, respectively, individuals are unable to function at work, handle financial affairs or manage domestic responsibilities and the inability to complete activities of daily life make full institutional care a necessity. For corresponding stages and TFC score values see Table 1.

Table 1. ***Total Functional Capacity (TFC) scale***. Adapted from Shoulson 1979.

Disease Stage	**TFC Score**	**Years since diagnosis**
Stage I	11-13	0-8
Stage II	7-10	3-13
Stage III	3-6	5-16
Stage IV	1-2	9-21
Stage V	0	11-26

The UHDRS is the gold standard clinical tool for assessing the four domains of clinical capacity and performance in HD. The UHDRS assesses motor and cognitive function, behaviour abnormalities and overall functional capacity (Huntington Study Group 1996). The UHDRS has been found useful in tracking changes in the clinical features of HD over time and has excellent inter-rater reliability (Huntington Study Group 1996). The UHDRS provides a more specific quantification of capacity in the

four clinical domains of HD than the TFC and, therefore, will be used to score patients in this study.

2.1.1 Aetiology

Huntington's disease is attributed to a dynamic mutation in a single gene, IT15 (Ross et al. 1997), also known as the huntingtin gene (Bertram 2005), involving a repeat expansion in the coding region that affects protein structure (van Dellen et al. 2005). The product of this mutation is referred to as mutant htt. An increased number of CAG repeats, nucleic acids cystine, argnine and guanine, which code for the amino acid glutamine, in the HD gene on chromosome 4p16.3 causes disease expression (Myers 2004). CAG repeats occur normally 6-35 times, increased to 40-121 repeats in HD (Reddy et al. 1999; Myers 2004). There is an inverse correlation between repeat length and age at onset (Saft et al. 2003; Young 2003), paternal transmission is sensitive to allele expansion, and this instability of transmission contributes to the anticipation observed in HD and other repeat disorders (Ross et al. 1997). The normal function of huntingtin is unknown (Albin & Tagle 1995), but has been linked to the development and maintenance of normal brain function (Young 2003) and is thought to function primarily cytoplasmically in cytoskeletal function or vesicle recycling (Ross 2002). Huntingtin is also associated with organelles such as endoplasmic reticulum, the nucleus and golgi-complex (Cattaneo et al. 2005). The aetiology of Huntington's disease remains unknown, two main theories have surfaced in an attempt to explain the cause and course of neurodegeneration in this disease: conformational toxicity through amyloid-like protofibril formation (aggregation or inclusion bodies) and altered gene expression (Valera et al. 2005).

2.1.2 Aggregation

The abnormally expanded mutant htt is cleaved or truncated by the ubiquitin proteasome system (UPS) (Valera et al. 2005). The UPS performs a variety of cellular functions, most importantly the removal of abnormal or incorrectly assembled proteins (Valera et al. 2005). This truncation results in the production of toxic polyglutamine

containing fragments that interact with other intracellular proteins, including components of the proteasome, aggregating in the cytoplasm and nucleus forming inclusion bodies (van Dellen et al. 2005). Protein-protein interaction is implicated in the neurodegenerative process of Huntington's disease (Sharpe & Ross 1996). It has been suggested that glutamine repeats acts as polar zippers, joining proteins with an affinity for each other (Perutz et al. 1994). Repeat expansions may then acquire excessive affinities for each other or regulatory proteins when expanded in disease conditions (Sharpe & Ross 1996; Perutz et al. 1994), and this excessive affinity may account for the cascade of events leading to the formation of inclusion bodies. A hypothetical pathway for formation of inclusion bodies involves a cascade of binding reactions from soluble mutant htt monomers to oligomers which are linearly assembled into protofibrils which form fibrils which form filaments that together with other cellular proteins such as molecular chaperones, transcription factors, cytoskeletal proteins and components of the proteasome system, form inclusion bodies (Valera et al. 2005). The function of aggregation is controversial (Reddy et al. 1999). Evidence of protein aggregates in non-neural tissue refutes their role in cell death (Hague et al. 2005); also preferential location of Huntington aggregates in striosomes in HD support a positive, possibly neuroprotective role in the disease (Menalled et al. 2002). Evidence has also been found to suggest a neuroprotective role of aggregation in a study examining wild type htt aggregation in vivo, results show wild type htt modulates neuronal sensitivity to apoptotic death due to NMDA receptor mediated excitotoxicity (Leavitt et al. 2006; Cattaneo et al. 2005).

2.1.3 Altered Gene Expression

Altered gene expression, resulting from the mutation of the huntingtin gene, may result in deregulation of brain derived neurotrophic factor (BDNF) (Canals et al. 2004), altered endocytosis and vesicular transport, abnormalities of synaptic transmission, mitochondrial dysfunction (Schulz & Beal 1994), the activation of apoptotic pathways and impairment of the UPS (Valera et al. 2005; van Dellen et al. 2005). BDNF protects

striatal neurons and is regulated by huntingtin through protein interactions (Canals et al. 2004; Cattaneo et al. 2005). BDNF has been shown to regulate the age of onset and severity of motor dysfunction through protection of striatal enkephalinergic neurons in transgenic mice, suggesting that administration of exogenous BDNF may delay or halt disease progress (Canals et al. 2004; van Dellan et al. 2005). Wild type htt stimulates BDNF vesicular trafficking, and mutant htt inhibits it, as well as interacting with huntingtin associated proteins to enhance vesicular transport intra-cellularly (Cattaneo et al. 2005). A disruption of this function would lead to reduced or abnormal protein trafficking, affecting endo and exo-cytosis at synaptic terminals (Cattaneo et al. 2005). Abnormalities of synaptic transmission can be due to the disruption in the expression of genes encoding synaptic and intra-neuronal signaling proteins, this could lead to the disruption of cortico-striatal networks, via the reduction of dendritic spines in medium spiny neurons of the striatum (van Dellan et al. 2005). Mitochondrial dysfunction is a leading mechanism implicated in the neural degeneration found in a number of diseases (Schulz & Beal 1994). In HD brain tissue there is an increased level of lactate and decreased mitochondrial respiratory chain function (Andreassen et al. 2001). Creatine administration has been found to improve this condition, as well as increasing survival and delaying motor symptom onset in HD mice (Andreassen et al. 2001). Markers of mitochondrial activity have been found to be reduced in transgenic HD mice, as well as decreased oxidase activity in human HD brains (van Dellan et al. 2005) supporting a role for mitochondrial dysfunction in cell death, if not as a cause, at least as a contributing factor (Schulz & Beal 1994). Wild type huntingtin is neuroprotective, particularly due to the fact that it inhibits the formation of pro-apoptotic protein interactors. Also, huntingtin can act as a substrate for a kinase, which activates pro-survival pathways (Cattaneo et al. 2005). Excitotoxicity, resulting from the prolonged activation of excitatory receptors (for example glutaminergic receptors in the basal ganglia), leads to cell damage and death (Doble 1999). Medium spiny neurons, those preferentially affected in HD, receive large amounts of glutaminergic input and their vulnerability to excitotoxicity may be increased by decreased glutamate uptake by glial cells in HD

(Shin et al. 2005). Cell death is a secondary issue in Huntington's disease: it is cell dysfunction that plays a more influential role in disease expression (van Dellen et al. 2005). Impairment of the ubiquitin proteasome system (UPS) is easily related to formation of aggregates and inclusion bodies, due to the impaired ability of the UPS to remove abnormal or misformed proteins, as well as impaired removal of regulatory proteins leading to cellular deregulation and cell death (Valera et al. 2005). These two mechanisms and their associated consequences are supportable hypotheses in the search to understand the aetiology of Huntington's disease, although they are still shrouded in controversy due to discovery of incongruent findings in human and animal models (Valera et al. 2005).

2.2 Basal Ganglia Pathophysiology

Models of the basal ganglia have been used to map a number of clinical findings in movement disorders such as Parkinson's disease and Huntington's disease. In order to understand the progression and expression of Huntington's disease, as well as the unique movement characteristics of chorea, it is important to first understand the role of the basal ganglia in movement.

The basal ganglia (BG) is comprised of the striatum (caudate and putamen), the globus pallidus (internal and external segments), the subthalamic nucleus and the substantia nigra (pars compacta and pars reticulata). The thalamus is closely linked to the basal ganglia, although not considered a part of the structure, it acts as a relay nuclei in many basal ganglia loops. The BG nuclei facilitate transport of sensorimotor, limbic and cognitive information through five pathways organized in parallel loops: the motor, oculomotor, limbic and two prefrontal loops (Alexander et al. 1986). When investigating movement disorders, specifically HD, the motor loop is of primary concern, particularly because of its role in the planning and execution of movement. The motor loop begins in the primary sensory and motor cortical areas, as well as the supplementary and premotor areas. These areas contain projections to the putamen, the input nuclei of the BG located in the striatum (Alexander et al. 1986). From the putamen the loop continues to the

output nuclei, internal segment of the globus pallidus and substantia nigra pars reticulata which project to the ventral lateral (VL) and anterior thalamus (VA) (Wichmann & DeLong 1996). The thalamus then completes the motor loop with projection back to the cortex that facilitates information transfer to the brainstem and spinal cord (Yelnik 2002; Alexander et al. 1986). (Fig 1).

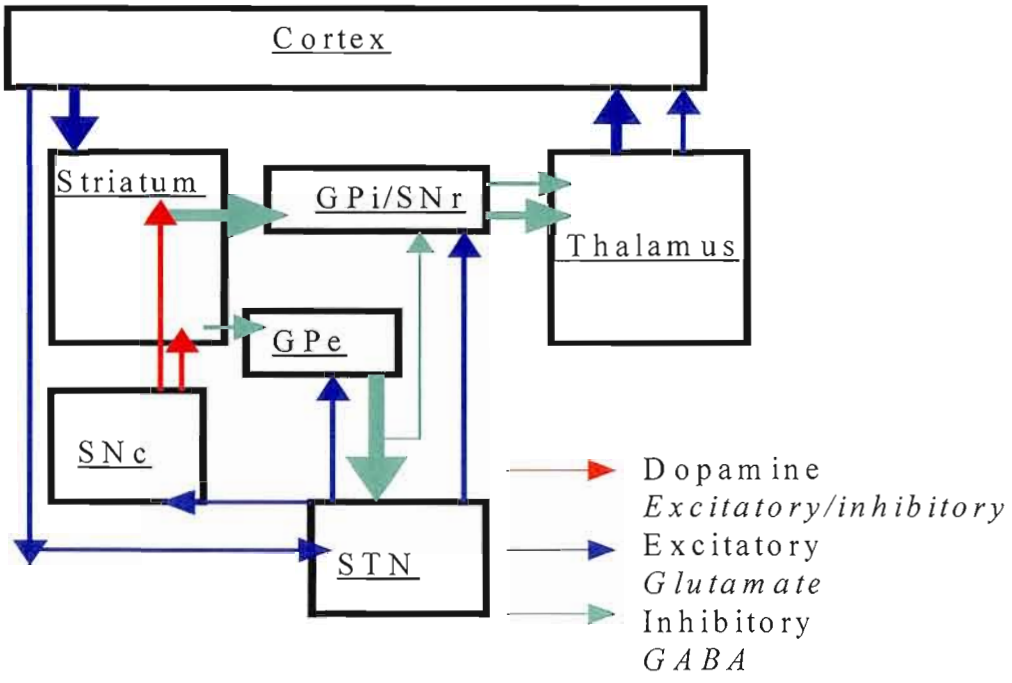

Figure 1. ***Model of the BG.*** This figure outlines the current model of the Basal Ganglia. The motor loop begins in the cortex and projects to the striatum, the major input nuclei of the BG. The GPi and SNr are the major output nuclei of the BG, and the thalamus serves as a relay nuclei back to the cortex. (Adapted from Albin et al. 1989)

2.2.1 Direct and Indirect Pathways

The popular view of the BG motor loop is that of two opposing parallel pathways, the direct and indirect pathways, and that an increase or decrease in movement is based on manipulation of GPi output (Mink 1996). The direct pathway is activated by dopamine at the D1 receptors in the striatum that channels GABA, an inhibitory neurotransmitter, along projections to the GPi and SNr. The GPi has

inhibitory projections to the thalamus, the disinhibition of the thalamus in the direct pathway increases excitatory glutamatergic activity to the motor cortex (Silkis 2002; Wichmann & DeLong 1996). The indirect pathway is inhibited by dopamine at the D2 receptors of the striatum that also channel GABA, via connections to the GPe, which projects to the STN (Mink 1996; Silkis 2002; Wichmann & DeLong 1996). The subthalamic nucleus (STN) then projects to the GPi via excitatory glutamatergic connections. These excitatory connections reduce inhibition of GPi, increasing inhibitory GABA released to thalamus, thus decreasing excitatory glutamatergic projections to the motor cortex (Mink 1996). The direct pathway facilitates desired movements through increased thalamocortical activity, while the indirect pathway inhibits undesired movements by decreasing thalamocortical activity. (Fig. 2)

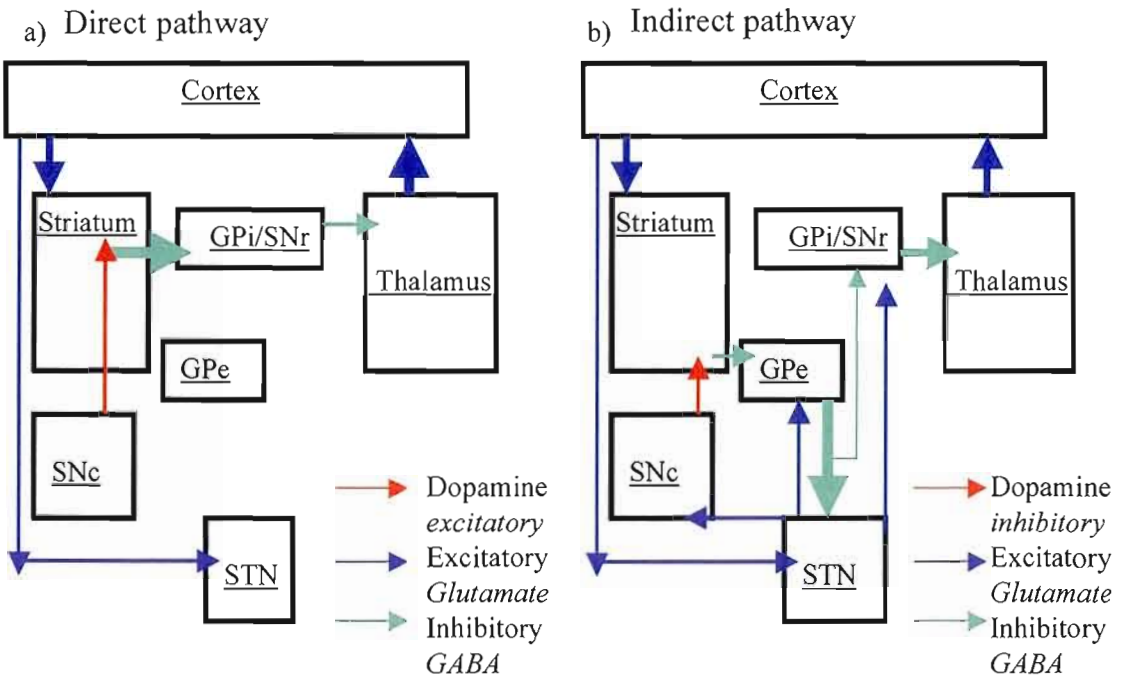

Figure 2. ***Direct and Indirect Pathways***. a)The direct pathway begins in the striatum at the site of the D1 receptors, inhibiting the GPi/SNr via GABAergic projections, the GPi have GABAergic projections to the thalamus. b)The indirect pathway begins at the D2 receptors in the striatum and have GABAergic projections to the GPe which has GABAergic projections to the STN, the STN has glutamenergic projections to the GPi. Excitation of the GPi/SNr by the STN activates GABAergic projections to the thalamus. (Adapted from Albin et al. 1989)

2.3 Basal Ganglia in Huntington's disease

Huntington's disease is characterized by progressive and initially selective striatal degeneration, causing a loss of GABAergic medium spiny neurons, specifically those projecting to the GPe and SNr (Weeks et al. 1997; Joel 2001). According to the conventional BG model in HD, the selective loss of striatal projection neurons, specifically enkephalin containing GABAergic neurons projecting to the GPe (Tang et al. 2005), in the indirect pathway leads to reduced tonic inhibition of thalamocortical activity leading to hyperkinesia (Bhidayasiri & Truong 2004; Weeks et al. 1997). This suggests a deficit in inhibition which is supported by evidence that patients exhibiting hyperkinetic movements such as chorea have difficulty with voluntary suppression of these movements (Hashimoto et al. 2001). Hypokinesia of voluntary movement also occurs in HD (Bilney et al. 2003) and may be explained by the disruption of connections between the associative striatum and motor circuit, which are involved in the sequencing and selection of motor programs (Joel 2001). In this explanation, the coexistence of chorea and bradykinesia in early HD is suggested to be due to the intrusion of undesirable motor programs in the normal flow of motor acts, suggesting a deficient inhibition mechanism, and implying that chorea may be mechanically responsible for bradykinesia in early stages of HD (Hashimoto et al. 2001; Albin et al. 1989). Bradykinesia in late HD has been described, similar to that of Parkinson's disease bradykinesia, as a deficit in the direct pathway, this would result in a mechanically isolated bradykinesia not resulting from chorea, but a mechanism of it's own. (Fig 3) Another interpretation of the model has been presented by Mink (2003) theorizes that cortical motor pattern generators are "gated in" and "gated out" by selective facilitation and surround inhibition, and a disruption, or random temporal patterning of this gating may be the cause of involuntary movement, specifically chorea in Huntington's disease.

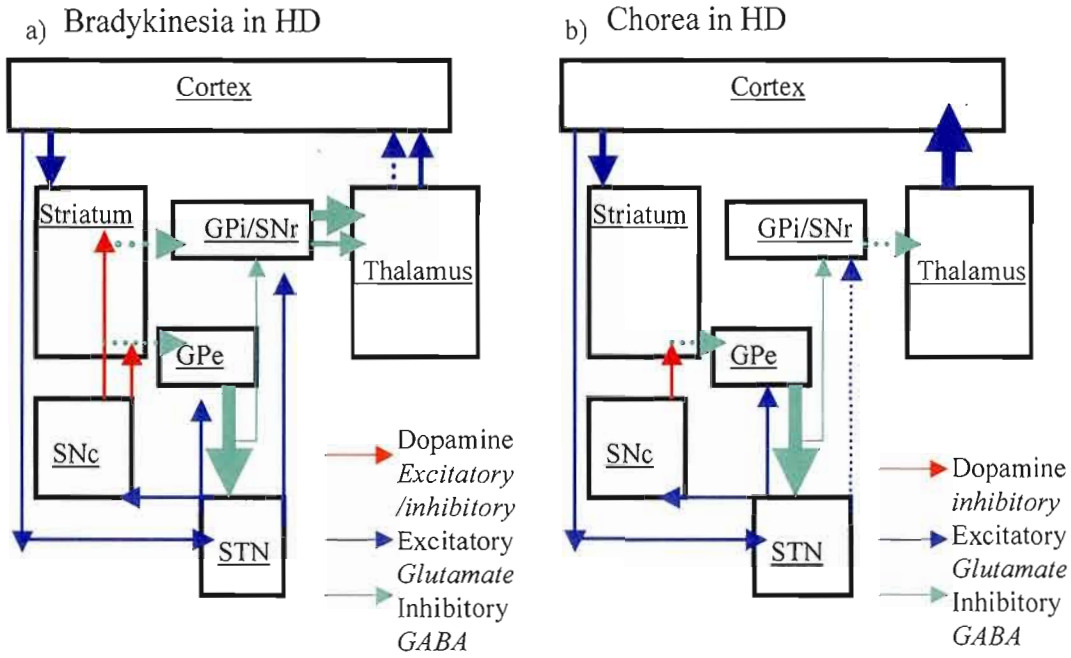

Figure 3. ***BG in Huntington's Disease.*** Thick arrows highlight increased activity from normal and dotted arrows marked decreased activity. A) One theory of bradykinesia in HD is a general degeneration of both indirect and direct pathways. B) Chorea in HD is thought to occur due to increased inhibition of the subthalamic nucleus (STN) decreasing inhibition of the thalamus and increasing thalamocortical activity. (Adapted from Albin et al. 1989)

2.4 Motor Symptoms

Huntington's disease is considered a mixed movement disorder due to the presence of both hypokinetic and hyperkinetic symptoms, the most clinical feature of which is chorea (Weeks et al. 1997; Bilney et al. 2003; Gardian & Vecsei 2004). Secondary motor symptoms of HD are rigidity, dystonia, akinesia, bradykinesia and oculomotor deficits (Hamilton et al. 2003; Gardian & Vecsei 2004; Bilney et al 2003; Berardelli et al. 1999).

2.4.1 Chorea

Chorea comes from the Greek *choros* for 'chorus' meaning both dance and song (Higgins 2001). Chorea is classified as irregular, flowing, non-stereotyped movement that occurs at random and possesses a writhing quality (Bhidayasiri & Truong 2004;

Yanagisawa 1992). Chorea that is proximal and of large amplitude is referred to as ballistic, and irregular, forceful, writhing movements, generally in the extremities, are referred to as athetosis (Bhidayasiri & Truong 2004). Aggravated by anxiety and stress, chorea begins in peripheral limbs and progresses to more proximal 'ballistic' movement (Higgins 2001; Bhidayasiri & Truong 2004). Chorea is often reduced in later stages of HD (Berardelli et al. 1999) and can coexist with hypokinetic features of the disease, such as bradykinesia (Thompson et al. 1988; Joel 2001).

2.4.1.1 Classification of Chorea

There are three main classifications of chorea based on the method of contraction and occurrence: primary or idiopathic, secondary and other sources. Primary chorea includes those forms idiopathic or genetic in origin, such as Huntington's disease, neuroacanthocytosis, Wilson's disease, senile chorea, benign hereditary chorea and dentatorubral pallidolysian atrophy (DRPLA) (Quinn et al. 1998; Bhidayasiri & Truong 2004). Secondary chorea includes those cases caused by infectious or immunological conditions such as Sydenham's chorea, drug induced chorea, immune mediated chorea and vascular chorea, to name only a few (Bhidayasiri & Truong 2004). Other sources of chorea include those due to vitamin B1 and B12 deficiencies, exposure to toxins and paraneoplastic symptoms (Bhidayasiri & Truong 2004). Huntington's disease is the most common cause of chorea.

2.4.2 Bradykinesia

Bradykinesia is a frequent finding in HD in both early and late stages of the disease(Garcia-Ruiz et al. 2002). Bradykinesia can be defined as abnormal slowness of movement, specifically referring to a slowness in the execution of a task (van Vugt et al. 2003). Bradykinesia is believed to be attributed to degeneration of output from the basal

ganglia to supplementary motor areas involved with initiation and maintenance of sequential movements (Berardelli et al. 1999).

2.4.3 Rigidity

Rigidity is defined as the inability to fully relax or completely stretch a muscle voluntarily. In HD abnormal EMG responses to muscle stretch and changes in SEP (sensory evoked potential) and long latency stretch reflexes suggest ineffective gating of afferent information to the brain from the periphery (Mink 1996; Abbruzzese & Berardelli 2003). Rigidity occurs at later stages of adult-onset HD or in the akinetic rigid type.

2.4.4 Dystonia

Dystonia can be defined as abnormal co-contractions of antagonist muscle groups that result in twisting movements and abnormal postures (Raike et al. 2005). Underlying neural mechanisms of dystonia involve dysfunctional output from the basal ganglia and cerebellum (Raike et al. 2005).

2.4.5 Akinesia

Akinesia is defined as slowness of movement, referring specifically to slowed reaction or initiation of movement (van Vugt et al. 2003). Akinetic/rigid is a form of Huntington's also known as Westphal's and is characteristic of early/juvenile onset and later stages of the disease in normal adult progression. Akinesia is thought to result from general damage and decrease of striatal projections in the BG.

2.4.6 Oculomotor Deficits

Oculomotor deficits in HD include delayed initiation of voluntary saccades, reduced number of correct saccades and reduced saccadic velocity (Blekher et al. 2004). Abnormalities of saccades may be accounted for by the extensive loss of striatal projection to SNr that plays a major role in controlling saccadic eye movement (Reiner et al. 1988). These deficits may contribute to the visual inattention and visuospatial

deficits exhibited in HD (Weeks et al. 1997; Kim et al. 2004; Boulet et al. 2005; Hamilton et al. 2003).

2.4.7 Possible Neural Mechanisms

The hypokinetic features of HD, rigidity and akinesia, are associated with the loss of striatal neurons projecting to both the GPe and GPi (Albin et al. 1990). Bradykinesia in the early stages of HD is suggested to be the result of under activity of the indirect pathway and the inappropriate termination of muscle activity (Joel 2001), due to the fact that the direct pathway appears to be preserved early in the disease. However, this assumes it is bradykinesia, the slowness of movement, and not bradyphrenia, slowness of thought, which is inhibiting HD patient performance, although the latter is more likely the cause. Bradykinesia in the later stages of HD may be due to a similar mechanism as bradykinesia seen in Parkinson's disease, resulting from under activity of the direct pathway (Joel 2001). There seems to be a dynamic shift in the influence of the direct vs. the indirect pathway on motor symptoms as the disease progresses. In PET studies bradykinesia shows no correlation to loss of either D1 or D2 receptor binding, which suggests overall decreases not selective degeneration are the cause of bradykinesia in HD (Turjanski et al. 1995). The hyperkinetic, involuntary characteristics of HD chorea suggest a disruption in the indirect pathway in the basal ganglia motor loop (Weeks et al. 1997; Bhidayasiri & Truong 2004). Using the conventional BG model, selective loss of striatal projection neurons in the indirect pathway would lead to reduced inhibition of the GPe, reducing inhibition of the thalamus resulting in hyperkinetic movement (Weeks et al. 1997, Reiner et al. 1988). Notably, a PET study of D1/D2 receptor binding in HD found a reduction in both D1/D2 receptors in a patient exhibiting chorea only, which would refute the theory of selective striatal degeneration as the cause of choreic movements (Turjanski et al. 1995). Abnormal motor cortical excitability in HD has been raised as a possible mechanism for choreic movements (Abbruzzese et al. 1997; Brusa et al. 2005), although recent evidence has challenged those findings (Priori et al. 2000; Hanajima et al. 1999) and

controversy has resulted as to what factors and methodological issues may be at the roots of such contrary findings (Abbruzzese et al. 2000). A study looking at GPi firing rates found no significant difference between hypokinetic Parkinson's patients and hyperkinetic HD patients, although the pattern of firing was different (Tang et al. 2005). The high firing rates in HD may be attributed to the presence of bradykinesia (Tang et al. 2005). The reported coexistence of bradykinesia with chorea in HD suggests there is a more complicated answer to the motor symptoms of this disease, possibly a malfunction in the motor program selection which is expressed in HD patients difficulty in planning and sequencing action (Kim et al. 2004; Boulet et al. 2005). Kanazawa (1989) proposed three mechanisms for choreic movements in HD: massive neuronal loss, receptor hypersensitivity and post-synaptic component loss.

2.4.7.1 Massive neuronal loss

First, choreic movements may be the result of the massive loss of GABAergic inhibitory neurons in the striatum. This would induce disinhibition of the nigra dopaminergic neurons and causes activation of these neurons and choreic movement. The drawback to this proposal is that loss of GABA in the substantia nigra does not always correlate with generation of choreic movement (Kanazawa 1989; Tang et al. 2005).

2.4.7.2 Receptor Hypersensitivity

The second possible neural mechanism underlying choreic movements is that there are hypersensitive dopaminergic receptors in the striatum that are causing hyperkinetic movement. Receptor hyper-sensitivity, specifically at the D1 receptors, may be due to huntingtin protein induced toxicity or a compensatory mechanism for decreased dopamenergic input (Spektor et al. 2002). However it is generally accepted that dopaminergic receptors are decreased in HD and post-synaptic components are more influential in HD (Spektor et al. 2002: Turjanski et al. 1995).

2.4.7.3 Post- synaptic component loss

The third possible mechanism is that a massive loss of striatal neurons causes a loss of post-synaptic components of dopamenergic terminals that then acts to change existing spared striatal dopamenergic terminals. Ginovart and colleagues (1997) found a decrease in the density of post-synaptic dopamine receptor in the striatum in HD along with decreased binding to dopamine transporter that may suggest malfunctioning in the production, processing and transport of dopamine transporter, which plays an essential role in regulating dopamenergic neurotransmission. Both pre and post-synaptic markers of dopa transmission have been implicated in cognitive performance in HD (Backman & Farde 2001).

2.5 Psychiatric Symptoms

Psychiatric symptoms are a key element in the triad of features distinguishing HD, the others involving motor and cognitive impairment (Paulsen et al. 2001). HD patients exhibit a variety of psychiatric symptoms, preceding the onset of motor symptoms in up to 31% of cases (Lawrence et al. 1998; Snowden et al. 2002; Naarding et al. 2001; Seneca et al. 2004), predating motor manifestations by up to a decade (Paulsen et al. 2001). This pre-clinical presentation of symptoms has been the target of observation and research in an attempt to slow the progression of the disease by attacking the first signs of impairment (Paulsen et al 2001).

HD patients can express a wide array of psychiatric abnormalities including dysphoria, agitation, irritability, apathy and anxiety, with 3-6% of cases exhibiting schizophrenic like psychosis (Naarding et al. 2001; Paulsen et al. 2001). Dementia in HD is classified as subcortical (Weeks et al. 1997; Naarding et al. 2001). Psychotic symptoms have been observed earlier in disease progression, decreasing as cognitive impairment becomes more prominent (Leroi & Muchalon 1998).

Treatment of psychiatric symptoms can be complicated, especially due to adverse side effects of medications that include motor abnormalities such as parkinsonism. Depression in HD can be treated similarly to major depression in non-HD

patients, although sensitivity to sedation and anti-cholinergic induced cognitive decline should be monitored (Leroi & Michalon 1998). Management of aggressive symptoms, ranging form irritability to intermittent explosive disorder should focus on underlying cause of behavior, neuroleptics and antidepressants have been found effective in therapeutic treatment (Mendez 1994;Leroi & Michalon 1998).

Changes in sexuality, expressed through inappropriate behaviour and hypoactive sexual desire, have been reported in HD and may be related to underlying neurotransmitter deficits (Leroi & Michalon 1998). No studies have systematically examined the management of sexual changes in HD (Leroi & Michalon 1998). Sleep disorders have been reported in HD with varying severity, Weigand and colleagues (1991) found decreased sleep efficiency, decreased slow wave sleep and prolonged sleep latency in HD, while others found minimal to no differences between HD patients and controls.

Once again, as with motor symptoms, the measurement tools and patient selection criteria have made it increasingly difficult to compare between studies. Medication remains a factor, as therapies prescribed for motor symptoms may cause or aggravate psychiatric abnormalities in HD.

2.6 Treatments

There is no current therapy that is able to delay or prevent the onset of Huntington's disease (Bhidayasiri & Truong 2004) and therefore treatment is symptomatic (Bilney et al. 2003). Physiotherapy, occupational therapy and speech pathology address motor impairments and limitations experienced by patients with HD (Bilney et al. 2003), while an increasing number of drug trials attack the neurological process of the disease (Qin et al. 2005). Researchers have examined the effects of the following agents on HD motor symptoms: anti-dopamenergic, NMDA antagonists, GABA agonists, DOPA Agonists, Nootropics, antioxidants and neuroprotective agents (Bonelli et al. 2004). Only anti-dopamenergic agents showed majority positive results, specifically tetrabenazine and fluphenazine (Bonelli et al. 2004).

Treatment of chorea in HD is difficult due to the severity of side effects experienced with drugs prescribed to manipulate movement in neurodegenerative disorders; for example the aggravation of psychiatric systems and negative effect on voluntary movement. Therefore, drug treatments are suggested only when chorea is debilitating (Bhidayasiri & Truong 2004; Bonelli et al. 2004). Initial recommendations for the treatment of chorea in HD involve discontinuation of medication that may have involuntary movement as a side effect. There are a wide variety of anti-choreic agents on the market, including neuroleptics that block central dopamine receptors as well as dopamine depleting agents such as tetrabenazine, although these options come with serious side effects and only minimal evidence of symptomatic relief (Bonelli et al. 2004; Bruneau et al. 2002).

2.6.1 Anti-dopamenergic agents

Anti-dopamenergic agents such as clozapine and fluphenazine are also classified as anti-psychotics and act to competitively block dopamine and seratonin receptors, although side effects associated with the use of anti-psychotics include dystonia and pseudo-parkinsonism (Brenner 2004). Recently tetrabenazine, an anti-dopaminergic agent initially designed for use as an anti-psychotic, has been found to decrease chorea in HD patients in a randomised control study (Huntington Study Group 2006).

2.6.2 NMDA Antagonists

Amantadine is an example of an NMDA receptor antagonist used in the treatment of HD (Qin et al. 2005). The degeneration in HD is thought to be due in part to sensitisation of NMDA receptors on residual striatal neurons (Qin et al. 2005). An antiviral drug originally used for the treatment of influenza, when used in Parkinson's disease, amantadine works by releasing dopamine from nigrostriatal neurons (Brenner 2004).

2.6.3 GABA Agonists

GABA agonists are used to treat movement disorders because of their intense sedative properties (Soares et al. 2004), although there has been little success with their use in HD (Bonelli et al. 2004). GABA-ergic drugs act to enhance the activity of the inhibitory neurotransmitter GABA in the brain. GABA-ergic drugs act on the metabolism or its reuptake into neurones of glia, as well as mediating the synaptic release of GABA (Meldrum 1982).

2.6.4 DOPA Agonists

DOPA agonists, or dopamine receptor agonists, directly activate dopamine receptors in the striatum, specifically D2 receptors leading to inhibition of the indirect pathway (Brenner 2004).

2.6.5 Nootropics

Nootropics, such as piracetam, are considered 'cognition enhancing' agents, used in the treatment of various dementias, although poor predictive ability in animal trials have kept them from general acceptance (Gualtieri et al. 2002). Piracetam has antithrombotic and neuroprotective properties, it alters the physical properties of plasma membrane, increasing its fluidity and protecting against hypoxia, increasing red cell deformability and normalizing aggregation of hyperactive platelets (Winnicka et al. 2005).

2.6.6 Antioxidants

Neurodegeneration in HD is associated with oxidative stress that is manifested by lipid peroxidation, protein oxidation and other markers (Butterfield et al. 2002). Antioxidants agents are used to combat the oxidative stress that occurs in neurodegenerative disease, by slowing progression and limiting the amount of neuronal cell loss (Mossmann & Behl 2002). Agents such as CoEnzyme Q10 has been shown to protect against striatal lesions in HD mice, and is especially effective in the mitochondria, as the enzyme is a co-factor in the electron transport gene (Beal 2002).

2.6.7 Neuroprotective Agents

Neuroprotective agents such as Lamotrigine, also used as an anti-epileptic, blocks sodium channels and interferes with neuronal membrane conduction and the release of neurotransmitters such as glutamate (Brenner 2004). Estrogen, a natural neuroprotective agent, has been synthesized and found effective in cytoprotection and mitoprotection, and has implications for treatment in HD (Simpkins et al. 2005).

2.6.8 Surgery

Deep brain stimulation (DBS) and striatal transplantation surgery have been examined in the treatment of chorea in HD (Hebb et al. 2006; Moro et al. 2004; Hauser et al. 2002; Furtado et al. 2005; Lee et al. 2005). Evidence from rat models (Lee et al. 2005) has shown functional recovery with administration of human stem cells, although clinical testing in humans shows conflicting evidence, with no benefit from transplantation in 7 HD patients (Furtado et al. 2005).

3. RATIONALE

Treatment for chorea may have a deleterious effect on motor performance in patients with HD. For instance, some parkinsonism may be induced by the dopamine depleting agents used in treatment of chorea, resulting in increased motor impairment due to bradykinesia. The wealth of research examining the motor abnormality in HD have focused on tasks requiring timing and or accuracy, with very few studies examining or quantifying the chorea or it's effect on voluntary movement. Many patients participating in the following studies were on anti-choreic drugs at the time of testing, altering the natural effect of the involuntary movement and causing or aggravating hypokinetic features of movement due to the sedating effects of medication. The following is a brief critical review of studies examining motor dysfunction in HD. Reilmann and colleagues (2001) used grip force as a measure of progression of HD in ten patients over a three-year period. The task involved precision grip and lifting of an instrument with two force torque sensors measuring grip and load at the thumb and

index finger. Participants were instructed to lift the object to a specified 10cm height and hold for 6 seconds. Object weight was manipulated with 10 consecutive trials at each weight, and order of trials randomized across patients. Results showed more variability in the follow-up period, with more variability in grip force with lighter compared to heavier object weights. Chorea was reflected in position and orientation changes in object location during the static phase of the task. Variation in these movements was found between subjects but measures did not change during follow-up testing, the only measure of motor function that changes over time was rigidity, as measured by the UHDRS. Increased variability over time was attributed to presence of chorea. The conclusion made in this study was that grip force is a useful tool in measuring progression of motor impairment in HD (Reilmann et al. 2001). There are several issues to be raised concerning this study. The first is that chorea is a phenomenon of whole body involuntary movement, classifying chorea as a displacement of the thumb and index finger during a six second task is an inaccurate measure of the influence of chorea on voluntary movement. Second there were multiple components to the task, precision grasp, lift to a specific height, maintenance of position at that height of 6 seconds. Patients with HD are shown to have difficulty in sequencing movement (Agostino et al.1992) and sub-movement cueing (Curra et al. 2000) which may be due to a slowness in initiation of movement (akinesia), slowness of thought (bradyphrenia) or slowness in execution or inability to generate adequate force to complete the task (bradykinesia). The third complication in this study lies in the fact that all patients were on multiple medications, all of which changed from the initial to the follow-up data collection, possibly complicating results by influencing the variability recorded in the follow-up period. The task is sequenced and goal directed which can complicate performance in HD patients by adding a cognitive component, not providing a clear picture of motor behavior in HD.

Flexion and extension at the finger and elbow have also been used to measure motor behaviour in HD (Hefter et al. 1987; Verbessem et al. 2002). Hefter (1987) used self-paced isometric contraction and rapid alternating forefinger movements.

Hyperkinesic and voluntary contractions were compared in patients exhibiting clear hyperkinesias, using EMG activity. HD patients exhibited prolonged times for self-paced contractions as well as prolonged time to peak force. In the rapid alternating finger movement HD patients also exhibited slowed and more irregular movement, in comparison to controls. The majority of hyperkinetic contractions were found to be slower than voluntary contractions of a similar amplitude. Controversial points in this study include the fact that hyperkinesias were recorded in only one area, i.e. distal upper limbs, and once again all subjects were heavily medicated. Therefore is it difficult to isolate the source of the slowness and variability found in their performance. Also, the signal-to-noise ratio (i.e. the amplitude of the intended movement versus the chorea) was low, probably limiting the motor impairment to a mechanical one. Verbessem and colleagues (2002) used unimanual and bimanual voluntary movement involving flexion and extension at the elbow to test motor performance in male patients with HD. Unimanual tasks were performed at maximal speed, while bimanual movements were performed in-phase and anti-phase at different cycling frequencies. Results showed that subjects with HD required more time to complete one movement cycle, and had increased variability in measures of range and cycle duration when compared to controls. Speed of cycling and accuracy were correlated with disease duration. Another aspect of the study that is problematic, is the nature of the movement itself, unimanual and bimanual movements involved flexion-extension at the elbow which is a multi-phase movement. Performance on this task could be influenced by three different symptoms, akinesia, bradyphrenia and bradykinesia, therefore we are no closer to understanding why HD patients appear to be slower then controls, a piece of information integral to the management of motor symptoms in HD.

Reaction time has been a widely used measure of motor disability in HD patients, as well as many other neurodegenerative conditions. Van Vugt et al. (2003, 2004) utilized simple reaction time paradigms of response to negative stimuli and button pressing to determine the cause of slowness in HD. In the response to painful stimuli it was hypothesized that motor slowness in HD resulted from failure in activation of

agonist muscles and inhibition of unwanted antagonist activity. Results showed that in HD patients there was impaired antagonist inhibition prior to and during voluntary agonist contraction, and this was strongly correlated with delayed motor initiation, akinesia, and slow movement execution, bradykinesia (van Vugt et al. 2003), supporting the initial hypothesis. Another study by van Vugt (2004) looked at a button-pressing task as a measure of reaction time. Results showed that HD patients required more time for movement initiation and execution, displaying akinesia and bradykinesia, respectively. Both these impairments were present in early stages of the disease and became progressively worse with disease progression. These studies improved on previous research by isolating the various sources of slowness in movement in an attempt to determine at what stage in movement HD patients are impaired. Jahanashi and colleagues (1993) looked at reaction time in choreic HD, Parkinson's and cerebellar disease. Results showed that patients with HD had significantly longer simple reaction times than patients with PD, performance improved with auditory cueing but patients with HD were still slower than patients with PD. Patients with HD also exhibited slower movement time than the PD group, an indication of the presence of bradykinesia. Whether these delays were induced by motor bradykinesia, or by bradyphrenia remains to be determined. It is interesting to note that mean age in the PD group was significantly greater than that of the HD group, so age was not a factor in performance of the simple reaction time test. One interesting note in this study is the fact that only one of the seven HD patients was medicated, providing evidence for the coexistence of chorea and bradykinesia, although chorea was not recorded during testing, it was measured with a subjective clinical scale prior to participation.

Kim and colleagues (2004) used fMRI to examine the performance of a serial reaction time task in patients with HD. The task consisted of an asterisk appearing on a screen in one of four boxes each associated with one of four buttons, patients were required to push the button of the box in which the asterisk appeared. An implicit learning condition was created with trials following the same 12 item sequence 6 trials in a row. The purpose was to evaluate the nature and degree of functional changes in the

brain in the earliest stages of HD. Reaction time in the HD patients was longer then controls, and HD patients showed a lack of implicit learning, a deficit consistent with cognitive impairment reported in HD (Kim et al. 2004). Striatal activation was highly variable in the HD group, suggesting early functional loss, this data is consistent with previously demonstrated early atrophy in these same structures in HD.

Carella and colleagues (2003) investigated the possibility that bradykinesia in HD is task dependent. They investigated the influence of visual control on the ability of HD patients to complete a tracing task. Patients exhibited increased movement time and peak velocity in the visual control condition compared to controls, with an increase in movement time and decrease in peak and mean velocity in the blindfolded condition as compared to their own visual control values. Error scores did not differ significantly between HD group and control in the visual control task. Investigators suggest that the increased time spent in the deceleration phase may have been a compensatory method in response to irregular movements in HD patients. In the blindfolded condition the HD group exhibited significantly more variability and error. There was a lack of correlation between chorea scores and kinematic variables, leading investigators to conclude that chorea was not the source of irregular movement causing error in the task. These findings suggest that abnormalities of motor control are present in HD when movement accuracy, and not velocity, is required.

Lemay et al. (2005) also examined HD subjects' ability to trace material with and without sensory manipulation, in this case patients received direct or indirect (through a monitor) visual feedback. Patients showed larger and more frequent deviations from the object to be traced when receiving indirect visual feedback. There were also significant group differences in velocity with patients exhibiting slower movement than controls, especially slower movement toward the circle, then away from it. Un-medicated patients were analysed separately and compared to medicated HD and there were no significant differences found. The results of this study imply that error feedback is not impaired in HD in situations with direct visual feedback, although sensory manipulation, such as that of indirect feedback elicits dysfunctional

performance. Investigators concluded that this dysfunction in indirect visual feedback may be due to the inefficient use of error feedback, not a fundamental problem in error feedback control (Lemay et al. 2005).

Boulet and colleagues (2005) recorded aiming movements toward peripheral targets in HD to determine the effect of transformed visual feedback on movement control. Subjects were required to move a pen from a central point to a fixed peripheral target with indirect visual feedback on a monitor. Patients with HD showed significantly lower average speeds that controls, although there was no significant difference in peak velocity. Patients with HD showed less precision than controls when one and both horizontal and vertical axis were inverted. The data suggests that the deficit in on-line feedback control is related to the attention demands of the task, and results from problems with executive control.

Peg insertion has been used as a measure of motor performance in treated and untreated HD patients, controls and HD gene carriers (Saft et al. 2003). Participants were required to transfer 25 pegs to 25 holes in a computer based contact board as quickly as possible. The peg insertions score did not differ between HD groups and controls, although elapsed intervals between groups were significantly different. Differences were found between HD gene carriers and diagnosed patients with HD. Motor symptoms were quantified using a subjective clinical scale prior to testing and no mention was made of involuntary movements during the insertion task. Investigators admit that the task is restricted to movement of the upper limbs and therefore is unable to incorporate issues of whole body involuntary movement. Once again this task has multiple stages that may pose cognitive and mechanical sequencing difficulty for patients with HD.

Timed motor tests, such as the CAPIT test used in Parkinson's disease, have been used to assess motor function in HD (Garcia-Ruiz et al. 2002). Tests included pronation-supination, finger dexterity, movement in between two points and a walking task. HD patients were slower than controls, with deterioration in performance at follow up. This study concluded that bradykinesia was the cause of this slowness and a

significant factor in motor impairment in HD. This conclusion is controversial due to the fact that the majority of participants were being medicated for motor symptoms that may have lead to the slowness in task execution, therefore casting doubt on the origin of bradykinesia in these patients.

Comparison between studies is made difficult by the fact that there was no single method of movement quantification used, many studies selectively omit patients deemed 'too choreic', and many tasks involve complex sequencing of movement and cognitive processes which are known to be impaired in HD patients (Curra et al. 2000; Agostino et al. 1992; Brandt et al. 2005).

The coexistence of hypokinetic (bradykinesia) and hyperkinetic (choreic) movement abnormalities provides significant difficulty in isolating the source of dysfunction during movement. Bradykinesia has been recorded in HD patients of the akinetic rigid type, as well as those exhibiting only chorea, especially in those with severe chorea (Thompson et al. 1988). Clinical studies in HD indicated that difficulties with voluntary movement become more pronounced as chorea subsides (Thompson et al. 1988; van Vugt et al. 2004). Aggravation of bradykinesia has been associated with a decrease in chorea, and decrease in chorea related to a worsening of reaction time (van Vugt et al. 2004). This suggests that involuntary movements may not be the only, or even the most influential source of motor disability in HD (Thompson et al. 1988). Therefore the first general aim of this study will be to determine the mutual influence of chorea and voluntary movement in patients with HD.

To date only one study has systematically quantified tri-dimensional movement patterns in conditions of disordered movement. Ghassemi and colleagues (2006) quantified whole body involuntary movement in patients with Parkinson's disease, with and without dyskinesias, during a rapid alternating movement (RAM) task. In the RAM task, dyskinesias appeared to play a positive role in performance, and results implied that a reasonable assumption for this was the presence of cortical over activation associated with dyskinesias counteracting the reduction of thalamocortical activation associated with bradykinesia (Ghassemi et al. 2006). The same assumptions may be

applicable to the coexisting presence of bradykinesia and chorea in HD, as the bradykinesia in both PD and HD share similar characteristics during simple and complex movements (Thompson et al 1988). Simultaneous quantification of chorea and bradykinesia is critical for isolating the effect of each symptom on voluntary movement and evaluating the efficacy of pharmacological therapies in HD.

The issue of motor slowness in HD is addressed in the second general aim of this study, which is to determine if bradykinesia coexists with chorea in early HD, and if so what is the nature of it's interaction with hyperkinetic features of the disease, e.g. chorea, as well as it's influence on motor performance. Two theories have been proposed to explain bradykinesia in early and late HD, suggesting an indirect and direct pathway malfunction, respectively. In order to illuminate which of these model theories may be correct the influence of chorea and bradykinesia on movement must be isolated.

The current gold standard evaluation method of disease severity and progression in HD is the Unified Huntington's Disease Rating Scale (UHDRS) (Huntington Study Group 1996; Hurelbrink et al. 2005). Other clinical measures, such as the Behaviour Observation Scale Huntington (BOSH) are also used to determine psychiatric and motor abnormalities in patients with HD (Timman et al. 2005). Clinical rating scales, while beneficial, are not able to detect sub-clinical changes as well as some components of voluntary movement (Beuter et al. 2004). Clinical measures focus on simple tasks that fail to incorporate whole body activity during testing. An objective measure capable of capturing whole body involuntary movement in HD is needed to assess the progress of the disease and help shed light on the neuro-mechanisms underlying the relationship between voluntary and involuntary movement in neurodegenerative diseases (Hurelbrink et al. 2005). A quantitative measure capable of recording abnormal movement is integral for the evaluation of new therapeutic treatments and surgical interventions (Beuter et al. 2004), by distinguishing hypo and hyperkinetic features, their isolated and combined effect on voluntary movement.

4. HYPOTHESES

4.1 Hypothesis I

Chorea is aggravated by stress (Bhidayasiri & Truong 2004) and has been observed to increase during movement (Mink 1996). Based on these observations we hypothesize that chorea will increase during the completion of voluntary movement tasks.

4.2 Hypothesis II

Bradykinesia is an accepted feature of both akinetic rigid and choreic forms of HD (Thompson et al. 1988: Garcia-Ruiz et al. 2002). What is not known, however, is whether chorea is mechanically responsible for the bradykinesia when both symptoms are present. Here, we hypothesize that during a RAM task, the chorea will not be directly responsible for bradykinesia when both symptoms are present.

5. METHODOLOGY

5.1 Subjects

5.1.1 Participants

This study included two subject groups, one comprised of diagnosed adult-onset Huntington's disease patients, and the other comprised of age/gender-matched controls. Cohen's method for power calculation was used to determine number of subjects required. Based on whole body involuntary movement values of a similar disease population, Parkinson's disease dyskinetic (Ghassemi et al. 2006), a minimum of 2 subjects were needed for comparison of whole body involuntary movement. For the bradykinetic measures such as range and velocity, a minimum of 14 subjects were required for comparison, as calculated by a t-test with Welch's correction of degrees of freedom for unequal variances.

5.1.2 Recruitment

Participants were recruited from the London Health Science Movement Disorders Clinic. All participants were referred to the study by the neurologist Dr. M. Jog.

5.1.3 Inclusion/Exclusion Criteria

All participants completed a UHDRS with a certified nurse to establish the presence of chorea and severity of motor and psychiatric symptoms. Early stage choreic HD patients, diagnosed with adult onset HD, with little to no psychiatric disturbance were included in the study. Age matched controls were free of any neurologic or motor disturbances. Individuals with advanced or juvenile onset Huntington's disease were not included in this study. Individuals expressing bradykinesia/akinesia as the prominent motor symptom or severe psychiatric symptoms were not eligible for participation. All participants were able to stand, walk or sit without the use of assistive devices. Individuals with metal implants (i.e. joint stabilizing plates or pins) were not included in the study due to the possibility of metallic interference with the testing apparatus. Age/gender matched controls were not considered if they suffer from any psychiatric conditions or motor impairment. All medications being taken by patients were documented.

5.1.4 IRB Concerns

All participants read and signed an informed consent document detailing the procedures, risks and benefits of participation in this study. Participants were assigned a subject number, and all documents containing personal information were stored in a locked cabinet accessible to the principal and co-investigators exclusively. Participants were able to abstain from participation at anytime without consequence. There was no monetary gain to participating in this study although compensation was arranged for travel and parking costs.

5.2 Independent Variables

This study involved the comparison of whole body involuntary movement and motor performance between two groups in two conditions.

The two groups included one comprised of patients with adult onset Huntington's disease and the other, a control group, made up of healthy age/gender matched participants.

There were two experimental conditions in this study, activity and rest. During the active task participants were asked to participate in a motor activity while both their performance in that activity, as well as their whole body involuntary movement was recorded. During the rest period participants abstained from voluntary motor tasks.

5.3 Dependent Variables

The two measurements of interest in this study were whole body involuntary movement and performance on a rapid alternating movement (RAM) task. Whole body involuntary movement is the sum of movement in all limbs, and is examined in terms of displacement in space. Performance of a voluntary task, rapid alternating pronation-supination cycles, provides a measure of motor performance. Variables of interest within performance of the RAM task include range, velocity and irregularity. Range is a measure of the maximal excursion achieved during pronation-supination cycling. Velocity is a measure of the maximal instantaneous velocity achieved from peak to peak during a pronation-supination cycle. Irregularity is a measure of the variability in RAM amplitude.

5.4 Data Analysis

5.4.1 WBIM

The time series provided by each sensor was divided into 7s epochs for analysis. The mean position for x, y and z was subtracted from the actual position to provide a displacement time series around a neutral position for each epoch. The RMS values for each x, y, z time series are squared, the mean of the three values calculated and the root taken, to attain the three dimensional vectorial amplitude for each sensor. Values for each epoch are averaged; the sum of all the mean vectorial amplitudes over all sensors

was then calculated to determine whole body involuntary movement. Values for sensors located on the performing arm were then compared to those of controls. The mean control value was subtracted from the values calculated for patients with HD and the remaining displacement in those sensors was treated as chorea. Therefore a value for WBIM was calculated with all other sensors on the body and the chorea value for the performing arm, as determined by subtracting the mean movement associated with performance of the task. WBIM was also analysed topographically to determine if chorea in a patient is localized to either the upper/lower body or right/left side.

5.4.2 RAM

An automated algorithm was used to identify each peak and trough of the pronation-supination cycle. Three characteristics were calculated range, velocity and irregularity. Range is the mean angular displacement over a complete pronation-supination cycle in degrees. Velocity, maximal instantaneous velocity from peak to peak, was calculated in degrees per second over a complete pronation-supination cycle. RAM cycle amplitude irregularity was calculated by normalizing the pronation-supination time series (mean=0, SD=1), applying a low pass (1Hz) filter and obtaining the standard deviation of the resulting linear envelope. A higher score reflected greater variability in RAM amplitude, therefore a more 'irregular' performance. The first 7s of the pronation-supination cycling was analysed for RAM performance as fatigue may become a problem, and this time period has been successful in prior work with similar populations (Ghassemi et al. 2006).

5.5 Procedure

Participants were asked to arrive at the lab at the appointed time, in comfortable clothing. Participants were met at the main doors of the facility and escorted to the lab by the investigator. Participants were seated and given a copy of the letter of informed consent to read and sign, and any questions regarding procedure and participation were addressed at this point. The letter of informed consent was available in both French and

English, with investigators available to address questions in either language to ensure complete comprehension of participation.

Once consent has been given participants will be assigned a subject number and asked to detail anthropometric data (i.e. height and weight) and current prescription medication regimens.

Participants were asked to move into the testing area where a lightweight shirt will be placed over existing clothing. An investigator then palpated the location of each of the 15 sensors and attached the sensors using adjustable Velcro bands. Investigators were gender matched to participants for palpation and placement of sensors. Sensors were placed at the following locations: head, thorax, sacrum, right/left scapula, right/left upper arm, right/left forearm, right/left hand, right/left shank and right/left foot.

5.5.1 Data Quantification

5.5.1.1 Whole body involuntary movement (WBIM)

To quantify whole body involuntary movement in 3 dimensions an electromagnetic measurement system with 6 degrees of freedom, the Flock of Birds magnetic motion tracker system (Innovative Sports Training, Chicago, IL), was used. The magnetic tracker contains an extended range transmitter that permits accurate recording within a 12ft radius. A custom shirt, shoes and gloves are used to fix 15 sensors adjacent to the joint axes of limbs under consideration. Each sensor provides displacement (x,y,z) and orientation (pitch, roll, yaw) of each limb segment. To facilitate testing a 3x4x6 foot area was calibrated, using an antropometer and square foot tiles to record 72 points, one point every 0.304m (1 ft) in all three axis, defining sensor position in respect to the location of the transmitter coil. The calibrated space had an accuracy of approximately 0.005m. Each sensor has a sampling rate of 100Hz.

5.5.1.2 Motor Performance

Motor performance was quantified through the use of a rapid alternating movement (RAM) task, requiring pronation-supination cycling at maximal voluntary

speed and excursion. RAM was recorded simultaneously with WBIM using forearm rotational sensors. Two handballs were attached to the end of a lightweight wooden dowel, the other end of which was attached to a potentiometer, to detect rotational movements during pronation-supination, with a resolution of 0.3 degrees. The analog output from the potentiometer, sampled at 100Hz, was digitized and stored for analysis.

5.6 Experimental Procedure

Once participants are connected to all sensors, they were asked to step onto the testing platform where a calibration recording was taken. During this recording participants were asked to stand upright with their arms at their sides, in anatomical position. Participants were then asked to stand with arms out in front for a period of 60 seconds. Participants were seated and asked to hold the foam handballs, with arms bent at the elbows, approximately 3 inches, 120 degrees from their sides. Participants were instructed to maintain this position, at 'rest' for 20 seconds. They were then instructed, for a period of ten seconds, to perform pronation-supination of the dominant hand as fast and as complete a rotation as possible. Participants were asked to refrain from any other voluntary movement at this time, without restraining any involuntary movements that may occur. The non-dominant hand remained stationary during the RAM task. After ten seconds the participant was then asked to return to the rest state, both hands stationary, holding onto foam handballs, for another 20 seconds 'rest' recording. Three trials were recorded. Once the experimental procedure is completed, participants were debriefed and escorted out of the facility.

5.7 Statistical Analysis

A two-way analysis of variance (ANOVA) was used to determine the existence of group by condition interactions, with repeated measure for condition, for WBIM and amplitude of the opposite hand pre and during performance. Post hoc analysis was done to indicate which group comparisons yield significance. The Student Newman-Keuls method was used to test multiple comparisons because it utilizes a per contrast type I

error rate which is less conservative and affords greater power than the Tukey method (Glass & Hopkins 1970). A one-way ANOVA was used to determine statistical significance of RAM performance variables, such as range, duration, velocity and irregularity. A one-way ANOVA was also used to analyse WBIM by quadrant (i.e. upper/lower body, right/left side) to determine if chorea is topographic.

6. RESULTS – *SCIENTIFIC MANUSCRIPT*

Bradykinesia is not a "systematic" feature of adult-onset Huntington's disease; implications for basal ganglia pathophysiology

Running title: Huntington's chorea

Alison Fenney MSc(c)[1], Mandar Jog MD, FRCPC[2] & Christian Duval PhD[1]

[1] *Departement de kinanthropologie, Université du Québec à Montréal, Montréal, Québec, Canada*

[2] *Clinical Neurological Sciences, University of Western Ontario Health Centre – University Hospital, London, Ontario, Canada*

Corresponding author:

Christian Duval PhD

Département de Kinanthropologie

Université du Québec à Montréal,

C.P. 8888, succursale Centre-Ville

Montréal (Québec) Canada

H3C 3P8

Tel. : #: (514) 987-3000 ext: 4440

Fax: (514) 987-6616

Courriel: duval.christian@uqam.ca

ABSTRACT

Our goal was to determine whether bradykinesia is present in choreic adult-onset Huntington's disease (HD) patients, and determine the impact of chorea on their voluntary movements. We recorded whole-body involuntary movements (WBIM) and voluntary motor acts simultaneously, using a magnetic tracker system, in fifteen choreic HD patients and fifteen healthy age-, gender-matched control subjects. Participants were asked to perform two distinct tasks; a rapid alternating movement (RAM) task, yielding measures of bradykinesia, and a manual-tracking (MT) task yielding a measure of chorea intrusion during accurate movements. Results show that patients with HD presented with deviations from the target that hindered their ability to match the target velocity during the MT task. Furthermore, error in performance was correlated with the amplitude of whole-body chorea (*Rho* = 0.67), illustrating the deleterious effect of chorea during accurate movements. However, patients with choreic HD presented with significantly higher RAM range and velocity than matched controls, therefore ruling out the idea that bradykinesia is a systematic feature of HD, even when chorea is predominant. The present results imply that patients may have benefited from an intact direct pathway ("select ON" pathway in the focused attention model of basal ganglia function) that allowed them to supersede any dysfunctions associated with the progressive alteration of the "control function" (striatal-globus pallidus-subthalamic) pathway responsible for generating the chorea. Finally, the present results suggest that patients with adult-onset HD having chorea would greatly benefit from improved treatments aiming at reducing their involuntary movements while maintaining proper motor function. *Key Words*: whole-body involuntary movements, chorea, basal ganglia, Huntington,kinetic

1. INTRODUCTION

Huntington's disease (HD) is usually considered a mixed movement disorder due to the presence of both hypokinetic and hyperkinetic symptoms, the most significant clinical feature of which is chorea (Weeks et al. 1997; Bilney et al 2003; Gardien & Vecsei 2004). There is ample evidence to suggest that the chorea itself negatively affects motor function, specifically accuracy (Bilney et al. 2003; Phillips et al 1996), reaction time (vanVugt et al. 2003; vanVugt et al. 2004; Jahanshahi et al. 1993; Kim et al 2004), sequencing and sub-movement cueing (Agostino et al. 1992; Curra et al. 2000), timed motor tests (Garcia-Ruiz et al. 2002) and gait regulation (Bilney et al.2005). Although there is extensive variability in motor symptom expression, the clinical features of typical adult onset HD are characterized by a progression from hyperkinetic to hypokinetic movements (Berardelli et al. 1999). Then, motor symptoms of HD may include rigidity, dystonia, akinesia and bradykinesia (Thompson et al. 1988; Berardelli et al. 1999; Bilney et al 2003; Hamilton et al. 2003; Gardien & Vecsei 2004). Aggravation of bradykinesia has been associated with a decrease in chorea, which in turn is related to a worsening of reaction time (vanVugt et al 2004). However, the time course of the appearance of bradykinetic features is still debated, especially since clinical and laboratory observations suggest that the two symptoms may coexist in both early and late stages of HD (Thompson et al. 1988; Joel 2001; Hasimoto et al. 2001; Kim et al 2004). Interestingly, past basal ganglia models suggest that bradykinetic and choreic features are the result of opposite neural disturbances (Albin et al. 1989; Alexander et al. 1986). More recently, Mink (2003) has suggested that chorea would be the result of impaired inhibition of competing motor pattern generators, and the presence of bradykinesia would be the result of the superposition of desired and undesired motor pattern generators. If this is indeed true, bradykinesia may simply be a result of biomechanical effect due to low signal-to-noise ratio, where the signal is the intended movement and the noise represents the involuntary movements. It then becomes important to make a distinction between "core" bradykinesia, which is the consequence of improper activation of cortical structures by the basal ganglia-thalamo-cortical output,

as seen in Parkinson's disease, and bradykinesia that is caused by mechanical disturbances, such as the intrusion of involuntary movements. Since the main treatment modality for chorea is to deplete dopamine with the potential side effect of drug-induced parkinsonism (Bonelli et al. 2004), determining whether "core" bradykinesia is a symptom of early HD, or simply the consequence of a low signal-to-noise ratio as described above, is imperative to assess whether accepted treatment may actually worsen an already existing and important feature of HD. Accordingly, the goals of the present study were: to isolate the impact of chorea on motor performance in patients with HD and determine whether "core" bradykinesia is being co-expressed with chorea during performance. In order to achieve this goal, whole-body involuntary movements (WBIM) were simultaneously quantified during two distinct motor tasks; a manual-tracking (MT) task that allowed for the quantification of choreic intrusions during accurate movements, and a rapid alternating movement (RAM) task that provided a measure of bradykinesia.

2. RESULTS

Table 2. Subject Characteristics

Subject #	Age/ Gender	Onset	UHDRS Motor	Disease duration	Initial/general symptoms	Meds
HD03	56/f	March 2003 (42 repeats)	33	3	Whole body chorea (low amplitude, continuous), RAM normal	Seroquel 25mg, effexor XR 75 mg, premarin 0.3 mg, progesterone 100 mg, ditropan XL 5mg
HD04	33/f	Early 2000	7	6	Chorea in extremities and face, ram (evidence of chorea/mild bradykinesia)	Multivitamin
HD05	61/f	1994		10	Chorea, RAM mildly impaired	Zyprexa 2.5mg & % mg, Temazepam 30mg, Bupropion SR 150mg, Crestor 10mg
HD06	54/f	2004 (43 repeats)		2	Mild-mod chorea, chorea of eyes, hands, trunk & tongue, RAM normal	Ativan 1 tablet, Tylenol #2, Meloxicam 15mg, Sertraline 1 tablet
HD07	36/m	2001 (43 repeats)		5	Started with twitching, now choreic, RAM normal	Olanzapine 2.5 mg
HD09	61/f	Jan 2000		6	Started with Chorea in lower limbs, now generalized chorea, RAM abnormal in upper and lower	Imovane 7.5mg
HD010	50/f	2001		5	Generalized chorea in trunk, limbs and legs	Salmon oil, centrum omega 3, Citalopram, Besacoydyl, serroquel
HD011	62/f	1995		11	Tremor since age of 30, with anxiety and depression, now choreic, RAM impaired in right upper limb	Estrogen 0.9mg, Inderal LA 60mg, Novo gabapentin 300mg, Paroxetine 20mg, Codeine Contin 150mg, Clonazepam 0.5mg, Seroquel 200mg, Ibuprofen 400mg
HD012	58/f	April 2001		5	Moderate generalized chorea, RAM normal	Aricept 5 mg, Oxybatynin 5mg, Larazepam, Omega 3
HD013	63/m	2001 (43 repeats)		5	Generalized chorea, RAM abnormal with intrusion of choreic in upper and lower limbs	Nitoman 12.5mg (tetrabenazine), celexa 20mg, L-thyroxin
HD014	52/f	2001	17	5		Effexor 150mg, Clonazepam 0.5mg, Estace, Glucomine (for arthritis), CoQ10
HD015	64/m	(42 repeats) initially misdiagnosed with Tourette's 2004	53	2	Muscle rigidity all 4 limbs, RAM impaired, chorea, dystonia upper right	Quetrapine 200mg, Mirtazapine 45 mgh.s, Glyburide 2.5mg, Metformin 500mg, ocusate NA 100mg, Ritazopine
HD016	60/f	2004 (~41 repeats)		2	Body and face chorea	Indocid 100mg, Estrogen, Amitriptyline 50mg, Losec 20mg, Ativan, Ethyl EPA study
HD019	79/f	2001	44	5	Ram slow with dystonic posturing[R], chorea	Hydrochlorothiazide 12.5mg, Bisopiolo 7.5mg, Atorvastatin 10mg, Ramipril 10mg, Nitrofurantoin 100mg, Alendronate
HD20	50/m	1990		16	Chorea, no rigidity or tremor	Cogentin 2mgx3, Olanzapine 10mgx3, Salicylate 800mgx4, Haldol, Seroquel 150mgx2, Ferrous Fumerate, Clomipramine 50mgx2, Lactulose 30mlx2, tylenol 325mg
Mean ± SD	**56.9±12.3**			**5.6± 3.5**		
Controls	**55.2±13.8**					

FIGURE 4 illustrates the changes of WBIM amplitude during the rest and active conditions of MT and RAM. ANOVA reveals a *group* effect for WBIM during MT (F = 17.111, $p < 0.05$) and RAM (F = 39.790, $p < 0.05$) confirming the presence of significant chorea at rest and during voluntary movements in the HD group. RAM movements generated a *condition* effect that was present in both groups (F = 10.530, $p <$ 0.05), but not during MT, which suggests that the increase of WBIM amplitude with voluntary movement is related to the velocity of the performed motor act.

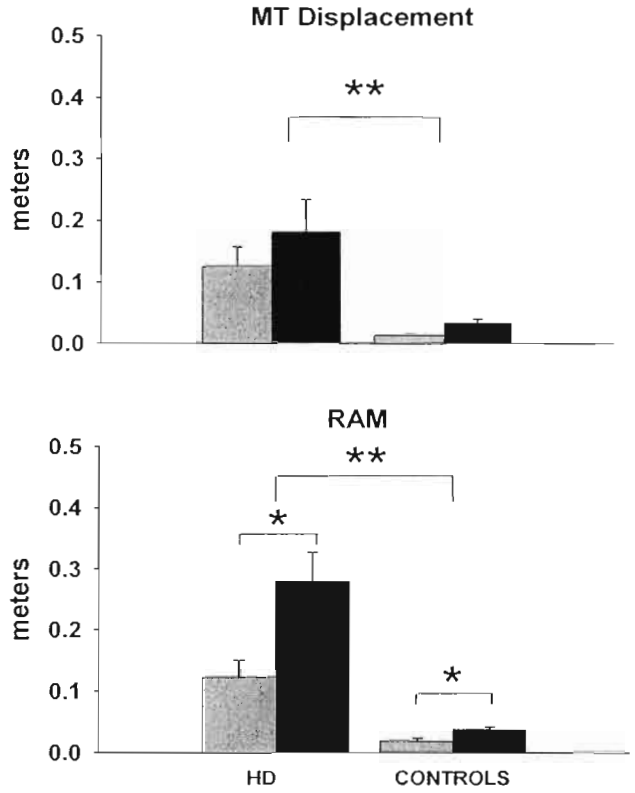

Figure 4. *Whole Body Movement (WBM) at rest and during activity.* WBIM for manual tracking in displacement during MT (top) and RAM in the *rest* (gray) and *active* conditions. Amplitude was higher for the choreic HD group, confirming the presence of chorea in all conditions. The amplitude of WBIM increased significantly during movement in both groups during voluntary movement, but significantly more during RAM. While the increased WBIM in the controls could be qualified as motor overflow, the increase of WBIM in HD patients represents an increase of chorea. *significant difference within group at $p < 0.05$. **significant difference between groups at $p < 0.05$.

FIGURE 5 illustrates the amount of error (performance minus target) present during MT. In displacement, the difference did not reach the threshold for statistical significance (t=250, p=0.481), despite a clear trend towards more deviation from the target. The HD group exhibited high variability in error as well as WBIM amplitude, therefore, a correlation was done to determine if a relationship existed between these variables. Results indicate that indeed patients with higher WBIM presented with increased deviations from target (Rho=0.67, p<0.05). Error in velocity (difference between the target velocity and performance velocity) was significantly higher for the HD group (t=340, p <0.05), suggestive of a difficulty in matching the target velocity during the different phases of movement.

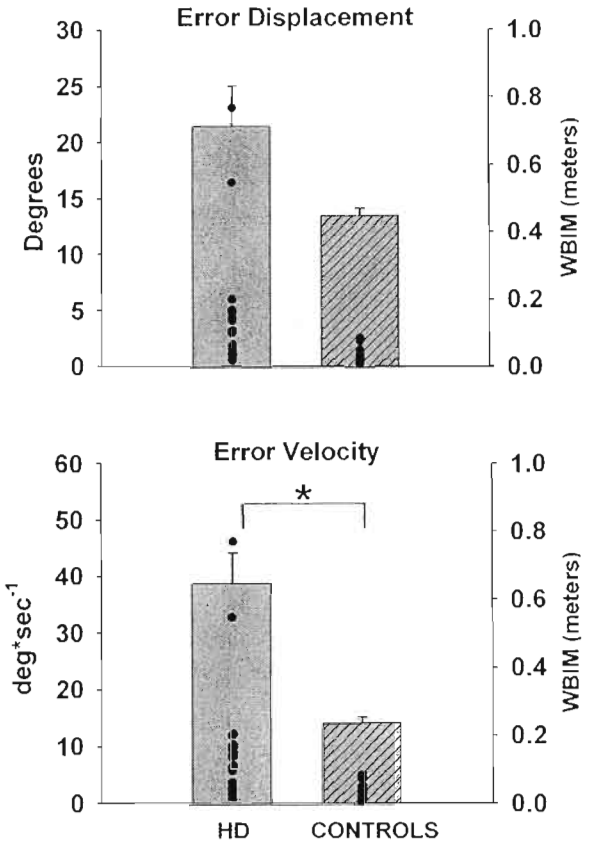

Figure 5. ***MT Performance.*** Manual tracking performance is evaluated using error in performance. Although the Error in displacement (*top*) did not reach significance, patients demonstrated an increased difficulty in following the target. When examining their ability to match the target velocity (*bottom*) patients with choreic HD demonstrated significant error. This error was highly correlated with the level of chorea (*Rho* = 0.67). *significant difference between groups at $p < 0.05$.

FIGURE 6 illustrates the RAM performance for RANGE, VELOCITY and IRREGULARITY. Patients with HD had significantly higher RANGE (t=4.398, p<0.05) and VELOCITY (t=3.072, p<0.05) than control subjects, suggestive of hypermetria. Although there was a trend towards a more irregular quality of performance in the HD group, differences did not reach significance (t=1.996, p>0.05).

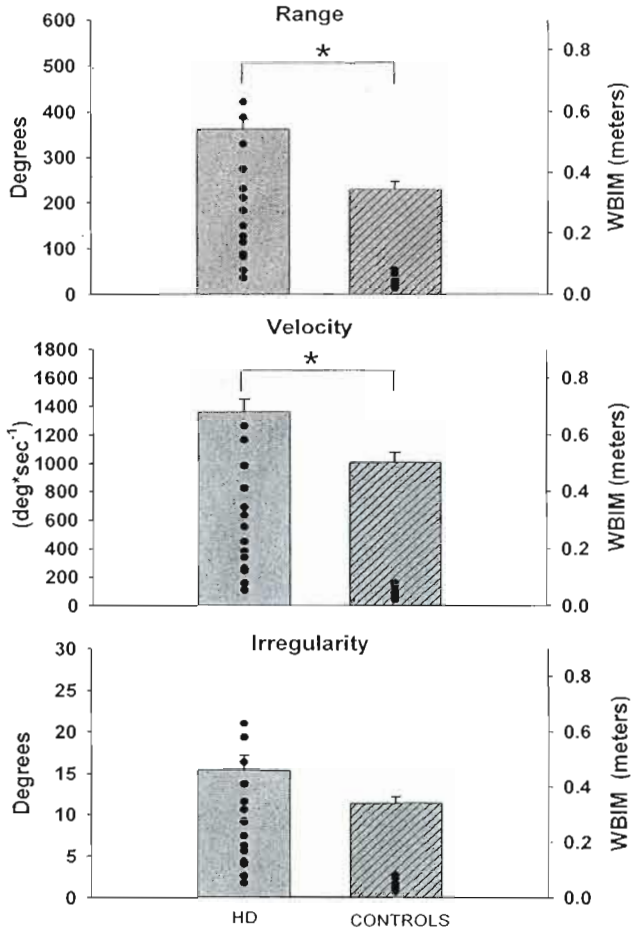

Figure 6. *RAM Performance.* Despite receiving similar instructions, patients with choreic HD presented with hypermetria, as they significantly had higher RANGE (*top*), and VELOCITY (*middle*) than age-gender matched controls. Since the velocity generated by subjects may be related to the range of movement, we also present results (bottom) from a subset group (six HD patients and their controls) who could be matched for equal RANGE. In that case, the VELOCITY generated by patients was equal to that of their matched controls, confirming that patients with choreic HD were able to develop fast movements. *significant difference between groups at $p < 0.05$.

FIGURE 7 shows example of MT performance and RAM performance from one patient with HD who had clear choreic intrusions in their MT performance, but had a slightly better performance then the control subject during RAM.

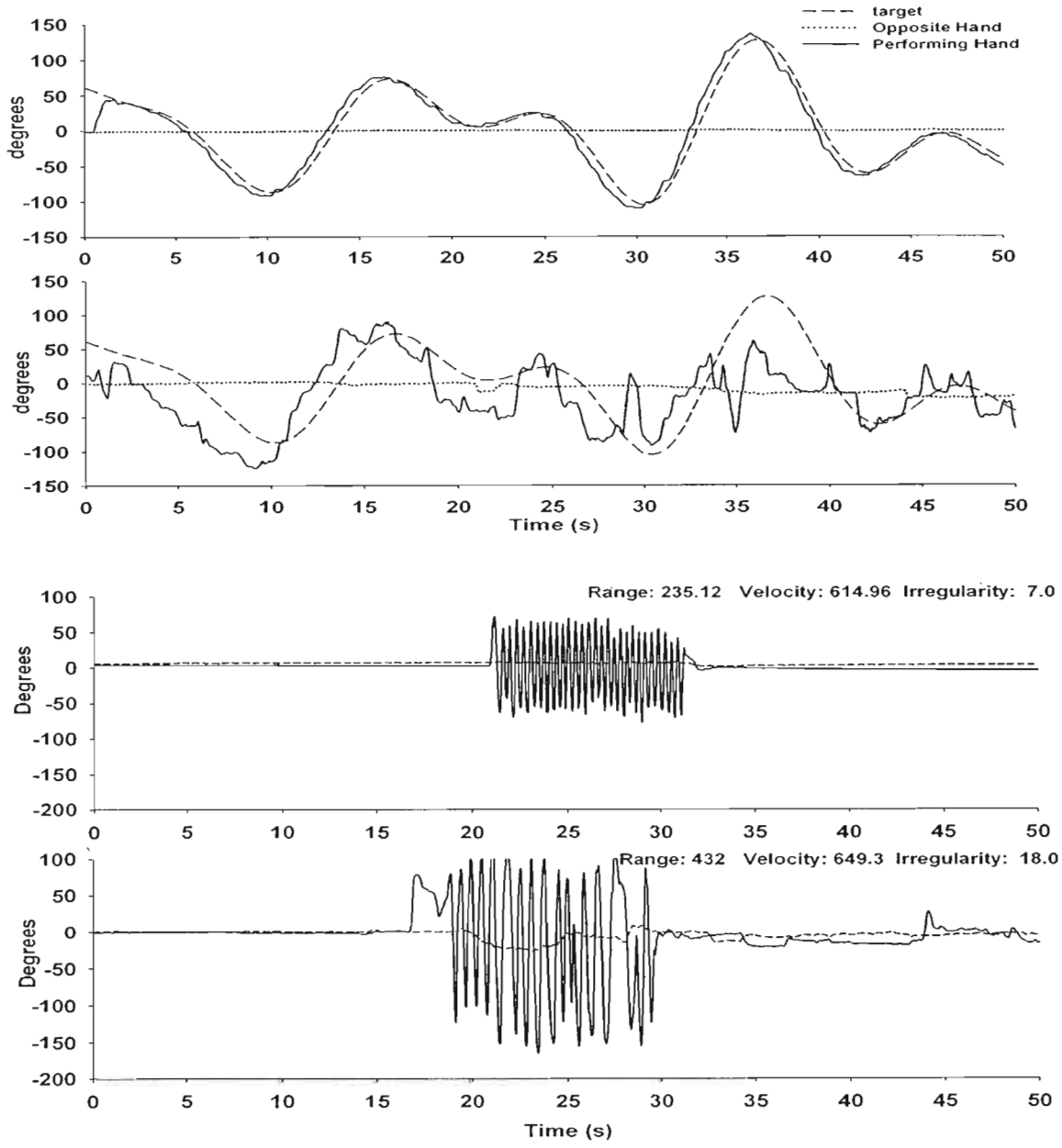

Figure 7. *Performance traces*. Examining the performance of HD subjects compared to controls on a trial-by-trial basis reveals clear qualitative differences in performance signals. This example illustrates the typical motor performance, during one trial, of a patient with relatively high levels of chorea. The intrusion of choreic movement is readily visible during the MT task (*4a*). However, that same patient is able to perform the RAM task with greater amplitude and velocity than its counterpart in the control group (*4b*). While the "quantity" of movement is good, the "quality" is less discernable; the RAM movements present with more irregularity than the control subject.

3. DISCUSSION

Chorea

Patients had significantly greater WBIM compared to controls, confirming the presence of chorea. Beyond this confirmation, the effect of voluntary motor activity on amplitude of WBIM in patients with chorea is well demonstrated. Patients and controls both exhibited increased WBIM amplitude during motor activity, especially during RAM, with the HD group providing the most dramatic example of this trend. While the increased WBIM in the control group could be characterized as motor overflow, the increased WBIM in the HD group is the result of increased chorea. These results are similar to those of dyskinetic PD patients, where increased dyskinesias were observed during voluntary motor acts (Ghassemi et al. 2006; Lemieux et al. 2007). This may imply that both PD and HD hyperkinetic symptoms are sensitive to increased cortical facilitation brought about by neural activity related to voluntary movements.

MT

Patients with HD expressed a significantly greater amount of error in velocity during the MT task compared to controls. There was a direct correlation between the magnitude of chorea and performance error, in both displacement and velocity. We found no correlation between disease duration and age with performance variables. This suggests a predominant influence of chorea on manual tracking in patients with HD, and the greater the chorea, the greater the difficulty in completing such precision target-oriented tasks. Differences between groups for displacement did not reach significance, which suggests that velocity error differences are influenced by small deviations from the target which are corrected quickly, but none the less register as movement away from the target. It is reasonable then to suggest that the deviations from target were a direct cause of choreic intrusions in the motor performance.

RAM

Patients with HD had RAM performance superior to that of controls, suggesting that patients were able to perform fast repetitive movements, despite significant increases in WBIM during activity. The HD group displayed a tendency for more irregularity of performance, which although not significant, highlights a difference in the *quality* of performance between groups. This evidence rules out the existence of "core" bradykinesia in patients with chorea, and suggests that bradykinesia reported in the literature is due to the use of tasks that had a low signal-to-noise ratio (here we imply that the noise is the chorea and the signal is the intended movement). For instance, several studies utilized tasks requiring multi-joint movements where purposeful slowing of movement was surely needed to compensate for choreic intrusions during precise motor acts (Kim et al 2004; Hefter et al. 1987; Verbessem et al. 2002; Shaft et al 2003; Lemay et al 2005; Boulet et al 2005) Patients with HD have shown difficulty in sequencing multi-joint movement and sub-movement cuing (Agostino et al. 1992; Curra et al. 2000); this fact may facilitate the recording of mechanically-induced bradykinesia in patients, due to the exaggerated time-scale of each component of a multi-joint movement, highlighting the presence of any direct influence of chorea on pace of movement (vanVugt et al. 2003; vanVugt et al. 2004; Boulet et al. 2005;). Accordingly, slowness of performance recorded in previous studies (Jahanshahi et al. 1993; Garcia-Ruiz et al. 2002; Verbessem et al. 2002) may have been the result of chorea. Then, to compensate for involuntary choreic movements, subjects may have attempted to "voluntarily" slow their performance in favour of accuracy. Another possibility is the fact that cognitive symptoms, which are well-described in HD, may have also contributed to bradykinesia being detected in other studies, as the complexity of the task used may have been higher in some experiments. The simple nature of our task limited the influence of bradyphrenia on the performance of patients. Interestingly, results obtained using our device did not correlate with clinical observations that RAM were problematic in these patients. This probably stems from the fact that clinical RAM

differs greatly as it requires patients to either tap repetitively the index on the thumb, or tap the palm and dorsum of the hand on the knee, in an alternating fashion. Both these tasks possess a lower signal-to-noise ratio compared to full pronation-supination movements.

IMPLICATIONS FOR CURRENT BG MODELS OF CHOREA

Selective atrophy of the brain in HD occurs in the globus pallidus and subthalamic nucleus, with the most severe effects reserved for the corpus striatum (Sharp & Ross 1996). In the neostriatum, the medium spiny neurons degenerate early, while the larger aspiny interneurons are left intact (Albin et al. 1989; Albin et al. 1990; Hedreen & Folstein 1995; Reiner et al. 1988). The specific cause of chorea seems to correspond to an early selective loss of GABAergic neurons expressing enkephalin (D2) situated in the indirect pathway (Reiner et al. 1988). In HD, the degeneration of D2-mediated striatal neurons causes a disinhibition of the lateral pallidal projections to the subthalamic nucleus. This causes the subthalamic nucleus to be exceedingly inhibited. The chorea, then, would be generated by a loss of subthalamic excitatory influence upon the medial pallidal neurons, yielding a decreased pallidothalamic inhibition upon thalamo-cortical pathways (Joel 2001). Consequently, the presence of chorea corresponds to a fundamental interruption of the indirect pathway, which involves the striatal-external pallidum, subthalamic nucleus and Gpi (Crossman et al. 1988; Jackson & Crossman 1984; Mitchell et al. 1989). Later in the disease, a decrease of thalamo-cortical activity can be seen when bradykinesia and rigidity, rather than chorea, are the predominant symptoms (Weeks et al. 1997). Then, it is postulated that GABAergic neurons of the direct pathway may begin to die. However, it is possible that the direct pathway may begin to be affected in the earlier stage when chorea is present (Joel 2001). The fact that patients participating in the present study were able to perform fast movements as well as controls may suggest an intact direct pathway. Voluntary movements are then facilitated by an intact direct pathway, while chorea would be generated by dysfunction of the indirect pathway. The present results also suggest that

two competing motor programs do not necessarily cause bradykinesia, as long as the signal-to-noise ratio is high. This is what we can observe during the RAM task. As soon as this ratio drops, as seen in the MT task, the undue influence of chorea becomes clear. The results may also suggest that an intact direct pathway (select ON pathway as described in the focused selection model from Mink, 1996) supersedes a dysfunctional "control function" (the equivalent of the indirect pathway in the Delong's model) pathway, since patients were able to generate fast movements. This was the case for patients with PD having dyskinesias where bradykinesia was detected with involuntary movements (Ghassemi et al. 2006). In that study, the performance was not correlated with either the amplitude of dyskinesias, rigidity or tremor, suggestive of the presence of "core" bradykinesia concomitantly with peak-dose levodopa-induced dyskinesias. Another interesting finding in the present study, and in the study of dyskinetic PD patients (Ghassemi et al. 2006; Lemieux et al. 2007) is the increased amplitude of involuntary movements during voluntary motor acts. This suggests that the efficacy of the hyperdirect pathway, or select OFF pathway (Mink 1996), is limited in these hyperkinetic disorders. This pathway has been linked to inhibition of motor behaviors (Nambu et al. 2002; Aron et al. 2006), and is proposed to be the main inhibitor of competing motor patterns in the focused attention model of Mink (1996).

Clinical Implications

The relevance of this study revolves around the clinical cost/benefit analysis of clinically treating chorea in patients with HD. Prior studies have suggested the onset or aggravation of bradykinetic features of the disease with drug treatment for chorea (Bonelli et al. 2004). The present study has determined conclusively that chorea disrupts performance in tasks requiring accuracy, but that "core" bradykinesia is not a feature of HD when chorea is present. This fact strongly suggest that any bradykinesia detected after dopamine antagonist administration is the result of the drug effect, not simply an aggravation of an underlying slowness of movement that has begun to develop simultaneously with the presence of chorea. It may also suggest that patients who do

present with severe hypokinesia or bradykinesia after dopamine antagonist administration may have already begun the transition from the hyperkinetic phase to the hypokinetic phase of the disease. Then, the medication may simply catalyze this transition. This hypothesis, however, remains to be confirmed. Interestingly, the patient base used in this study received a wide variety of drug treatments, and dosages. After examining subgroups of patients based on their medication regimen, no relationship was found between drug intake and RAM performance. Robust significance and correlation between variables rules out the possibility that other factors such as mild cognitive impairments, oculomotor deficits, or sensorimotor integration deficits influenced motor performance.

Based on the fact that "core" bradykinesia is absent in patients with HD chorea, that chorea was mostly responsible for errors during the MT task, and that chorea may have played a significant role in the bradykinesia found in other studies utilizing low signal-to-noise ratio tasks, it is reasonable to suggest that chorea, when present, is predominantly responsible for motor dysfunctions in patients with HD, and should be at the centre of symptomatic treatment of early HD.

CONCLUSIONS

Our results unequivocally show that bradykinesia is not a systematic feature in HD when chorea is predominant, but that chorea is a main source of error in performance during accurate movements. Accordingly, patients with HD would greatly benefit from treatments aimed at reducing chorea while maintaining proper motor function. In addition, this study may be the first to indicate a clinical validation of differential degeneration of the indirect vs. direct pathways and their relationship to chorea and bradykinesia, thereby adding to current models of basal ganglia dysfunction in HD.

4. EXPERIMENTAL PROCEDURES

Participants

Thirty participants, fifteen patients with HD (12 women, age: 56 ± 12) and fifteen age/gender matched control subjects (12 women, age: 55 ± 13) were tested. Patients were recruited through the London Health Sciences Movement Disorders Clinic. Control subjects were recruited from the general population. Each participant provided informed consent. Choreic HD patients, diagnosed with adult onset HD, with little to no psychiatric disturbance that may impede their understanding of the tasks were included in the study. Individuals expressing bradykinesia/akinesia as the prominent motor symptom or severe psychiatric symptoms were not eligible for participation. Age-matched controls were free of any neurologic or motor disturbances. All experiments were approved by the institutional Human Research Ethics Board.

Quantification of Whole-Body Involuntary Movements (WBIM)

In order to capture whole-body chorea in 3 dimensions, a 6-degrees-of-freedom electromagnetic measurement system, the *MotionMonitor*™ magnetic motion tracker was employed (Innovative Sports Training, Chicago, Illinois). This methodology has been validated in dyskinetic patients with Parkinson's disease. Details on the apparatus and experimental procedures are described elsewhere (Ghassemi et al. 2006; Lemieux et al. 2007; Gour et al. 2007). In brief, subjects were outfitted with a custom shirt, Velcro bands, gloves and shoe covers onto which 15 sensors (receivers) that provided time series signals of both position (x, y, z) and orientation (pitch, yaw, roll) were attached. They were placed adjacent to the joint axes, such as the posterior surface of the head, the first thoracic vertebrae, sacral bone, superior spine of the scapulae, lateral surface of the forearms and upper-arms, back of the hands, as well as the lateral aspects of the calves and dorsal surface of the feet. During the calibration phase of the experiment, each sensor was then assigned to the Center of Mass of the limb by way of a digitization process. Using a stylus receiver, bony landmarks were palpated, and the centroid method

was used to form coordinate systems at the Center of Mass of each limb segment. Based on the height and weight of the subject, and using integrated anthropometric tables, an automated algorithm assigned a particular sensor to the Center of Mass of the limb on which it was positioned.

Motor tasks

Manual tracking (MT)

Participants were seated and asked to hold, in each hand, a foam handball that was attached to rotational sensors. Recordings were taken in this position for 60 seconds to provide data for the 'rest' or inactive condition. Then, participants were asked to match the position of a computer generated horizontal target line (generated by DasyLab8.0 software, DASYTEC, National Instruments Company, Amherst NH) with a line they controlled via pronation-supination movement of the dominant hand only. The target line was presented on a large projector screen placed 1.5 meters in front of participants. The tip of the target line moved from left to right, at a variable velocity (between 0.25 to 0.75 HZ), and amplitude (20 to 120 degrees). Although the target displacement remained similar between trials, it was not possible for participants to anticipate changes of either target amplitude or velocity due to the irregular nature of its displacement. They were given the opportunity to practice the task prior to recording in order to familiarize themselves with the actions required to match the moving target. Three trials in the rest and active conditions were recorded. A pause of one minute was given between trials so that participants may rest their arms. This task was previously used and proven effective to detect intrusions of large involuntary movements such as levodopa-induced dyskinesias (Lemieux et al. 2007) or PD tremor (Duval et al. 2001; Duval et al. 2006) during voluntary movements.

Rapid alternating movements (RAM)

For the RAM task, testing included three trials of 60 seconds during which participants were instructed to maintain the 'rest' position described above for 20

seconds, arms bent at their side, holding one foam ball in each hand. Subjects were then instructed to perform pronation-supination of the dominant hand as fast and as complete a rotation as possible, for a period of ten seconds. After ten seconds the participants were asked to return to the rest state for the remaining 20 seconds. Three trials were recorded in each condition with periods of rest in between trials. RAM tasks have been validated by us (Duval et al 2001; Duval et al 2006*a*; Duval et al 2006*b*; Ghassemi et al 2006) and others [Okada & Okada 1983; Beuter et al. 1999; Fimbel et al 2005] to measure slowness of movement in different populations, and represent the ability of subjects to generate high velocity and to maintain it for several seconds. It is a natural movement that has little to no learning curve associated to it. Furthermore, this task is purely internally generated, which is known to utilize basal ganglia (Cunnington et al 2000). In fact, activation of the putamen and globus pallidus is known to be related to the velocity (Cunnington et al 2000; Turner et al 1998) and amplitude of movement (Turner et al 2003). Also, this task has relatively large amplitude in displacement and velocity, which reduces greatly the likelihood of biomechanical effect, and is simple enough to minimize greatly the influence of cognitive problems known in both diseases studied, which renders this task ideal to detect "core bradykinesia"

Signal Analysis

Whole-body involuntary movements (WBIM)

Each sensor time series was divided into 7-second epochs. Then, the mean position for x, y, and z was subtracted from the actual position of x, y and z, yielding a displacement time series around a neutral position for each of the epochs. We then squared the root mean square (RMS) values for each of the x, y and z time series, and calculated the mean of these three squared RMS values. Finally, we computed the root of this mean, thus yielding three-dimensional vectorial amplitude for each sensor. Values obtained from each 7-second epoch were then averaged. WBIM amplitude was determined by computing the sum of all these mean vectorial amplitudes over all

sensors. Sensors allocated to the performing limb (i.e., hand, forearm and upper arm) were excluded from analysis. WBIM was calculated in both displacement (meters) and velocity ($m \cdot s^{-1}$).

MT

To quantify displacement ERROR (in degrees) for the MT performance, the target line was subtracted from the subjects' performance. Then, the mean of the absolute values of the remaining signal was computed. ERROR velocity was also calculated by subtracting target velocity from the velocity of performance, obtaining an ERROR value in $deg \cdot s^{-1}$. The goal was to determine if differences existed between groups in their ability to match target velocity.

RAM

An automated algorithm was used to identify each peak and trough of the pronation-supination cycle. Three characteristics were then calculated: range, velocity, and irregularity. Range is the mean angular displacement over a complete pronation-supination cycle in degrees. Velocity represents the maximal instantaneous velocity from peak to peak, and is provided in degrees per second. Irregularity is a measure of the variability in RAM amplitude. Only the first seven seconds of the pronation-supination cycles were analysed for RAM performance as fatigue may confound results (Ghassemi et al. 2006; Duval et al. 2006; Duval et al. 2001).

Statistics

To date, no studies have analysed WBIM and motor performance in patients with HD and controls, nor compared motor performance using the motor tasks proposed here. However, based on results obtained in a previous study in dyskinetic Parkinson's disease patients (Ghassemi et al. 2006) a minimum of 2 subjects is needed to obtain a power of 0.80 for comparison of WBIM amplitude between patients and controls. For

performance measures such as range and velocity, 15 subjects are required for comparison to obtain a power of 0.80. In order to compare *group* (patients vs controls), *condition* (rest versus active), and *group x condition* interrelations, we used a two-way analysis of variance (ANOVA), with repeated measures for condition. Post hoc analysis (Newman-Keuls) was used to indicate which group comparisons yielded significance. T-tests were used to determine statistical significance between groups for each RAM and MT performance characteristic. Finally, we used Spearman's Rank correlations to examine possible interactions between age, disease duration, WBIM amplitude and motor performance characteristics. The threshold of significance was set at $p < 0.05$ for all aforementioned measures.

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7. GENERAL CONCLUSION

We hypothesized that chorea in patients with HD would be aggravated by stress, i.e. increased by performing a motor task, and that chorea would not be the cause of bradykinesia when both symptoms are present.

It became obvious during testing that in order to fully capture the dynamics of motor performance in patients with HD, the RAM task must be accompanied by one that isolates intrusions of chorea during movement, hence providing a measure of chorea's influence on motor tasks demanding accuracy. Accordingly, we also included in our result section the motor performance of participants during a manual-tracking (MT) task, which would compliment and broaden implications of performance outcomes.

Our study illustrated that chorea indeed increases during voluntary movement, across several motor tasks, in patients with HD. The absence of bradykinesia in patients with HD in our study suggest that slowness of movement reported in the literature may be due to inappropriate signal to noise ratio of performance tasks (Agostino et al.1992, Curra et al. 2000, Hefter et al. 1987, Verbessem et al. 2002), which were unable to distinguish between influence of chorea and bradykinesia. In fact, chorea may have been directly implicated in the slowness of movement, when present. Also, the effect of disease phase and expression cannot be ruled out as a factor in the presence of more hypokinetic features of HD in these previous studies. It is hard to determine what the source of this bradykinesia was, as previous studies have not simultaneously recorded chorea with performance measures.

Our results also support previous hypotheses (see model by Penney & Young, Weeks et al. 1997, Reiner et al. 1988) that suggest that the direct pathway remains intact during the most 'choreic' phases of adult onset HD. This compliments our original hypothesis, illustrating that the presence of chorea in patients with HD does not cause bradykinesia during a motor task.

This study has shown, through correlations between whole-body involuntary movements (WBIM) and error in performance in displacement and velocity, that chorea

is the main source of performance error in subjects with choreic HD, and therefore, warrants therapeutic development and aggressive treatment.

Strengths of the Present Study

The current study is the first to simultaneously WBIM and motor performance in patients with HD chorea. The quantification of movement in 3-dimensions provides a foundation for the analysis of innumerable characteristics and qualities of whole-body voluntary and involuntary movements that are crucial for understanding human movement in health and disease.

The measures incorporated in this study, i.e. rapid alternating movement and manual tracking tasks, were able to isolate, with exceptional precision, the impact of hypo- and hyper- kinetic features of movement in these subjects, shedding light on the dynamic interrelationships between voluntary and involuntary movement in HD. In order to fully understand and effectively treat symptoms of movement disorders, such as HD, there must be an acknowledgment of the effects of each symptom in isolation and interaction with one another. These measures enable the isolation and comparison of the effects of hypo- and hyperkinetic movement, providing a foundation on which to build a better model of the pathways eliciting the concomitant release of hypo-, hyperkinetic motor symptoms, as well as voluntary motor behaviours.

Limitations of the Present Study

Limitations of the present study include subject number, variability of subject characteristics and lack of clinical rating scale data. Although subject number was low, n=15, this number satisfied statistical requirements for the comparison of both WBIM measures and those of motor performance on rapid alternating and tracking tasks (see power calculation in *statistics* section). In fact, this study represents one of the largest studies using quantitative methods to examine chorea and its impact on voluntary movements.

It became obvious during testing that our inclusion criteria were unrealistic and would severely limit the context and implications of our work. Therefore, we increased the breadth of our inclusion criteria so as to add those receiving medication and who use assistive devices. Subjects varied in age, disease duration and medication type/dosage. Despite the challenge this variability in subject characteristics may have posed, we recorded robust trends in performance and magnitude of WBIM that diminished the role any one factor may have had on findings. Surprisingly, almost all patients showed similar levels of performance in both tasks, reducing greatly the variance within that group.

We were unable to obtain UHDRS clinical rating data for all subjects. However, keeping in mind that the purpose of this study was not to correlate UHDRS scores with performance on our motor tasks, in addition to the fact that WBIM values clearly show that HD subjects tested were choreic, this limitation did not compromise the findings of this study in any way.

Qualitative analysis of recordings in both patients with HD and control subjects raised the issue of movement strategies (i.e. upper and lower arm involvement in the completion of pronation-supination activity) utilized during motor tasks. It became apparent that the variability in strategy, and therefore amount of movement in the performing arm, was significant. For instance, some subjects had their elbow moving more than others during the RAM or MT. Therefore, to remove the influence of 'movement strategy' on whole-body displacement during recording, we removed the performing arm sensors (those located on the hand, lower and upper arm of the performing arm) from calculations of whole-body movement. Removal of these performing arm sensors did not impact significance between groups on any of the variables compared.

Future Implications and Research

In future work continuing in the analysis of motor performance in RAM and MT tasks, adding grip force quantification would allow for another dimension of movement

interaction. Grip force recorded simultaneously with WBIM will provide insight into the dynamics of performance, which grip force alone, is unable to provide. This would synchronize muscle activation with behavioural output and allow comparison of activation levels and points of error or accuracy in performance.

Analysis of patterns in WBIM, in a topographical, as well as mathematical sense would continue to shed light on the characteristics of involuntary and voluntary movement. Also, comparing the present data with that of other disorders with similar clinical manifestations could greatly increase our understanding of subtle similarities and difference in types of involuntary and voluntary movements in basal ganglia disorders.

Future research and therapy should focus on the efficient tailoring of medication to reduce chorea while maintaining optimal motor performance, i.e. avoiding sedative effects of overmedication. Manipulating dosage and medication schedules would enable peak performance of anti-choreic agents, enhancing efficiency on scales of both economy and quality of life. Analysis of the relationship between pathophysiological variables, such as CAG repeats and volumetric fluctuations, would enable a more comprehensive understanding of how structural and behavioural changes in the time-course of disease progression may alter the final out-put of motor organization and pathways. This information is not only fundamental in understanding Huntington's disease and other basal ganglia disorders, but will enhance our understanding of these basic pathways in healthy conditions as well. Quantification of WBIM, simultaneously with motor performance, is an integral stepping-stone in the comprehensive analysis of the cause and progression of movement disorders.

Continued research which incorporates simultaneous 3-dimensional capture of whole-body movement is, we believe, pivotal to advancement and discovery in basal ganglia disorders.

ANNEX-1 ETHICS UQAM

Université du Québec à Montréal

Case postale 8888, succursale Centre-ville
Montréal (Québec) Canada H3C 3P8
Comité institutionnel d'éthique de la recherche avec des êtres humains

Montréal, le 6 mars 2006

Monsieur Christian Duval
Professeur
Département de kinanthropologie

Objet : Projet de recherche intitulé : «*Étude des mouvements involontaires et volontaires chez les personnes ayant la maladie de Parkinson ou la maladie de Huntington*».

Cher monsieur,

Suite au complément d'information reçu et aux recommandations émises par le Comité, il m'est agréable de vous confirmer l'acceptation de votre protocole de recherche au plan éthique. Vous trouverez ci-joint le certificat de conformité à l'éthique émis par le Comité et valide pour un an.

Le recrutement et l'expérimentation étant réalisés en milieu hospitalier, le Comités s'attend à recevoir une copie du certificat d'éthique émis par le CIÉR de chacun des établissements concernés, ainsi qu'une copie des formulaires de consentement approuvés par ces derniers.

Le Comité vous demande de lui faire parvenir un bref rapport d'évolution de votre projet au plus tard un mois avant la date d'échéance du présent certificat. Le formulaire utilisé à cette fin est disponible sur le site Web du SRC[1]. Entre-temps, il est de votre responsabilité d'informer le Comité des changements majeurs qui pourraient être apportés à votre projet concernant la participation des sujets.

Le Comité vous remercie d'avoir porté votre demande d'approbation à son attention et vous souhaite le plus grand succès dans la poursuite de vos travaux.

Marc Bélanger, Ph.D.
Professeur
Vice-Président

1 http://www.recherche.uqam.ca/ethique/humains-suivi-continu.htm

UQÀM

Université du Québec à Montréal
Case postale 8888, succursale Centre-ville
Montréal (Québec) Canada H3C 3P8
Comité institutionnel d'éthique de la recherche avec des êtres humains

No. 060515
.061187

Conformité à l'éthique en matière de recherche impliquant la participation de sujets humains

Le Comité d'éthique de la recherche avec des êtres humains de l'UQAM a examiné le protocole de recherche suivant :

Responsable(s) du projet : Christian Duval
Département ou École : Kinanthropologie
Titre du projet : «*Étude des mouvements involontaires et volontaires chez les personnes ayant la maladie de Parkinson ou la maladie de Huntington*».
Étudiant(s) réalisant leurs projets de mémoire ou de thèse dans le cadre du présent projet ou programme :
Alison Fenney, étudiante à la maîtrise en kinanthrologie.
Ce protocole de recherche est jugé conforme aux pratiques habituelles et répond aux normes établies par le «*Cadre normatif pour l'éthique de la recherche avec des êtres humains de l'UQAM*».

Le projet est jugé recevable au plan de l'éthique de la recherche avec des êtres humains.

Le présent certificat est valide jusqu'au 31 mars 2007.

Membres du Comité

Marc Bélanger, Professeur, Département de kinanthropologie
Henriette Bilodeau, Professeure, Département Organisation et ressources humaines
René Binette, Directeur, Écomusée du fier monde, Représentant de la collectivité
Shahira Fawzi, Enseignante retraitée de la CSDM, Représentante de la collectivité
Joseph Josy Lévy, Professeur, Département de sexologie et Institut Santé et Société
Francine M. Mayer, Professeure, Département des sciences biologiques
Christian Saint-Germain, Professeur, Département de philosophie
Jocelyne Thériault, Professeure, Département de sexologie

6 mars 2006
Date

Marc Bélanger
Vice-président du Comité

UQÀM

ANNEX-4 ETHICS CHUM

CENTRE DE RECHERCHE
Comités d'évaluation scientifique et d'éthique de la recherche
Équipe Hôtel-Dieu du CHUM
Édifice Cooper
3981, boulevard St-Laurent – Mezz 2
Montréal (Québec) H2W 1Y5

Téléphone : 514 – 890-8000 – Poste 14030
Télécopieur : 514 – 412-7394
Courriel : lynda.ferlatte.chum@ssss.gouv.qc.ca

Le 18 octobre 2006

Dr Christian Duval
Département de kinanthropologie

Université du Québec à Montréal
Case postale 8888, succursale Centre-Ville
Montréal, (Québec) H3C 3P8

Objet : HD 06.032 – Approbation FINALE CÉR

Étude des mouvements involontaires et volontaires chez les personnes ayant la maladie de Parkinson ou la maladie de Huntington.

Cher Docteur,

J'ai le plaisir de vous informer que le Comité d'éthique de la recherche, à sa réunion plénière du 18 octobre dernier, a évalué le projet mentionné ci-dessus.

À cette fin, ont notamment été examinés les documents suivants :

- Formulaire de présentation – Formulaire A – Annexe 2.1
- Formulaire de renseignements supplémentaires – Annexe 2.2
- Résumé du protocole
- Lettre de collaboration de médecins du CHUM (Hôtel-Dieu)
- Formulaire de consentement français de l'Institut universitaire de gériatrie de Montréal (version du 19 octobre 2006)

La présente constitue l'approbation finale, **valide pour un an à compter du 18 octobre 2006**, date de l'approbation initiale. Je vous rappelle que toute modification au protocole et/ou au formulaire de consentement en cours d'étude, doit être soumise pour approbation du comité d'éthique.

Le comité suit les règles de constitution et de fonctionnement de l'Énoncé de Politique des trois Conseils et des Bonnes pratiques cliniques de la CIH.

Vous souhaitant la meilleure des chances dans la poursuite de vos travaux, je vous prie d'accepter, Docteur, mes salutations distinguées.

MC Michoud

Marie-Claire Michoud, Ph.D.
Vice-présidente
Comité d'éthique de la recherche
Équipe Hôtel-Dieu du CHUM

MCM/lf

P.j. : Formulaire de consentement français approuvé

Cc : Par télécopieur au Bureau des contrats, Centre de recherche, Pavillon Masson, Hôtel-Dieu du CHUM (514) 412-7134

ANNEX-5 ETHICS CRIUGM

CENTRE DE RECHERCHE
INSTITUT UNIVERSITAIRE DE GÉRIATRIE DE MONTRÉAL

Affilié à l'Université de Montréal

Le 22 juin 2006

Dr Christian Duval
Chercheur
Centre de recherche de l'Institut universitaire de gériatrie de Montréal
4565, chemin Queen Mary
Montréal (Québec)
H3W 1W5

Objet : Votre projet intitulé : « ***Étude des mouvements involontaires et volontaires chez les personnes ayant la maladie de Parkinson ou la maladie de Huntington***» (projet 2006-0604)

Docteur Duval,

Le projet cité en rubrique a été réévalué par le Comité d'évaluation scientifique (CÉS). Les précisions et améliorations apportées au projet rencontrent nos critères d'évaluation (formulaire d'évaluation ci-joint). Par conséquent, votre projet est approuvé par le CES.

Je vous souhaite le meilleur succès possible dans la réalisation de votre étude.

Je vous prie d'accepter, Docteur Duval, l'expression de mes meilleurs sentiments.

Louise Demers, Ph.D, OT(C)
Présidente du comité scientifique

cc: Paule Savignac, Présidente du CÉR
Gisèle Semerjian, Secrétariat, CÉR

ANNEX-6 CONSENT FRENCH

INSTITUT UNIVERSITAIRE DE GÉRIATRIE DE MONTRÉAL

UQÀM
Université du Québec à Montréal

FORMULAIRE DE CONSENTEMENT À VOTRE PARTICIPATION À UN PROJET DE RECHERCHE

TITRE DU PROJET: Étude des mouvements involontaires et volontaires chez les personnes ayant la maladie de Parkinson ou la maladie de Huntington

RESPONSABLE: Dr Christian Duval PhD, professeur en Kinanthropologie à l'Université du Québec à Montréal et chercheur à l'Institut Universitaire de Gériatrie de Montréal.

COLLABORATEURS: Dr Sylvain Chouinard, MD, Clinique des troubles du mouvement, Hôtel-Dieu, CHUM.

Dr Pierre Blanchet, MD, Clinique des troubles du mouvement, Hôtel-Dieu, CHUM.

OBJECTIF DU PROJET: Le but général de la recherche est de déterminer quel est l'impact de ces mouvements involontaires sur les mouvements volontaires des personnes atteintes de l'une ou l'autre de ces maladies.

Nous vous demandons de participer à un projet de recherche. Cependant, avant d'accepter de participer à ce projet de recherche, veuillez prendre le temps de lire, de comprendre et de considérer attentivement les renseignements qui suivent.

Ce formulaire de consentement peut vous explique le but de cette étude, les procédures, les avantages, les risques et inconvénients, de même que les personnes avec qui communiquer au besoin.

Le présent formulaire de consentement peut contenir des mots que vous ne comprenez pas. Nous vous invitons à poser toutes les questions que vous jugerez utiles.

LIEU DE VOTRE PARTICIPATION:

Votre participation à cette étude se déroulera au centre de recherche de l'institut universitaire de gériatrie de Montréal (4565, chemin Queen Mary, Montréal, Québec, H3W 1W5, Canada).

NATURE ET DURÉE DE VOTRE PARTICIPATION:

Votre participation se limitera à une seule visite, d'une durée d'environ trois heures au total. Premièrement, on installera des senseurs par-dessus vos vêtements à l'aide de bandes élastiques et de velcro. Par la suite il y aura une période de calibration des appareils qui durera environ 15 minutes. Après cette période de calibration, on vous demandera de faire trois tâches motrices; la première consistera simplement à vous tenir debout, les bras à l'horizontal en avant de vous, et ce pour 60 secondes. Durant celle-ci, on vous demandera de compter à rebours de 100 à 0, en soustrayant le nombre 7 à chaque fois. Le but de cet exercice est simplement de maintenir votre attention durant la tâche. La deuxième tâche consistera à tenir une balle de mousse dans chaque main, en position assise. Au signal de l'expérimentateur, vous ferez des mouvements de pronation/supination (comme tourner une poigné de porte), et ce le plus rapidement possible pendant 10 secondes. Finalement, la dernière tâche consistera à suivre une ligne située sur un écran devant vous avec une autre ligne que vous contrôlerez par des mouvements de pronation/supination. Cette tache aura une durée de 60 secondes.

Chacune des tâches mentionnées sera répétée trois fois, avec une pause d'une minute entre les tâches. Ces explications vous seront répétées durant l'expérimentation.

AVANTAGES POUVANT DECOULER DE VOTRE PARTICIPATION:

Votre participation à cette expérience vous offre la possibilité de contribuer à l'avancement des connaissances scientifiques en permettant d'étudier les effets des mouvements involontaires sur les mouvements volontaires dans la maladie de Huntington et Parkinson.

INCONVENIENTS PERSONNELS POUVANT DECOULER DE VOTRE PARTICIPATION:

Il n'y a aucun inconvénient direct pouvant découler de votre participation. Cependant, votre participation peut impliquer une perte de temps liée à mes déplacements et au nombre de séances prévues par la recherche. Assurer vous que vous comprenez également qu'il est possible que vous ressentiez un certain état de fatigue au cours de votre participation.

RISQUES POTENTIELS:

Il n'y a aucun risque connu associé aux appareils de mesures utilisés dans la présente étude. Le seul inconvénient possible serait de ressentir une certaine fatigue une fois l'expérimentation terminée. Afin de minimiser cette fatigue, nous prévoyons de nombreuses pauses durant l'expérimentation.

COMPENSATION MONETAIRE:

Aucune compensation monétaire n'est remise pour participer à l'étude. Cependant des frais de déplacement jusqu'à un maximum de $20.00 pourront être remboursés sur présentation de factures.

INFORMATIONS CONCERNANT LE PROJET:

On répondra aux questions que vous poserez à propos du projet de recherche auquel vous accepter de participer. La divulgation de ces informations ne concernera pas voss propres résultats individuels.

RETRAIT DE VOTRE PARTICIPATION :

Il est entendu que votre participation au projet de recherche décrit ci-dessus est tout à fait volontaire, et que vous êtes à tout moment libre de mettre fin à celle-ci sans avoir à motiver votre décision, ni à subir de préjudice de quelque nature que ce soit. Le retrait de votre participation n'affectera d'aucune façon les services ou les traitements ultérieurs qui vous seront offerts. A votre demande, les données vous concernant pourront être détruites.

ARRÊT DU PROJET PAR LE CHERCHEUR :

Votre participation au projet peut être interrompue si des circonstances particulières surviennent comme, par exemple, des problèmes de santé pouvant affecter votre performance.

AUTORISATION DE TRANSMETTRE LES RESULTATS :

J'autorise les personnes responsables de ce projet à transmettre les résultats de mon évaluation à mon médecin traitant si cela était pertinent : OUI ( ) NON ( )

Nom et adresse du médecin traitant : .....

.....

CONFIDENTIALITE :

Il est entendu que les observations effectuées en ce qui vous concerne, dans le cadre du projet de recherche décrit ci-dessus, demeureront strictement confidentielles. Votre dossier sera codé de façon à ce qu'il demeure confidentiel et gardé dans une filière sous clé, où seuls les responsables du projet y auront accès. Les données nominales (nom, adresse ou toute autre indication) seront conservées pendant 5 ans et détruites ou anonymisées à la fin de ce délai. Pendant ces 5 ans, les données nominales seront conservées dans un fichier à part des données scientifiques. En cas de présentation des résultats de cette recherche ou de publication dans des revues spécialisées, rien ne pourra permettre de vous identifier ou de vous retracer.

Une exception sera faite dans les cas où les données de recherche devraient être révisées par un comité de déontologie, le comité d'éthique de la recherche ou par les organismes qui subventionnent cette recherche. Les membres de ces comités sont tenus de respecter les exigences de confidentialité. En outre, un tribunal peut, par ordonnance, autoriser un tiers à consulter les données de recherche vous concernant.

SIGNATURES, précédées des noms écrits en lettres moulées :

Je déclare avoir lu et pris connaissance du projet, de la nature et de l'ampleur de ma participation, ainsi que des risques auxquels je m'expose tels qu'exprimés dans le présent formulaire.

_____ _____

Nom du participant Signature du participant

Fait à _____, le _____.

Je, soussigné(e) _____, certifie :

a) avoir expliqué au signataire intéressé les termes du présent formulaire;
b) avoir répondu aux questions qu'il m'a posées à cet égard;
c) lui avoir clairement indiqué qu'il reste à tout moment libre de mettre un terme à sa participation au projet de recherche décrit ci-dessus. »

_____ _____

Nom du chercheur ou de son représentant Signature du chercheur ou de son représentant

Fait à _____, le _____.

ACCÈS AUX CHERCHEURS :

Le responsable du projet, Dr Christian Duval, chercheur et professeur, peut être rejoint aux deux endroits suivants :

Centre de recherche de l'Institut universitaire de gériatrie de Montréal
4565, chemin Queen Mary, Montréal, Québec, H3W 1W5.
Tél. : (514) 340-3540.

Département de Kinanthropologie
Université du Québec à Montréal
Case postale 8888, succursale Centre-Ville
Montréal, Québec, H3C 3P8
Tél. : (514) 987-3000 poste 4440

EN CAS DE PLAINTE

Pour tout problème éthique concernant les conditions dans lesquelles se déroule votre participation à ce projet, vous pouvez, après en avoir discuté avec la personne responsable du projet si possible, faire part de vos préoccupations à la responsable des plaintes de l'Institut universitaire de gériatrie de Montréal à l'adresse suivante : Madame Denyse Marier, Commissaire locale à la qualité des services Institut universitaire de gériatrie de Montréal, 4565, chemin Queen Mary, Montréal, Québec H3W 1W5, téléphone (514) 340-3517.

INFORMATION SUR LA SURVEILLANCE ÉTHIQUE

Le comité d'éthique de la recherche de l'Institut universitaire de gériatrie de Montréal a approuvé ce projet de recherche et s'assure du respect des règles éthiques durant tout le déroulement de la recherche. Pour toute information, vous pouvez rejoindre le secrétariat du comité d'éthique de la recherche au (514) 340-1424 poste 3250.

ANNEX-7 CONSENT ENGLISH

CHUM

INSTITUT UNIVERSITAIRE DE GÉRIATRIE DE MONTRÉAL

UQÀM
Université du Québec à Montréal

Consent Form to Participate in Research

A. Introduction

I _____ being asked to participate in a research study involuntary movements in Parkinson's disease or Huntington's disease.

It is important that I read and understand the nature of this study, duration, number of visits, benefits and risks. I should discuss any questions that concern me with the study team. This research project is supervised by Christian Duval PhD, from the Department of Kinanthropologie at Université du Québec à Montréal. This research project is conducted in collaboration with Dr Michel Panisset MD, Sylvain Chouinard MD, and Dr Jean-Pierre Blanchet MD PhD. From the movement disorders clinic at the Hotel-Dieu Hospital (CHUM) The research team also include Alison Fenney, a Graduate student at the Université du Québec à Montréal.

B. Purpose

Patients with either Parkinson's disease or Huntington's disease may suffer from involuntary movements. We intend to determine the impact of these involuntary movements on your daily activities.

C. Procedures

Approximately 14 patients with Parkinson's disease and 14 patients with Huntington's disease showing involuntary movements will participate in this study. In addition, ten subjects free of neurological disease will participate (control group). The total duration of the experiment is approximately 3 hours, which includes the receptor placement, the calibration, the measurements and removal of sensors. I was explained that if I am in the one of the patient groups, I will be asked to maintain my normal medication schedule.

Then, the motor performance will be tested.

Movement evaluation

I was explained that small sensors are placed on my body, using elastic bands. Then a calibration of the equipment will be done.

I will perform three different tasks: (a) standing with arms stretched in front of me for 60 s. (b) I will be seated comfortably on a chair, elbows flexed to 90° For this experiment, I will be asked to pronate and supinate (like trying to open a door using the doorknob) as fast as possible for 10 s, or (c) to follow a target presented on a computer monitor for 30 s, using a ball attached to a angular measuring device.

I was explained that instructions will be presented to me on a projector screen so that I will always know the task to be performed. During this time, the position of my body will be monitored using the sensors that were placed on my body. I understand that all of the above procedures are done for this research study exclusively and are not part of my usual clinical assessment of symptoms for Parkinson's disease or Huntington's disease

D. Risks of participation

I was explained that there are no known risks associated with the devices used in the present experiment, except for some fatigue. However, I may ask questions related to the methodology, this at any time during the experiment.

E. Benefits of participation

I was explained that I will not have any immediate benefits from participating in this study. But, this study will greatly improve our understanding of the effect of dyskinesia on voluntary movements. My neurologist will have access to the results for consultation. If I am interested, I may ask for a copy of the publication that may ensue.

I understand that I am participating in this experiment on a strictly volunteer basis and I am free to withdraw at any time prior to or during the experimental session, without prejudice to me effect on my medical care.

I understand that all the information obtained during the course of this study is strictly confidential and will not be released to anyone, including my doctor, without my written consent to the researchers. However, this information may be used to advance the body of scientific knowledge and may therefore be published in scientific journals where my anonymity will be entirely preserved.

f. Compensation

No monetary compensation is given to participate in the study. However, traveling expenses will be reimbursed.

g. Questions

I am entirely free to ask any question that I believe is relevant. Any question about the project, complaints, or comments may be addressed to any of the investigators involved in this research project. In addition, I am invited to ask any type of additional explanations if I have any

doubts about my willingness to participate in this research project. The coordinates of the researcher responsible for this study listed at the end of this consent form.

I understand that this research project has received approval from the UQAM's Institutional Ethics Committee regarding research involving human subjects. For questions regarding the responsibility of UQAM's researchers involved in this project, or to file any complains that could not be addressed directly to the researchers, I may communicate with the President of the Ethics Committee, Dr. Joseph Josy Lévy. He can be reached at (514) 987-3000 # 4483 or through the secretarial office of the Ethics committee at 987-3000 # 7753.

I have read the information above and discussed it with the investigator to my satisfaction. In addition, I am satisfied of the explanations that I have received. I am aware of the risks involved in participating in these experiments outlined in this consent form. I consent to be a subject in the research project entitled "Study of voluntary and involuntary movements in Parkinson's disease and Huntington's disease"

Date: _____ , _____ , 2005
(Month) (Day)

Name: _____ Signature: _____
(Print)

Witness: _____ Signature: _____
(Print)

Coordinates:

Christian Duval, Ph.D.: Telephone number: (514) 987-3000 extension 4440
E-mail: duval.christian@uqam.ca

CIÉR at UQÀM: secrétariat du Comité : service de la recherche et de la création
Université du Québec à Montréal
C.P. 8888, succursale Centre-ville
Montréal, QC
H3C 3P8
Telephone number: (514) 987-3000 extension 7753
E-mail: src@uqam.ca

Département de kinanthropologie : Université du Québec à Montréal
Case postale 8888, succursale Centre-ville
Montréal (Québec) Canada
H3C 3P8

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