



uOttawa

L'Université canadienne
Canada's university

**FACULTÉ DES ÉTUDES SUPÉRIEURES
ET POSTDOCTORALES**



uOttawa
L'Université canadienne
Canada's university

**FACULTY OF GRADUATE AND
POSTDOCTORAL STUDIES**

Crystal Gonsalves

AUTEUR DE LA THÈSE / AUTHOR OF THESIS

M.Sc. (Human Kinetics)

GRADE / DEGREE

School of Human Kinetics

FACULTÉ, ÉCOLE, DÉPARTEMENT / FACULTY, SCHOOL, DEPARTMENT

Bimanual Coordination in Huntington's Disease and Parkinson's Disease

TITRE DE LA THÈSE / TITLE OF THESIS

Ramesh Balasubramaniam

DIRECTEUR (DIRECTRICE) DE LA THÈSE / THESIS SUPERVISOR

CO-DIRECTEUR (CO-DIRECTRICE) DE LA THÈSE / THESIS CO-SUPERVISOR

EXAMINATEURS (EXAMINATRICES) DE LA THÈSE / THESIS EXAMINERS

Martin Bilodeau

Nicole Paquet

Gary W. Slater

Le Doyen de la Faculté des études supérieures et postdoctorales / Dean of the Faculty of Graduate and Postdoctoral Studies

**BIMANUAL COORDINATION IN HUNTINGTON'S DISEASE AND
PARKINSON'S DISEASE**

By
Crystal Gonsalves B.Sc. Honours
University of Ottawa, 2008

THESIS

Submitted to the Faculty of Graduation and Postdoctoral Studies in partial fulfillment of
the requirements for the degree of Master's of Science in Human Kinetics

School of Human Kinetics
University of Ottawa



Library and
Archives Canada

Published Heritage
Branch

395 Wellington Street
Ottawa ON K1A 0N4
Canada

Bibliothèque et
Archives Canada

Direction du
Patrimoine de l'édition

395, rue Wellington
Ottawa ON K1A 0N4
Canada

Your file *Votre référence*

ISBN: 978-0-494-41663-1

Our file *Notre référence*

ISBN: 978-0-494-41663-1

NOTICE:

The author has granted a non-exclusive license allowing Library and Archives Canada to reproduce, publish, archive, preserve, conserve, communicate to the public by telecommunication or on the Internet, loan, distribute and sell theses worldwide, for commercial or non-commercial purposes, in microform, paper, electronic and/or any other formats.

The author retains copyright ownership and moral rights in this thesis. Neither the thesis nor substantial extracts from it may be printed or otherwise reproduced without the author's permission.

AVIS:

L'auteur a accordé une licence non exclusive permettant à la Bibliothèque et Archives Canada de reproduire, publier, archiver, sauvegarder, conserver, transmettre au public par télécommunication ou par l'Internet, prêter, distribuer et vendre des thèses partout dans le monde, à des fins commerciales ou autres, sur support microforme, papier, électronique et/ou autres formats.

L'auteur conserve la propriété du droit d'auteur et des droits moraux qui protègent cette thèse. Ni la thèse ni des extraits substantiels de celle-ci ne doivent être imprimés ou autrement reproduits sans son autorisation.

In compliance with the Canadian Privacy Act some supporting forms may have been removed from this thesis.

Conformément à la loi canadienne sur la protection de la vie privée, quelques formulaires secondaires ont été enlevés de cette thèse.

While these forms may be included in the document page count, their removal does not represent any loss of content from the thesis.

Bien que ces formulaires aient inclus dans la pagination, il n'y aura aucun contenu manquant.


Canada

Acknowledgements

I would like to acknowledge the many people who contributed their efforts throughout the course of this study. Through working with Dr. Ramesh Balasubramaniam I have been able to develop my skills as an independent learner and broaden my understanding of the complexity of the human brain. Being a member of the Sensorimotor Neurosciences Laboratory has provided me with invaluable experience and knowledge within the field of motor control. Additionally, I would like to thank Megan McTavish for creating the computer program used to analyze the data in the study. I would further like to thank the members of the laboratory who have continually provided help and support through discussion during the various phases of the project.

With the encouragement and support from my family and friends this project was made possible. I would like to especially thank my parents who have constantly been there for me through their love and guidance.

Special thanks to the Natural Sciences and Resources Council of Canada and the Canadian Foundation of Innovation for providing the necessary funding to perform the experiments.

This project would not have been possible without the collaboration of the Parkinson's disease society and Dr. David Grimes. Thank you for aiding with patient recruitment.

Lastly I would like to thank the Parkinson's disease and Huntington's disease patients for lending their time to the experiment. Without these individuals' participation and dedication to the study it would not be possible to examine potential rehabilitation techniques for future patients.

Abstract

Special populations that suffer from Parkinson's disease (PD) and Huntington's disease (HD) display poorer performance in movement and bimanual coordination tasks. Both PD and HD are basal ganglia disorders with neuropathology distinct from one another. The production of internally guided movements is disrupted in PD and HD, therefore utilization of the external pathway may be able to stabilize movements for these groups. The current study examines the effect of auditory cueing for these two populations in timing performance. A total of 10 PD patients, 10 healthy controls (matched for age and gender) and 2 HD patients were examined on a repetitive bimanual finger tapping task. PD patients and healthy controls were asked to perform finger tapping at two different frequencies (1.0 Hz, 2.0 Hz) and two movement types (in-phase, anti-phase). Additionally half of the trials were performed with an external cue (metronome beat), while the other half were not (cue was turned off after 10 metronome beats). Results showed that PD patients were able to effectively use the cue to facilitate bimanual coordination as it was shown that absolute mean timing errors were decreased during the *cue trials*. PD patients were able to perform both movement types although the more complex mirror asymmetrical anti-phase trials were more difficult to perform. HD patients were not able to achieve the designated fast and slow frequencies that PD and healthy controls performed. The HD patients' movement was highly variable due to tremors and involuntary tics experienced by the patients. Through the examination of raw trajectories and polar plots of phase differences it was concluded that the external cue did not seem to stabilize bimanual coordination for the HD patients.

Table of Contents

Chapter I.....	1
Introduction	1
Chapter II.....	5
Review of Literature.....	5
2.1 <i>Approaches in bimanual coordination</i>	5
2.2 <i>Neural Networks involved in bimanual coordination</i>	8
2.3 <i>Constraints in bimanual coordination</i>	9
2.4 <i>Performance of concurrent tasks</i>	11
2.5 <i>Movement related potentials</i>	12
2.6 <i>Force and phase relationships</i>	13
2.7 <i>External sensory cues</i>	14
2.7.1 <i>External sensory visual cues.</i>	14
2.7.2 <i>External perceptual auditory cues.</i>	15
2.7.3 <i>Gait timing and lower limb dynamics in HD.</i>	17
2.8 <i>The objectives</i>	17
Chapter III.....	19
Method	19
3.1 <i>Variables and Indicators</i>	19
3.2 <i>Participants</i>	19
3.3. <i>Procedure</i>	21
3.4 <i>Apparatus</i>	22
3.5 <i>Data Analysis</i>	22
Chapter IV.....	24
Results	24
4.1 <i>General Results</i>	24
Chapter V.....	56
Discussion	56
5.1 <i>Parkinson's Disease Patients</i>	56
5.2 <i>Mean Relative Phase and Standard Deviation of Relative Phase</i>	57
5.3 <i>Absolute mean timing error</i>	59
5.4 <i>Standard deviation of the timing error</i>	60
5.5 <i>The role of external cueing</i>	60
5.6 <i>Huntington's Disease</i>	61
5.7 <i>Huntington's Disease patient DM</i>	62
5.8 <i>Huntington's Disease Patient NN</i>	62
5.9 <i>Comparison of PD and HD</i>	63
5.11 <i>Limitations and future directions</i>	64
5.12 <i>Conclusion</i>	65
References	66
Appendix I: Ethics Certificate.....	69
Appendix II: Standardized Tests	72
Mini Mental State Examination	72
Unified Parkinson's Disease Rating Scale	74
Unified Huntington's Disease Rating Scale.....	80

Thesis: Bimanual Coordination in Huntington's and Parkinson's Disease

Chapter I

Introduction

The study of bimanual coordination examines the neuromotor processes that govern the movement of two limbs in a fixed coordinative relationship with one another (Gazzaniga, Ivry & Mangun, 2002). Distributed arrays of neural networks are engaged in bimanual coordination, making such tasks more complex than unimanual movements (Verbessem, Op't Eijnde, Swinnen, Vanheluwe & Dom, 2002). Bimanual coordination is present and essential in every day movement patterns. Acts of daily living such as walking, brushing ones' teeth and eating rely on bimanual coordination for successful performance.

Bimanual coordination brings two effectors together that are spatially and temporally coupled during the performance of a task. While bimanual tasks may seem rather easy for healthy individuals to perform, bimanual coordination has been shown to break down due to pathology, especially with damage to the basal ganglia. The basal ganglia are sub-cortical structures consisting of four nuclei: the caudate nucleus and the putamen (comprise the striatum), the substantia nigra and the globus pallidus. The basal ganglia serve as a relay system to the thalamus and other cortical regions inherent to functional movement (Gazzaniga, Ivry & Mangun, 2002). As a result, patient populations with certain movement disorders have repeatedly been shown to perform bimanual coordination tasks with difficulty (Brown, Jahanshani & Marsden, 1993; Franz & Ramachandran, 1998; Johnson et al, 2000). These include patient groups with Parkinson's disease (PD) and Huntington's disease (HD).

HD and PD are neurodegenerative conditions resulting in compromised output from the basal ganglia (Guberman, 1994). The internal segment of the globus pallidus (GPi) is one of the output layers of the basal ganglia and projects to many cortical areas. PD is idiopathic and is characterised by the degeneration of dopaminergic cells in the substantia nigra (Guberman, 1994). This results in a depletion of the amount of dopamine available to the striatum therefore causing motor deficits. In PD, the GPi is under-inhibited by the striatum due to the lowered dopamine conditions causing an increased inhibition to the ventrolateral thalamus. The ventrolateral thalamus is a relay that takes information from the cerebellum (information about the current state of the effectors) and passes it to the cortex. The ventrolateral thalamus' signal is reduced in PD making it more difficult for the cortex to identify whether an assigned task has been completed. HD is an autosomal dominant disorder caused by a genetic defect of the IT-15 gene resulting in an abnormal number of CAG repeats. In HD, the putamen's inhibitory gamma butyric acid neurons or the putamen's projection to the substantia nigra pars compacta is destroyed (Guberman, 1994). This destruction results in motor deficits causing HD patients to produce random and frequent motion.

HD and PD populations have been examined in multiple, although usually separate, clinical studies. There has been a limited amount of research comparing these two groups (Johnson et al, 2000). Research regarding phase relationships in bimanual movements [e.g. in-phase (0° phase difference between two effectors) and in-phase (180° phase difference between two effectors)] in HD and PD has revealed that patients are slower, more variable and less accurate than healthy controls (Johnson et al, 1998; Johnson et al, 2000). Successful execution of bimanual movements is imperative as they

are required in everyday movement patterns. Investigating bimanual movement tasks in HD and PD patients is central to the study of these populations. Additionally, difficulties in movement initiation and execution are present in both diseases (Hefter, Homberg, Lange & Freund, 1987).

Many phase relationships are possible within bimanual coordination. It has been shown that the stability of movement is dependent on the relative phase position that is produced (Swinen, 2002). The most stable coordination mode is in-phase pattern which consists of a 0° phase difference between the two limbs. The anti-phase pattern is the second most stable relationship and is characterised by a 180° phase difference between the two limbs. The Haken Kelso Bunz (HKB) model of coordination defines movement patterns by their potential function (V). The model formulates that $V(= -a\cos(\phi) - b\cos(2\phi))$. When the ratio of b/a changes different modes of stability are achieved.

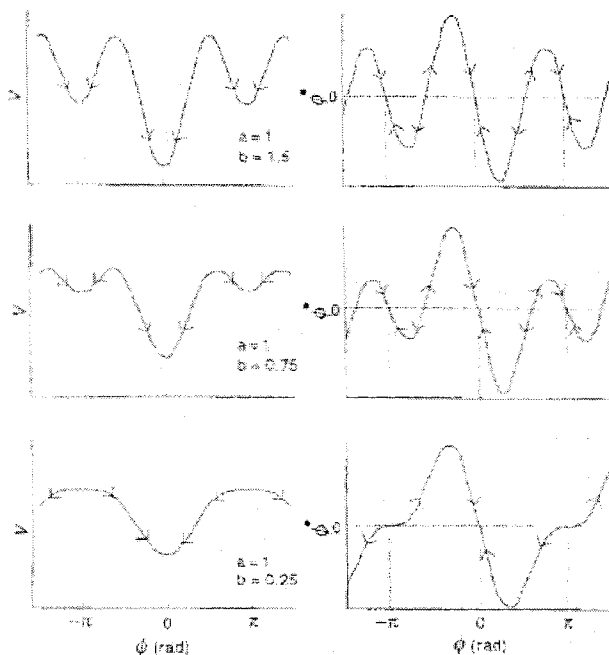


Figure 1. Potential functions as described by the HKB-Model. The deeper the valley indicates a more stable pattern. Adapted from Amazeen, Amazeen, & Turvey, 1998.

External perceptual cues (such as a metronome beat) have been shown to improve bimanual coordination performance in PD patients (Johnson, Cunnington, Bradshaw, Phillips, & Ianssek, 1998). The use of external auditory cues for the upper limbs has only been examined once in HD patients and the cue did not improve coordination patterns (Johnson et al, 2000). The extent to which external cues can aid in coordination patterns has not been examined extensively in HD. The current study looks at the possible role of external cueing in a simple repetitive bimanual experiment in HD and PD populations.

Information will be presented on research conducted in the field of bimanual coordination in HD and PD patients. The neuropathophysiology of both movement disorders will also be provided within the literature review. Bridging the information gaps in these areas of bimanual coordination is necessary for the development of meaningful rehabilitation techniques given the current lack of cure in either disorder.

The task of this thesis is to provide information in the field of motor neuroscience specific to bimanual coordination and the role of external cues for HD and PD patient populations. Specifically, this study examines bimanual coordination patterns through a repetitive tapping experiment to provide information on the fundamental brain mechanisms involved in HD and PD patients. The study also examines the variability and stability of coordinated movement for in-phase and anti-phase movement types through the analysis of relative phase positions, peak velocities, movement time and timing errors.

Chapter II

Review of Literature

2.1 Approaches in bimanual coordination

Many different theoretical approaches exist which aim to describe the underlying principles which regulate bimanual coordination patterns in the brain. A description of these approaches is necessary in order to understand the different scientific views. The four approaches which will be discussed include the generalized motor program (GMP), intermanual crosstalk, dynamical systems and the perceptual basis for coordination. Individual consideration of each approach poses limitations; however, a combination of the approaches may lead to a more comprehensive understanding of the neurological processes involved in the coordination of limbs.

According to the GMP model, a motor program specifying the shape of the movement is produced prior to the execution of the movement (Cardoso de Oliveira, 2002). The GMP model views the regulation of movement in a very broad manner. With regards to bimanual movement types, the degrees of freedom may be reduced since both limbs follow a common motor program (Cardoso de Oliveira, 2002). Furthermore, within this approach, temporal and force parameters must be considered and need to be specified during the coordination of different limbs. Spatiotemporal parameters are discussed within the GMP, but behavioural properties are not fully described. Therefore, although the GMP model may allow for the production of efficient movements (through the decrease in degrees of freedom) many issues are left unresolved such as assimilation and coupling of movements (Cardoso de Oliveria, 2002).

The model of intermanual crosstalk assumes that neural information can be transferred during the initiation and execution of movements; this can occur at various levels of the central nervous system (CNS) (Swinnen & Wenderoth, 2004). The intermanual crosstalk model differs from the GMP as it is a multi-level cross talk model (Cardoso de Olivera, 2002). The theory suggests that two levels of crosstalk are present. The lowest level of crosstalk exists through the interactions of the ipsilateral corticospinal tract. Most movements are regulated by the contralateral hemisphere of the effector; however, ten percent of the corticospinal fibers at the pyramidal decussation are uncrossed, suggesting that a minor interference occurs between ipsilateral and contralateral pathways (Cardoso de Olivera, 2002). Additionally, a higher level of crosstalk occurs between the two hemispheres of the brain. Specifically, in bimanual coordination tasks, the corpus callosum serves as the neural pathway for information exchange between the hemispheres of the brain (Swinnen, 2002). In order to perform bimanual movements successfully, the individual needs to overcome the neural interferences that result from intermanual crosstalk (Swinnen & Wenderoth, 2004). Research on callosotomy patients and patients with agenesis of the corpus callosum have shown that these populations are able to reproduce shapes with different orientation more effectively than shapes with similar orientations; a characteristic which is not observed in healthy controls (Swinnen, 2002; Swinnen & Wenderoth, 2004).

The dynamical systems approach theorizes that the behaviour of biological substrates is based upon the time dependent changes that are present (Swinnen & Wenderoth, 2004). Extensive research on phase relationships in movement has concluded that two coordination patterns exist as the most stable; in-phase and anti-phase

(Swinnen, 2002). In-phase movements (0°) simultaneously activate homologous muscles whereas anti-phase movements activate homologous muscles sequentially (180°). The in-phase movement is credited as the most stable pattern. Under speed stress PD patient research has found that the in-phase movement remains stable, however this is not true for the anti-phase condition (Almeida, Wishart & Lee, 2002). This may be due to a common motor pattern the limbs follow as discussed in the GMP model. It is possible to perform other phase relationships (e.g. 90°); this can be achieved through practice (Amazeen, Amazeen, & Turvey, 1998). Experiments using healthy control subjects have revealed that during anti-phase movements, increasing the oscillation frequency will produce a clear transition into the in-phase movement (Kelso, 1985 in Amazeen et al, 1998). Studies have concluded that the anti-phase movement is harder for PD and HD patients to perform (Johnson et al, 1998; Johnson et al, 2000). In-phase and anti-phase movements are produced in everyday living. This becomes relevant to rehabilitation techniques for HD and PD patients since tasks such as walking involve anti-phase movement patterns, and this pattern has been established as more complex for these populations.

An alternate version of the traditional dynamical systems approach for bimanual coordination has emerged. A perceptual basis for bimanual coordination states that coordination does not arise from motor neuron structures but from perceptually guided actions (Mechsner, Kerzel, Knoblich & Prinz, 2001). Mechsner et al (2001), constructed a bimanual crank test where subjects circled a flag in either in-phase or anti-phase conditions. The hands of the participants were hidden under a table while they circled two visible flags. With a gear system, the right flag circled in a 4:3 frequency.

According to previous research, the 4:3 frequency pattern is near to impossible to perform for novel subjects. It was found that the subjects in this experiment were able to perform the polyrhythmic frequency. Therefore, the successful performance of the task must be attributed to visual strategies employed by the subjects and not only motor neuronal structures as previously thought (Mechsner et al, 2000).

2.2 Neural Networks involved in bimanual coordination

The supplementary motor area (SMA) is an important structure to consider while examining bimanual coordination movements. In the past, the SMA was viewed as the only region responsible in bimanual coordination, however, lesion study research has proved that other areas are involved (Swinnen, 2002). The SMA plays a role in unilateral tasks which involve movement sequencing as well as internal pacing. PD groups have been found to exhibit an underactive SMA and output to the SMA is compromised in HD groups leading to decreased actions in internally paced tasks. It is now known that bimanual coordination involves many areas in the brain including the cerebellum, premotor cortex (PM), corpus callosum and the cingulated motor cortex (CMC) (Swinnen & Wenderoth, 2004). Coordination problems arise in patients with HD and PD as they have difficulties with internal cueing due to their respective pathoneurophysiology. The pathways which are involved in internal cueing are the basal ganglia, the SMA and the CMC (Swinnen & Wenderoth, 2004). Pathways involved in external cueing are the superior parietal cortex, PM, thalamus and lobe VI of the cerebellum (Swinnen & Wenderoth, 2004). The use of external cues is important for HD and PD patients since internal cueing is compromised. Through the utilization of external pathways movement productions in HD and PD may be improved.

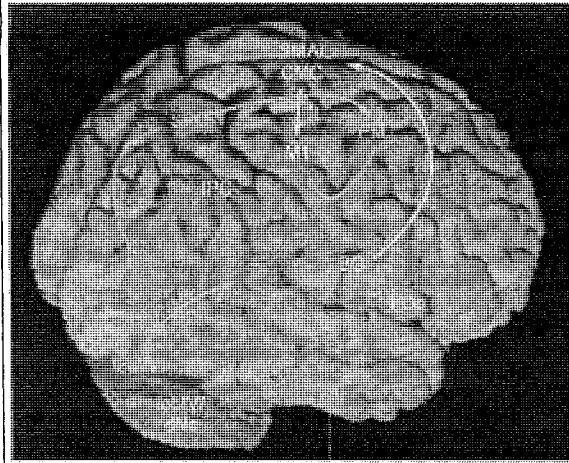


Figure 2. Internal and external pathways in the brain. The internal loop is shown in lighter shade. Adapted from Swinnen and Wenderoth, 2004

2.3 Constraints in bimanual coordination

There are a variety of factors which contribute to the stabilization and destabilization of symmetry. According to Von Holst, a maintenance tendency as well as a magnet effect exists during the coordination of movement (Amazeen, 1998). Von Holst used these terms to explain the movements of the Labrus fish and he was one of the pioneers in the study of coordination patterns. Upon observation of the Labrus, Von Holst concluded that each fin preferred to oscillate at its own frequency (this is termed the maintenance effect), however, while swimming, the fins oscillated at a common frequency (this is termed the magnet effect). Therefore coordination is regulated by the competition and cooperation of limbs (Amazeen, 1998). Competition can be introduced in a system through physical differences, or different levels of synergies that are present in the coordination of movement (Amazeen, 1998).

Within movement, numerous constraints are present and consequently coordination is produced more effectively when constraints act in accordance with one another (Swinnen & Wenderoth, 2004). Spatiotemporal constraints have shown that

effectors favour movement in synchrony. Also, simple rhythms (e.g. 1:1 or 2:1) are better produced than polyrhythms (e.g. 3:2 or 5:3) (Swinnen & Wenderoth, 2004), (however, recall the Meschner et al (2001), experiment, using perceptual cues). Similar to phase transitions observed from anti-phase to in-phase movements, polyrhythms are degraded to simple rhythms upon increasing frequencies. Additionally, the use of external cues has been used to aid the regulation of movement. Finger tapping with a metronome has revealed its ability to stabilize movement patterns when haptic contacts are present and coincide with the metronome beat (Swinnen & Wenderoth, 2004). Moreover, the use of sensory feedback is an important strategy to employ during the rehabilitation of different populations. Sensory techniques such as auditory pacing has been shown to improve movements in individuals with Down syndrome (Carson & Swinnen, 2002) and PD (Johnson et al, 1998) while older individuals benefit from augmented visual feedback (Carson & Swinnen, 2002)

Spatial constraints were investigated in phantom limb amputees (Franz & Ramachandran, 1998). Patients with phantom limb syndrome are able to move their phantom limb in a volitional manner even though the limb has been amputated. Comparisons between control subjects, amputees and amputees with phantom limb syndrome were made using a bimanual coordination task. Control patients also engaged in an imagery condition where bimanual movements were made with one limb while imagining the movement of the second limb. In-phase and anti-phase movement types were produced in the experiment. Results concluded that spatial coupling was present for phantom limb patients and controls (however, not for the imagery condition). These findings indicate that coupling arises from the individual's personal experience of their

production of movement since coupling was not observed in the imagery condition. The neural mechanisms of spatial coupling in healthy controls somehow remain intact for phantom limb patients.

Interhemispheric constraints exist, and can be examined through callosotomy patient research. Franz and colleagues (2000), conducted a study where callosotomy patients and healthy control subjects performed a variety of bimanual and unimanual tasks. The tasks were divided into familiar and novel pantomime gestures. Interestingly, the study found that for tasks requiring the same movement pattern, (pretending to thread a needle versus pretending to hook a fishing line) subjects could only perform the bimanual action if the task was familiar. This finding was in accordance with the hypothesis that the corpus callosum is involved in the learning process of new tasks. Therefore, it seems that well learned tasks are engrained in the brain and do not require an intact corpus callosum for successful performance (Franz, Waldie & Smith, 2000).

2.4 Performance of concurrent tasks

Concurrent tasks are performed in every day activities. The execution of simultaneous tasks may be effortless for healthy controls, but they are performed with greater difficulty for PD and HD patients. Bimanual movements in patients with PD, HD and cerebellar disease were studied while performing a pegboard purdue task and finger tapping task (Brown, Jahanshani & Marsden, 1993). The pegboard Purdue task consisted of placing a series of pegs in a vertical row of holes as fast as possible over 30 seconds, whereas the finger tapping task involved patients tapping a button as fast as possible over the same time period. When both tasks were combined, performance in tapping was found to deteriorate while the pegboard task was slightly improved indicating that there

was a possible trade-off between the attentional resources of the two tasks (Brown et al, 1993). Additionally, Georgiou, Phillips, Bradshaw, Cunnington & Chiu (1997) studied the movements of HD patients with and without a concurrent task. Participants completed a series of 12 vertical zig-zag patterns. Movements were made either to small or larger targets with either small or large distances between each target. The concurrent task consisted of recalling a five digit sequence while completing the 12 vertical movements. For the HD group, movement time of the right hand in the concurrent task was shown to deteriorate while it improved for the left hand. Possible reasons for the decline in performance for the right hand are due to the digit recall task i.e. a verbal task. The verbal task may have involved a higher degree of activation of the left hemisphere causing the performance of the right hand to decrease more so than the left hand.

2.5 Movement related potentials

The preparation and execution of movement patterns are impaired in HD and PD patients due to their respective pathoneurophysiology. Examination of movement related potentials (MRPs) can allow for the observation of changes in cortical activity in the preparation and execution of movement. Johnson, Cunnington, Iansek, Bradshaw, Georgiou and Chiu (2001) studied MRPs in HD using a sequential finger tapping button pressing task. The same paradigm was originally used to investigate MRPs in PD patients (Cunnington, Ianswek, Johnson & Bradshaw, 1997). A series of ten buttons were illuminated and subsequently extinguished at a rate of four seconds while subjects were either asked to perform the movement (sequentially depress each button till it extinguished), imagine the movement or watch the lights. Watching the lights served as the control group since it is believed that eye movements do not cause MRPs (Johnson et

al, 2001). Calculations for the execution component were made by subtracting the MRPs found in the imagined movement from the MRPs for performed movement. Similarly, the preparation component was calculated by subtracting the MRPs for the watching task from the imagined task. Johnson et al (2001) found that MRPs were reduced in HD patients for both the imagined and performed tasks, therefore cortical activation was reduced in this group. Interestingly, for the execution component significant differences were not found in peak amplitude and early slope of the movement. The results of this experiment are similar to those of the PD patients in the Cunnington et al study (1997). Cortical activity from the SMA is one component in MRPs. Therefore compromised output to this area in HD and PD may be attributed to the reductions in MRPs as compared to healthy control subjects.

2.6 Force and phase relationships

In object manipulation, response planning is needed to regulate grip force and object loss can occur if an inappropriate grip force is used. The control of grip force in coordination tasks has been studied in HD patients (Serrien, Burgunder & Wiesendanger, 2002). In the study, patients were asked to hold an object in a precision grip and move in either an in-phase or anti-phase movement. In healthy control subjects, grip force and load force are coupled to prevent object loss. For the HD patients in this study, grip force and load force were disproportionate to one another which led to increases in object loss. Additionally, it was found that HD patients were more variable during the anti-phase bimanual precision grip task as compared to the in-phase task. HD patients were also more variable than healthy control subjects. Difficulties in maintaining phase relationships for HD patients will be discussed further in the next section (studies

conducted by Verbessem et al 2002; Johnson et al, 2000) and the results are similar to this experiment. In HD, cerebral cortex atrophy increases with disease duration and severity. Atrophy of the frontal lobe can lead to impairments in planning, poorer results in motor tasks and deficits in maintaining attention.

2.7 External sensory cues

2.7.1 External sensory visual cues. Visual information has been used as a means to aid in the stabilization of movement. It is known that populations with PD and HD exhibit specific deficits within movement initiation and execution. The use of visual guidance may improve performance within these patient groups. Research on the reliance of advance visual information in HD has been examined (Georgiou, Bradshaw, Phillips, Chiu & Bradshaw, 1995). In this particular study, participants were asked to perform a series of ten button presses on a response board. While performing the task, visual information was either maintained, moderately reduced (when the current button was pressed, the next button was extinguished) or highly reduced (when the current button was pressed the next two buttons were extinguished) (Georgiou et al, 1995). Upon analysis it was found that movement time and button down time (button down time measures the preparation time for the movement) was significantly higher in the moderately and highly reduced conditions for the HD patients. The results suggest that as visual information is decreased, HD patients require more time to plan their movements as compared to healthy controls. The error rate was also increased for the patients during the highly reduced task demonstrating that movements are less effective when external cueing is diminished. Additionally the use of invalid and valid visual movement precues was explored in PD patients (Leis, Rand, Van Gemmert, Longstall,

Lou & Stelmach, 2005). When PD patients were given an invalid precue to a movement target, performance of reaction time, movement time and peak velocities worsened. However, the reaction times of the PD patients were not significantly different than elderly control subjects. This finding suggests that motor planning in PD is preserved while movement execution impaired (Leis et al., 2005).

2.7.2 External perceptual auditory cues. Bimanual coordination in HD using a bimanual crank apparatus was examined by Johnson et al, (2000). Participants performed bimanual rotary movements in-phase, anti-phase, at fast and speeds and with and without and external cue (metronome). Results concluded that HD patients were able to perform the in-phase movement task although the patient group was significantly more variable and less accurate during the fast condition. Additionally, in this study the HD patients could not perform the anti-phase coordination pattern. Deterioration of the anti-phase movement may be due to compromised function of the SMA. Upon examination of HD patients groups, no spontaneous transition from anti-phase to in-phase was found as the patients did not allocate their time in one particular phase type (Johnson et al, 2000). The symmetrical in-phase movement may be easier to execute since it is a simpler task and a common motor program may be used for both hands while performing the action. However, in a study by Verbessem et al. (2002), HD patients were able to perform the anti-phase bimanual movement. The movements produced by the HD patients were slower and more variable than healthy controls. The study suggests that patients were able to perform the anti-phase task since the experiment did not involve a multi-joint task, therefore the task was simpler than the one employed in the Johnson et al. (2000) study.

In the study by Johnson et al. (2000), the use of an external cue had no effect on the HD group. This was the first study to use external cues for the upper limbs in HD patients. The experimental paradigm used in this study was previously used to investigate bimanual coordination in PD patients (Johnson et al, 1998). In the latter study, external cues improved the accuracy and the stability of in-phase movements. PD patients could not perform the anti-phase movement task at either speed, however, the incorporation of the external cues allowed the patients to revert to the more stable in-phase motion. These findings illustrate the role of the basal ganglia in internally guided movements. Since external cueing benefited the PD group, these types of cues should be incorporated into rehabilitative strategies for this population. The HD patients may have been only able to focus on the primary task in the Johnson study (2000). It is likely that cueing did not improve HD performances due to deficits in attentional capacity. However, although external auditory cues have been shown to stabilize the performance for PD patients there have been conflicting results. Almeida, Wishart and Lee (2002) examined the effect of auditory cueing in PD at different movement speeds. Subjects were asked to produce continuous bimanual in-phase and anti-phase tasks. In addition to auditory cues, visual information was provided by real time Lissajous figures. The study found that the external cues did not benefit the PD patients. In Johnson et al study (1998) the cues were able to stabilize the in-phase condition, this was not observed in the Wishart study (2002). Moreover, in the Johnson et al study (1998), movement speeds were 0.5 Hz and 1.5 Hz whereas in the Wishart study (2002) movement speed increased from 0.75 to 1.25 and 1.75 Hz. Perhaps the use of external cues is not beneficial for complex continuous tasks for PD patients under speed stress. In the experiment, freezing and hypometria

were monitored and were only present in the anti-phase condition (8.1% and 5.1% respectively) which is also a novel finding for tasks of the upper limbs.

2.7.3 Gait timing and lower limb dynamics in HD. The ability of external auditory cues to stabilize lower limb movement for HD patients has been investigated. Upon observation, it is evident that HD patients have difficulties with gait patterns. Synchronization errors are present with external cueing, suggesting that HD patients may have a central timing disorder that may not be present in PD (Bilney et al, 2005). Bilney and colleagues (2005) examined gait timing in HD to a metronome beat of 80 and 120 beats per minute. Achieving walking patterns similar to healthy controls was difficult for the HD patients as reductions of step cadence and step length were present. The influence of an external cue showed that HD patients encountered problems with synchronizing their feet to the metronome beat. It was concluded that gait training techniques were imperative for HD patients as patients could alter their step performance when an external cue was present, however, the timing of the movement was still inaccurate. The inability to alter the step cadence to the external cue was also found in a study by Thaut, Miltner, Lange and Hoemberg. (1999), reinforcing the idea that a central timing disorder is present which may be causing deficits in the perception of time intervals.

2.8 The objectives

The *overall objective* of this experiment is to gain further insight into how bimanual coordination of movement is affected in two populations with basal ganglia damage, specifically HD and PD.

The *specific objectives* are:

1. To test *Hypothesis 1*: HD and PD groups will be more variable than the healthy controls while performing the bimanual tasks.

2. To test *Hypothesis 2*: An external auditory cue will facilitate the performance of the bimanual tasks for the PD and healthy control groups but have no effect on the HD group.

Chapter III

Method

3.1 Variables and Indicators

The stability and variability of bimanual coordination was analyzed in the presence and absence of an external metronome. Specifically, the dependent variables that were analyzed were mean relative phase (degrees) standard deviation of the relative phase angle (degrees), mean timing error (seconds) and standard deviation of the timing error (seconds) for the right and left fingers.

The mean relative phase depicts the accuracy of the coordination pattern produced by the fingers over time. The relative phase variability measures the variability in the coordination pattern. Absolute mean timing errors for the fingers measures the accuracy of the fingers tapping on the beat of the metronome while the standard deviation of the timing error for the fingers measures the variability.

Calculations for the mean timing errors were found by using impact times for the fingers and the metronome beat. The impact was measured from the time the finger tapped on the surface of the table and timing errors were calculated based on the difference between finger impact and the discharge of the metronome beat.

Relative phase was calculated using the Hilbert transform as described in the paper by Rosenblum and Kurths (1998).

3.2 Participants

Parkinson's Disease Patients

Eight male and two female patients with PD were tested. The participants' ages ranged from 56 to 85 years old with a mean age of 66.6 years. Duration of disease

ranged from 1 to 13 years with an average of 6.5 years. Prior to the experimental test, the Mini-Mental State Examination (MMSE) was given to ensure that participants were cognitively capable of performing the task. Mean scores on the test were 28.7/30. Motor impairments were assessed using the motor subscale of the Unified Parkinson's Disease Rating Scale (UPDRS). The mean values for the for PD patients was 22.9. Nine out of ten PD patients were taking medication to manage their Parkinsonian symptoms. All of the patients were testing during the "on" phase of their medication cycle.

Table 1 Clinical data for Parkinson's disease patients

Age (years)	Sex	MMSE	Duration of disease (years)	UPDRS motor subscale score	Medication	Side of disease onset
67	M	28	7	18	Sinemet CR Mirapex	right
60	M	27	10	14	Apo-levocarb Amantadine	right
75	M	28	13	52	Sinemet CR Sinemet CR Comtan	left
64	M	29	8	27	GenAmantadine Synthroid Eltroxin Apo-levocarb Sinemet CR	right
63	M	29	1	8	No medication	left
66	F	29	1	8	Mirapex	left
56	M	30	8	20	Mirapex	left
85	F	30	6	29	Carbolevodopa Apo-levocarb	left
64	M	29	3	25	Sinemet CR	right
66	M	28	5	28	Mirapex Sinemet CR	right

Healthy Controls

Healthy controls were matched for age and gender (eight male and two female healthy controls). Control subjects ages ranged from 52-82 years of age with a mean of 63.4 years. MMSE scores for control subjects was 29.6/30.

Huntington's Disease patients

Two HD patients participated in the study and that data for these patients were looked at separately. Patient DM was a 46 year old man who had been diagnosed with HD 4 years prior to the experimental session. DM scored a 28/30 on the MMSE and a 14 on the UHDRS. Patient NN was a 44 year old woman who had been diagnosed with HD 2 years prior to the experimental session. NN scored a 29/30 on the MMSE and a 25 on the UHDRS.

3.3. Procedure

Participants sat in a non-rotating chair in front of a table and were asked to perform the bimanual finger tapping experiment. A small reflective marker with tape was placed on the index fingers of the participants prior to the experiment. Participants were required to engage in eight different movement conditions including two movement types (bimanual in-phase and anti-phase). Finger tapping was performed on the surface of a table, with and without an external cue (metronome) and at a fast (2.0 Hz) and slow speed (1.0 Hz). During the trials with the external cue, the metronome stayed on for the entire length of the experiment. Participants were asked to perform one finger tapping cycle per metronome beat. The experiment consisted of 5 trials per condition lasting 30 seconds.

At the start of each condition instructions were given and the task was demonstrated by the experimenter. The participants engaged in a practice session before the experiment.

To diminish the incidence of muscle fatigue participants were given breaks between each trial block and were also told that they could elect to take a break during any point of the experiment.

3.4 Apparatus

The experiments were performed in the Sensorimotor Neuroscience Laboratory located at the University of Ottawa (MNT 320). The laboratory houses a VICON™ MX-40 system which records kinematic data at 200Hz. The VICON™ system captured the movement data from the reflective markers placed on the index fingers of the participants during the bimanual finger tapping experiment. A software generated auditory metronome produced a 1k Hz tone for 20ms to provide a periodic external movement cue.

3.5 Data Analysis

The 3-D kinematic data that was recorded from the two index finger markers was stored onto a conventional PC for reduction and analysis in MATLAB®. Variability and stability of movements were analyzed through the relative phase positions and timing errors. This information was extracted from the data and analyzed using MATLAB® and statistical packages.

A $3 \times 2 \times 2 \times 2$ [group (PD patients, healthy controls) x frequency (1.0 Hz, 2.0 Hz) x cue (cue, no-cue) x 2 movement type (in-phase, anti-phase)] mixed ANOVA with

repeated measures on the last three factors was performed on the dependent variables: mean relative phase, standard deviation of relative phase, absolute mean timing error of the right and left finger, and standard deviation of the timing error of the right and left finger. A paired samples t-test was performed on cue, frequency and side of disease onset. Significant main effect for the factors and interactions were reported at $\alpha=0.05$. The statistical analyses were done using SPSS software (SPSS for Windows Version 12.0, SPSS Inc.)

Chapter IV

Results

4.1 General Results

One of the predictions of this study was that the PD patients would be more variable and slower than healthy controls while performing the bimanual coordination task. Additionally, it was hypothesized that the external auditory cue (metronome) would stabilize the movement of the PD and Healthy controls (i.e. cue is more stable than the no cue condition). To assess the stability and variability of the bimanual movements, six different variables were measured. These variables were mean relative phase angle, standard deviation of the relative phase angle, absolute mean timing error of the left and right fingers and the standard deviation of the timing error for the left and right fingers.

All participants were able to successfully complete the bimanual coordination task however the variability among the groups while performing the tasks differed.

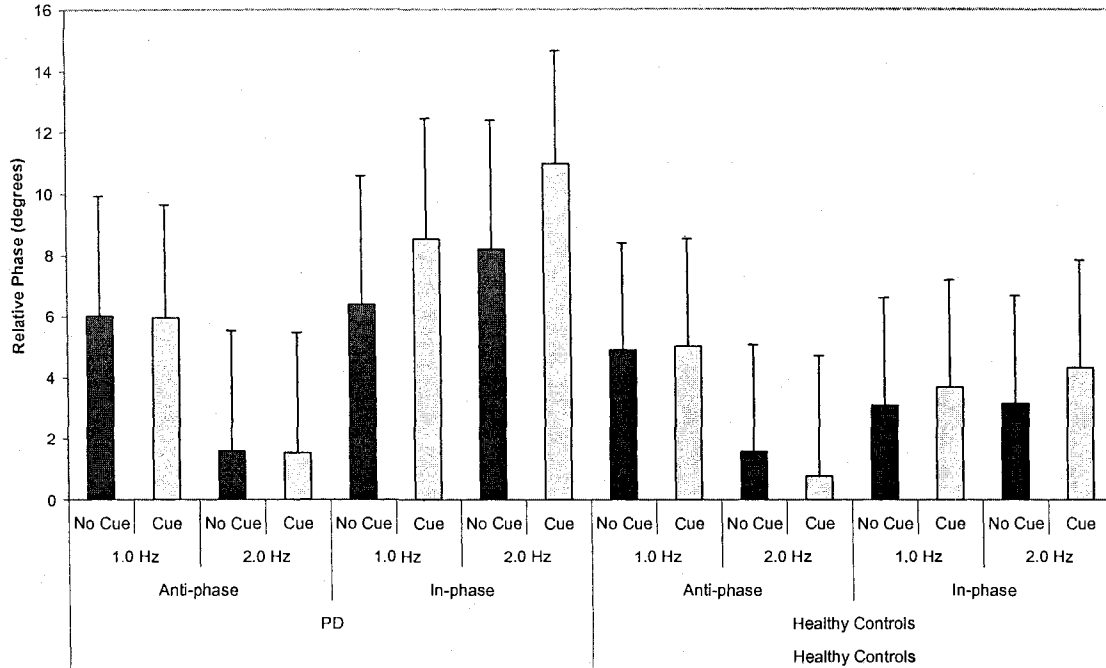


Figure 1. Deviation from Intended Relative Phase across all conditions for PD and Healthy Controls. Intended relative phase for the anti-phase condition was computed by subtracting the mean relative phase from 180 degrees.

Figure 1 shows the mean relative phase across all conditions for PD and healthy controls. Mean values for the anti-phase movement was computed by subtracting the intended phase from 180 degrees. The general pattern of results indicates that the presence of a cue does not seem to affect the relative phase pattern produced by the fingers for the coordination task across all subjects. No main effects or significant interactions were found.

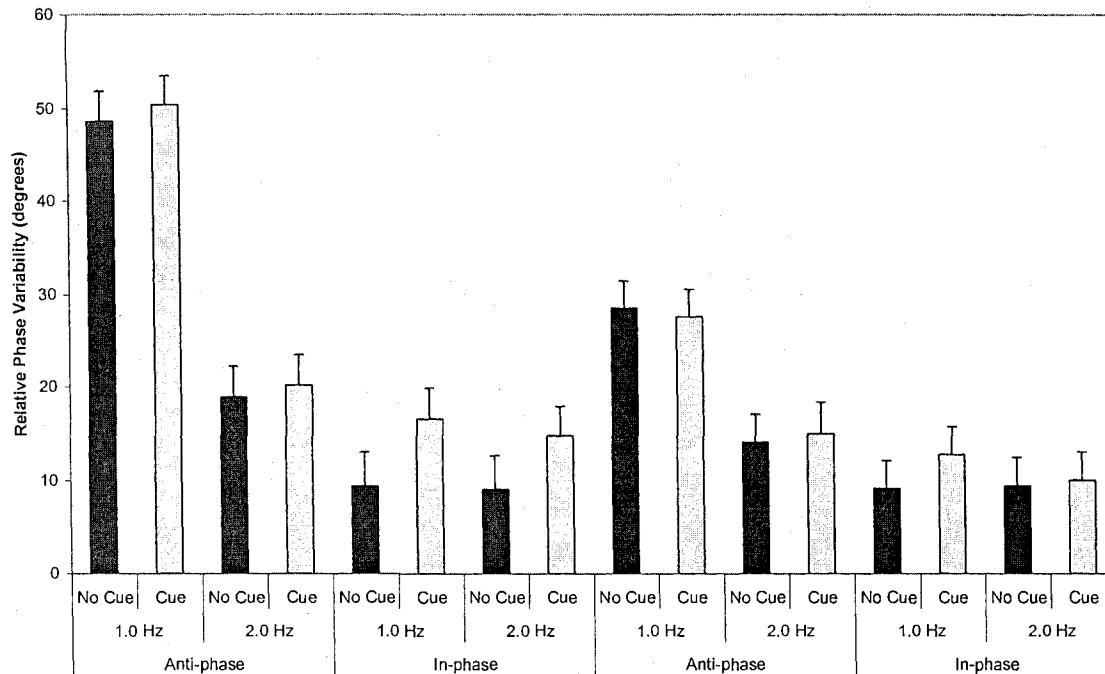


Figure 2. Standard Deviation of Relative Phase in PD and Healthy Controls

Figure 2 depicts the standard deviation of relative phase variability across all conditions. The general trend shows that the standard deviation of the relative phase was not affected by the cue/no cue condition. A main effect of group, [$F(1, 20) = 21.975, p < 0.05$] (See Figure 2a), frequency [$F(1, 20) = 49.265, p < 0.05$] (See Figure 2b) and movement type [$F(1, 20) = 103.254, p < 0.05$] (See Figure 2c) was found. A two way interaction between group x frequency [$F(1, 20) = 6.496, p < 0.05$] (See figure 2a); group x movement type [$F(1, 20) = 11.771, p < 0.05$] (See Figure 2a); frequency x movement type [$F(1, 20) = 40.347, p < 0.05$] was found (See Figure 2b). A significant three way interaction between group x frequency x movement type [$F(1, 20) = 6.569, p < 0.05$] was found (See Figure 2c).

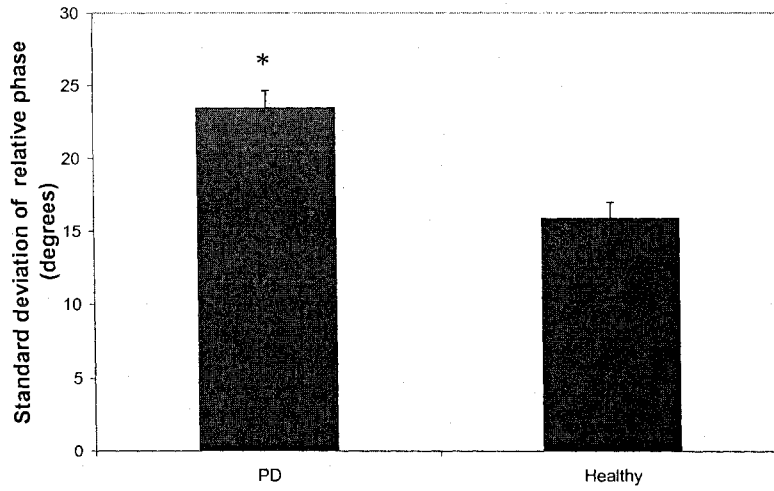


Figure 2a. The main effect of group on the standard relative phase variability in a bimanual task

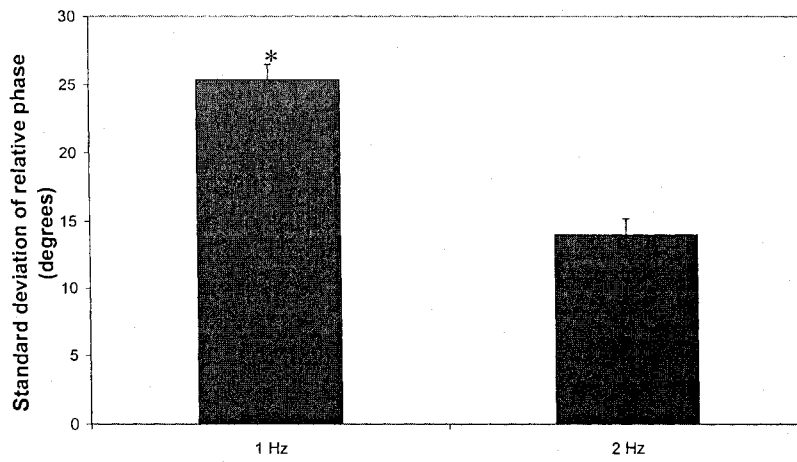


Figure 2b. The main effect of frequency on the standard relative phase variability in a bimanual task

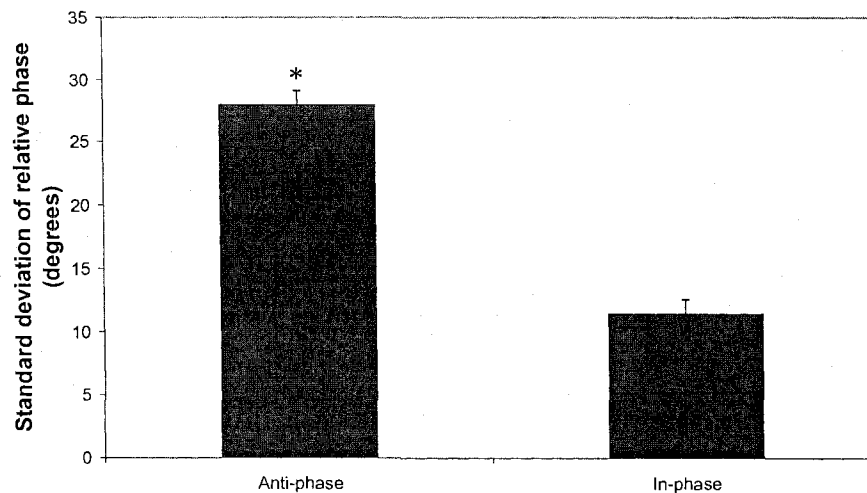


Figure 2c. The main effect of movement type on the standard relative phase variability in a bimanual task

Figures 2a, 2b and 2c depict the main interaction effects of group [$F(1, 20) = 21.975$, $p < 0.05$], movement type [$F(1, 20) = 103.254$, $p < 0.05$] and frequency [$F(1, 20) = 49.265$, $p < 0.05$] on the standard deviation of the relative phase variability in the bimanual coordination task. The group differences showed that the PD patients were significantly more variable than healthy controls for this dependent measurement. The main effect of movement type showed that the variability of the anti-phase movement pattern was more variable than the in-phase movement type across all subjects. A significant main effect was found for frequency; subjects were found to be less variable while performing the 2.0 Hz frequency as compared to the 1.0 Hz frequency.

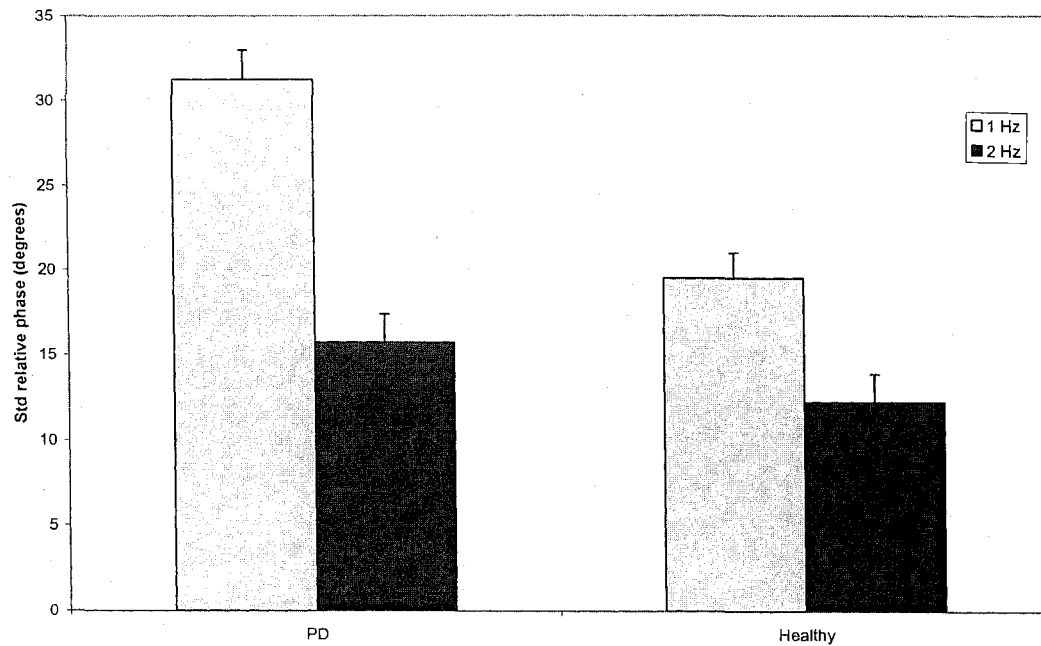


Figure 2d. The interaction of group and frequency on the Standard Deviation of the Mean Relative Phase in a bimanual task

Figure 2d depicts the interaction of group and frequency on the standard deviation of the mean relative phase variability [$F(1, 20) = 6.496, p < 0.05$]. It was found that PD patients were more variable in the standard variability of the relative phase angle produced when they were performing the 1 Hz frequency as compared to healthy controls. There was less variability between the two groups at the 2.0 Hz frequency.

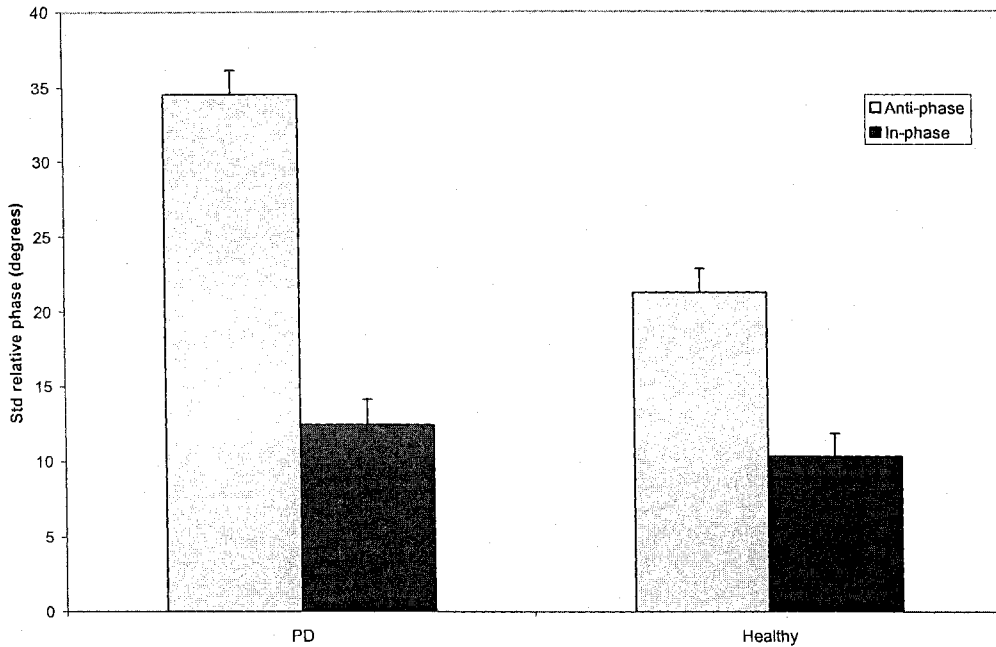


Figure 2e. The interaction of group and mode on the Standard Deviation of the Mean Relative Phase in a bimanual task

Figure 2e depicts the interaction of group and movement type on the standard deviation of the mean relative phase [$F(1, 20) = 11.71, p < 0.05$]. The standard deviation of the relative phase was more variable in the anti-phase movement type than the in-phase movement type for both groups. Additionally, the standard relative phase angle produced by PD patients was significantly more variable for the anti-phase movement type as compared to healthy controls. There was less variability between the two groups for the in-phase task for this measurement illustrating that it was more difficult to produce the anti-phase coordination pattern during the bimanual task.

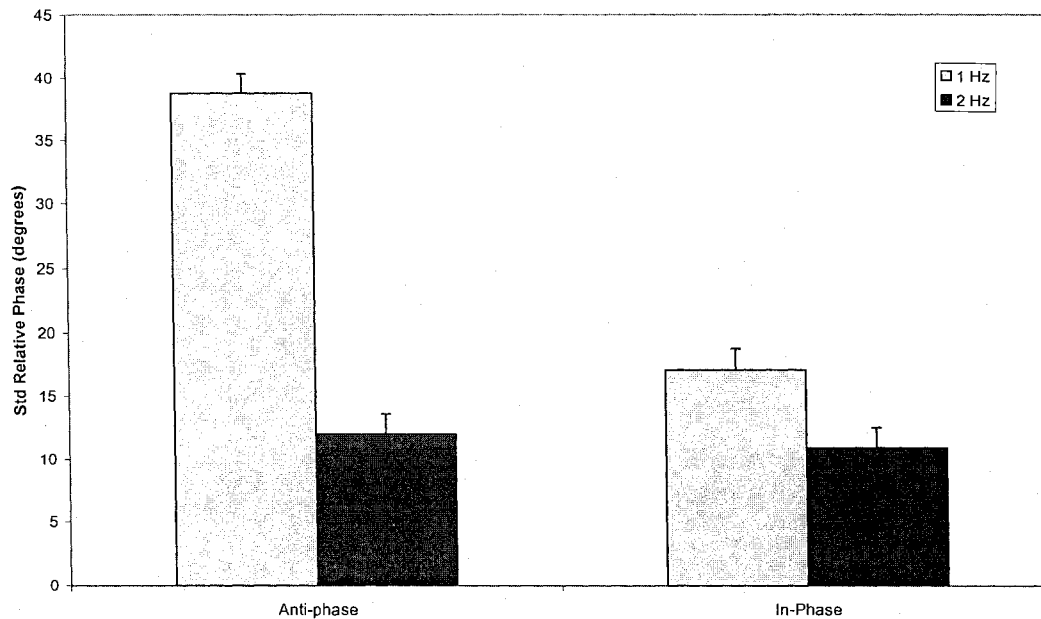


Figure 2f. The interaction of frequency and movement type on the standard deviation of relative phase variability

Figure 2f shows that a significant interaction between frequency and movement type was found for the bimanual coordination task [$F(1, 20) = 40.347, p < 0.05$]. Participants were more variable at the 1.0 Hz frequency when they performed the anti-phase movement type as compared to the in-phase movement type. This finding is expected since the anti-phase movement type is less stable than the in-phase movement type. However, it was hypothesized that subjects would be more variable when the speed was increased. Interestingly, no significant interaction was found for the means between the in-phase and anti-phase movement type for the 2.0 Hz frequency.

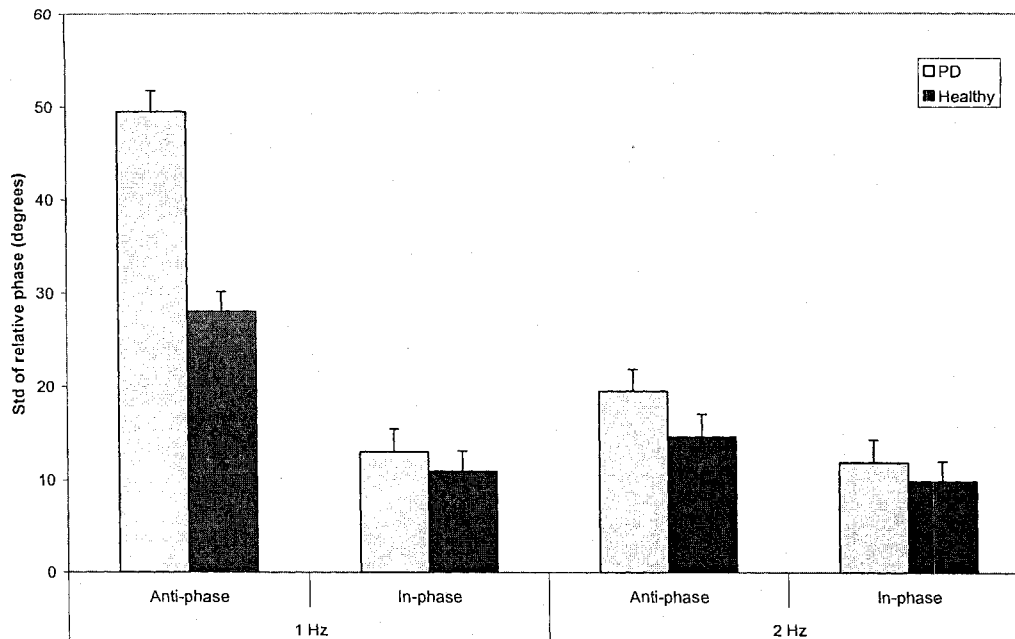


Figure 2g. The interaction of group x frequency x movement type on the standard relative phase variability in a bimanual task

Figure 2g illustrates that there is a significant interaction of group x frequency x movement type for standard relative phase variability [$F(1, 20) = 6.569, p < 0.05$]. It was found that PD patients were significantly more variable than healthy controls while performing the anti-phase task at the slower frequency. The standard deviation of the relative phase was also more variable for PD patients when the frequency was increased to 2.0 Hz for the anti-phase movement type. The groups performed similar during the in-phase conditions at the slow and fast frequencies.

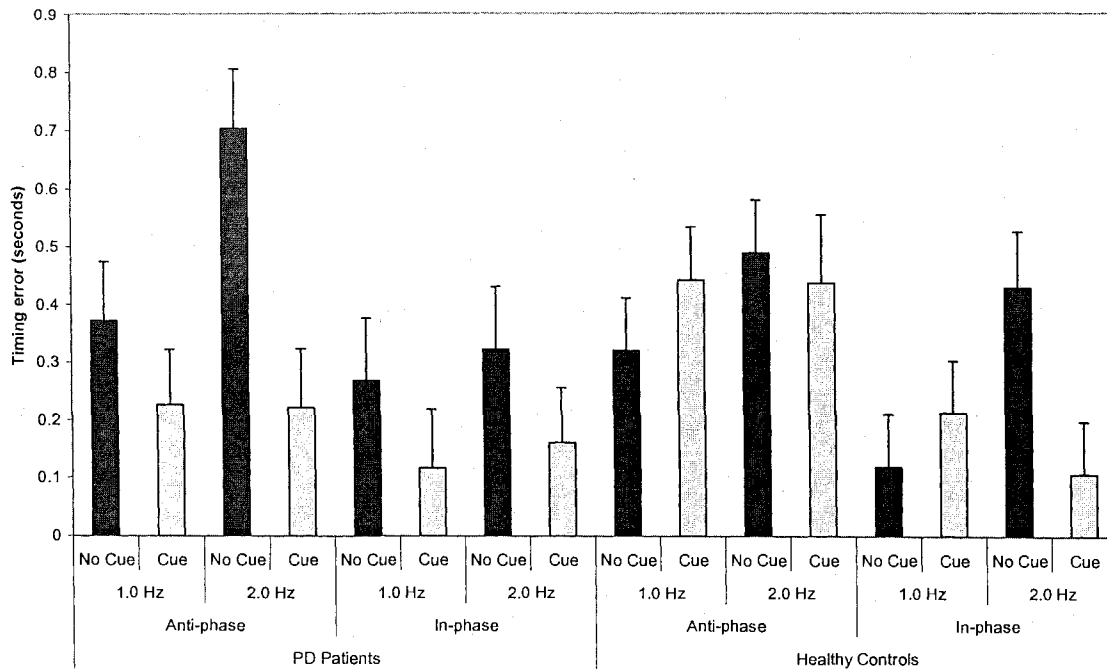


Figure 3. Mean Timing error for the Left finger across all conditions

Figure 3 depicts the absolute values for timing error for the left finger. Across all conditions PD patients were more variable in the no cue condition as compared to the cue condition. Timing error was also more variable for PD patients when the faster frequency was performed. A main effect for timing error of the left finger was found on cue [$F(1, 20) = 7.697, p < 0.05$] (See Figure 3a), frequency [$F(1, 20) = 3.976, p < 0.05$] (See Figure 3b), movement type [$F(1, 20) = 13.887, p < 0.05$] (See Figure 3c). A two way interaction of cue and frequency was found [$F(1, 20) = 5.573, p < 0.05$] (See Figure 3d).

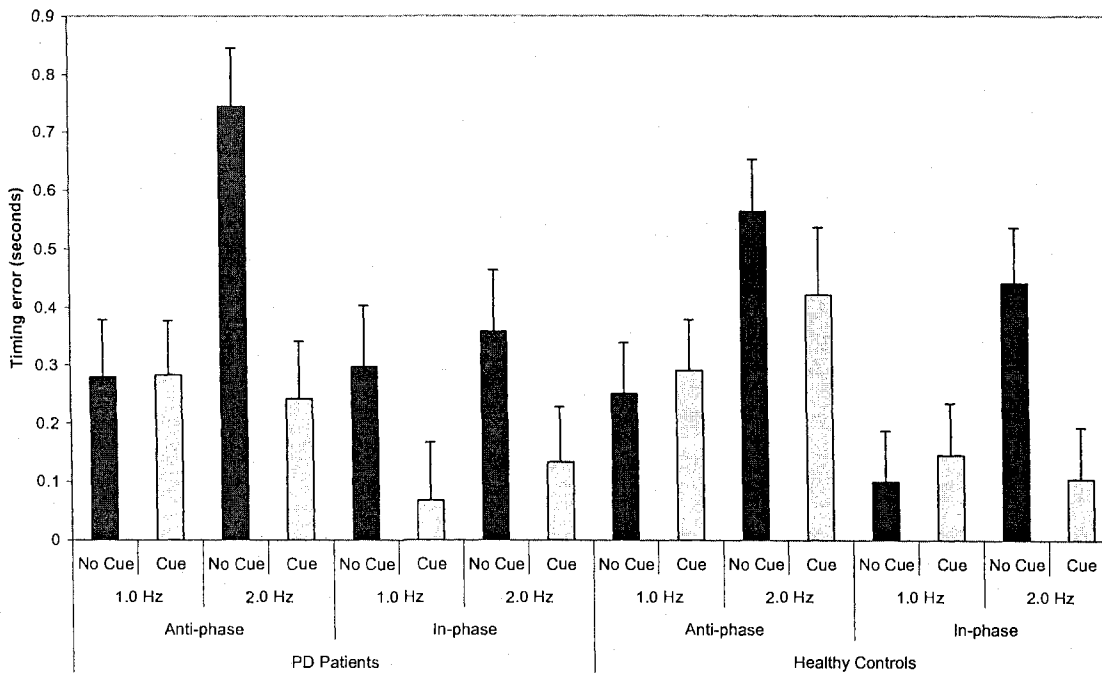


Figure 4. Mean Timing error for the Right finger across all conditions

Figure 4 shows the absolute values for timing error for the right finger. The general pattern of results indicates that both PD and healthy subjects had increased timing errors when performing the no cue condition. PD patients were also more variable than healthy controls in this condition. A significant main effect for cue [$F(1, 20) = 12.162, p < 0.05$]; frequency [$F(1, 20) = 11.242, p < 0.05$]; movement type [$F(1, 20) = 13.575, p < 0.05$] was found.

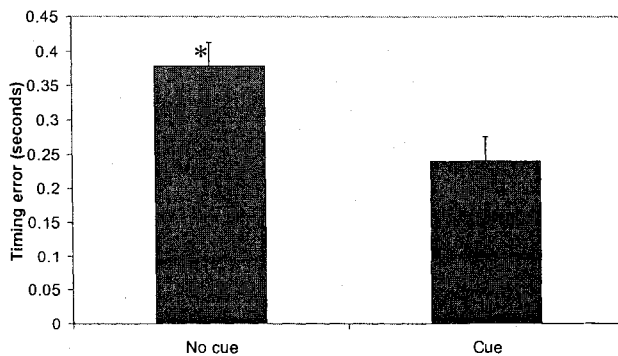


Figure 5a. The main effect of cue on the mean timing error of the left finger in a bimanual task

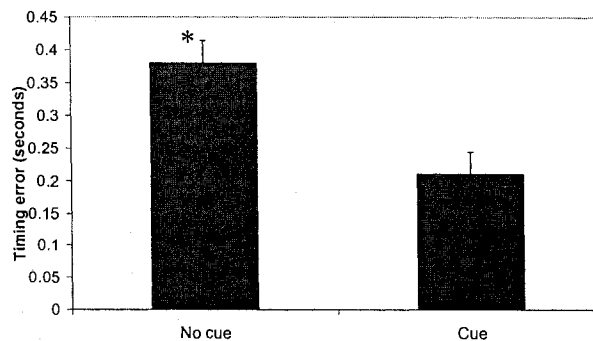


Figure 5b. The main effect of cue on the mean timing error of the right finger in a bimanual task

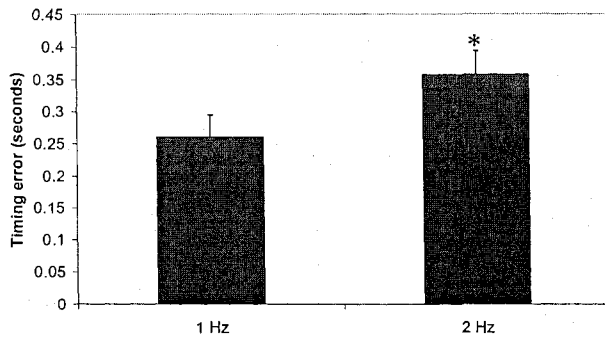


Figure 5c. The main effect of frequency on the mean timing error of the left finger in a bimanual task

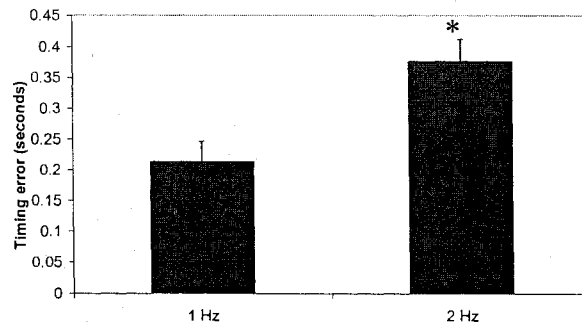


Figure 5d. The main effect of frequency on the mean timing error of the right finger in a bimanual task

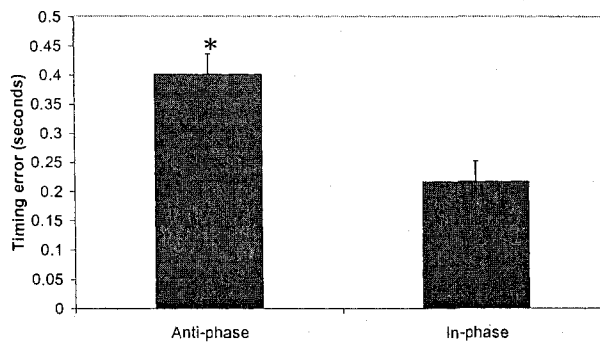


Figure 5e. The main effect of movement type on the mean timing error of the left hand in a bimanual task

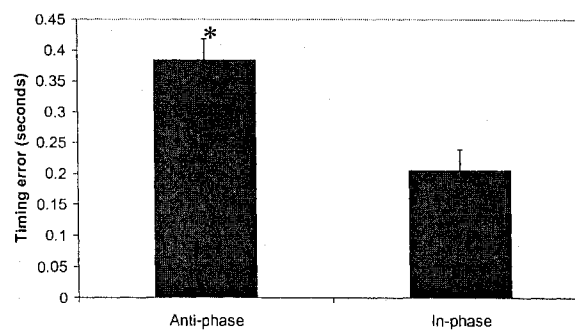


Figure 5f. The main effect of movement type on the mean timing error of the right finger in a bimanual task

The above figures depict the main interaction effects of cue [$F(1, 20) = 7.697, p < 0.05$]; [$F(1, 20) = 12.162, p < 0.05$], frequency [$F(1, 20) = 3.976, p < 0.05$]; [$F(1, 20) = 11.242, p < 0.05$]; and movement type [$F(1, 20) = 13.887, p < 0.05$]; [$F(1, 20) = 13.575, p < 0.05$] on the mean timing error of the left and right fingers respectively. Timing errors were significantly increased when no cue was present during the trials compared to when the cue was given. The 2.0 Hz trials was significantly more variable than the 1.0 Hz trials exhibiting that subjects were more accurate in their timing at the slower frequency. The mean timing error for the anti-phase movement type was found to be significantly more variable than the in-phase movement type. Subjects were nearly twice as variable in the anti-phase conditions for both right and left fingers.

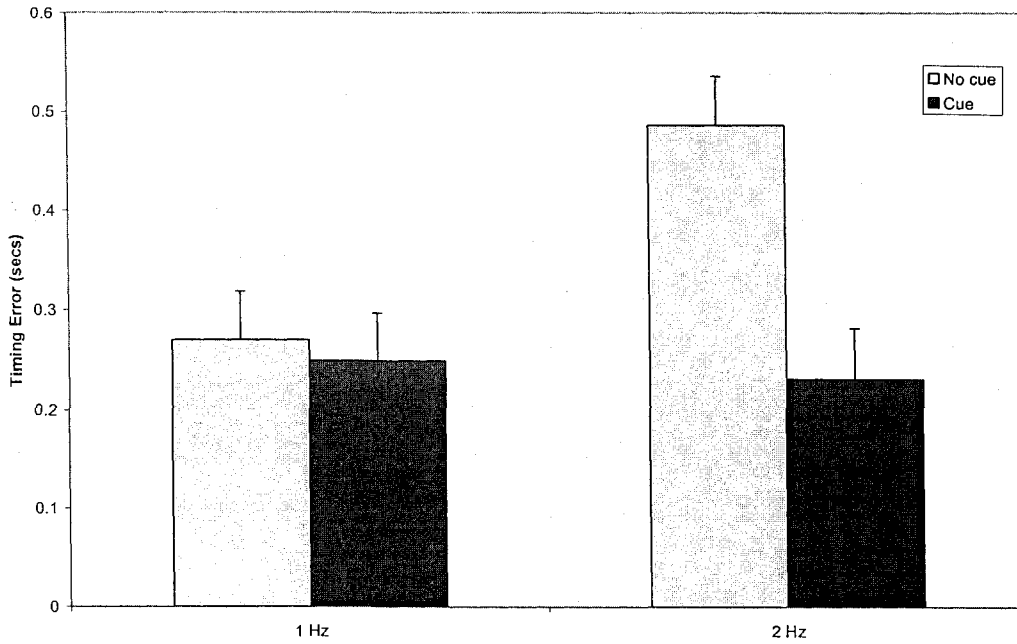


Figure 5g. The interaction of cue and frequency for the Absolute Mean timing error for the left finger

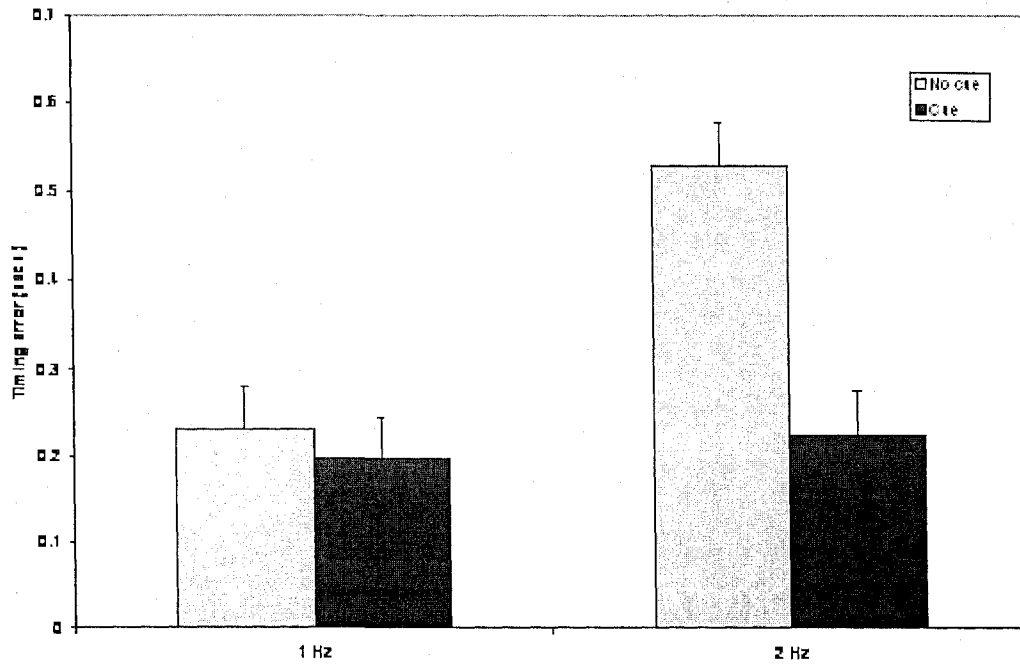


Figure 5h. The interaction of cue and frequency for the absolute mean timing error for the right finger

Figure 5g and 5h represent significant interactions found between cue and frequency for the mean timing error for the left [$F(1, 20) = 5.573, p < 0.05$] and right [$F(1, 20) = 7.659, p < 0.05$] fingers. For the no cue condition, the absolute mean timing errors for both fingers were higher when subjects performed at the faster frequency (2.0 Hz) as compared to the slower frequency (1.0 Hz). No differences were found between the fast and slow frequencies when subjects performed the cue condition.

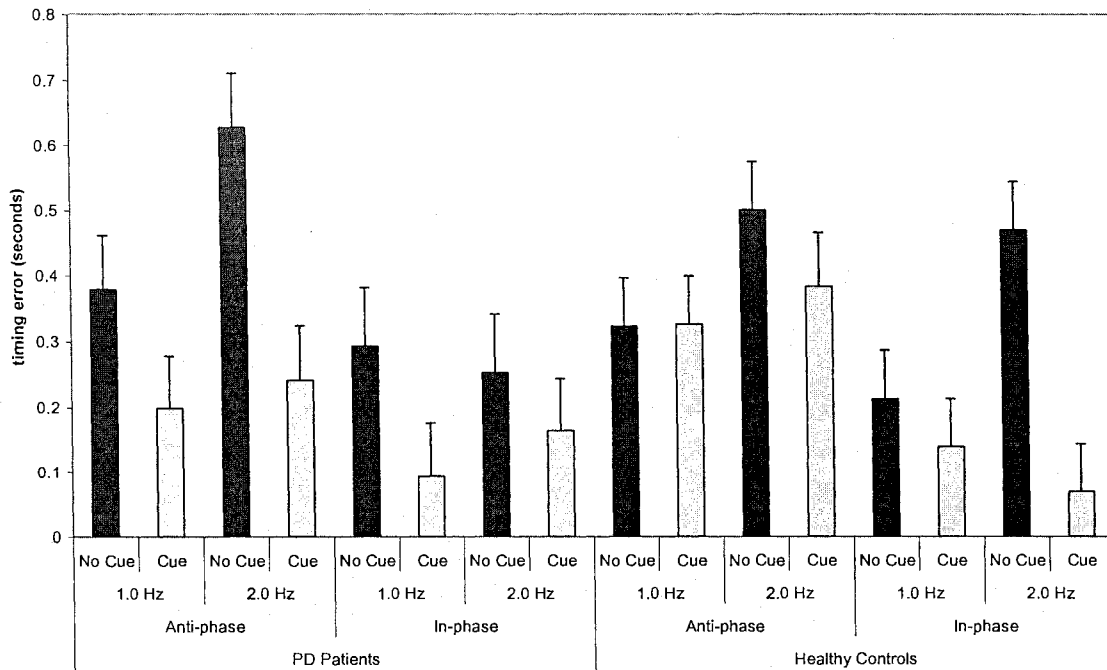


Figure 6. Standard deviation of the Left finger timing error across all conditions

Figure 6. A significant main effect for movement type [$F(1, 20) = 17.706, p < 0.05$] and cue [$F(1, 20) = 21.761, p < 0.05$] was found on the standard deviation of the left finger timing error finger. A paired samples t-test revealed that there was a significant difference for the continuation 1.0 Hz and 2.0 Hz condition [$t(27) = -2.232, p = 0.034$] detailing that both groups had increased timing error when they performed the faster

frequency. The standard deviation of the timing error for the left finger was reduced for both PD and healthy controls when an external cue was provided for the whole duration of the trial. Therefore the synchronization condition was able to reduce variability for both groups for the bimanual task unlike the continuation condition.

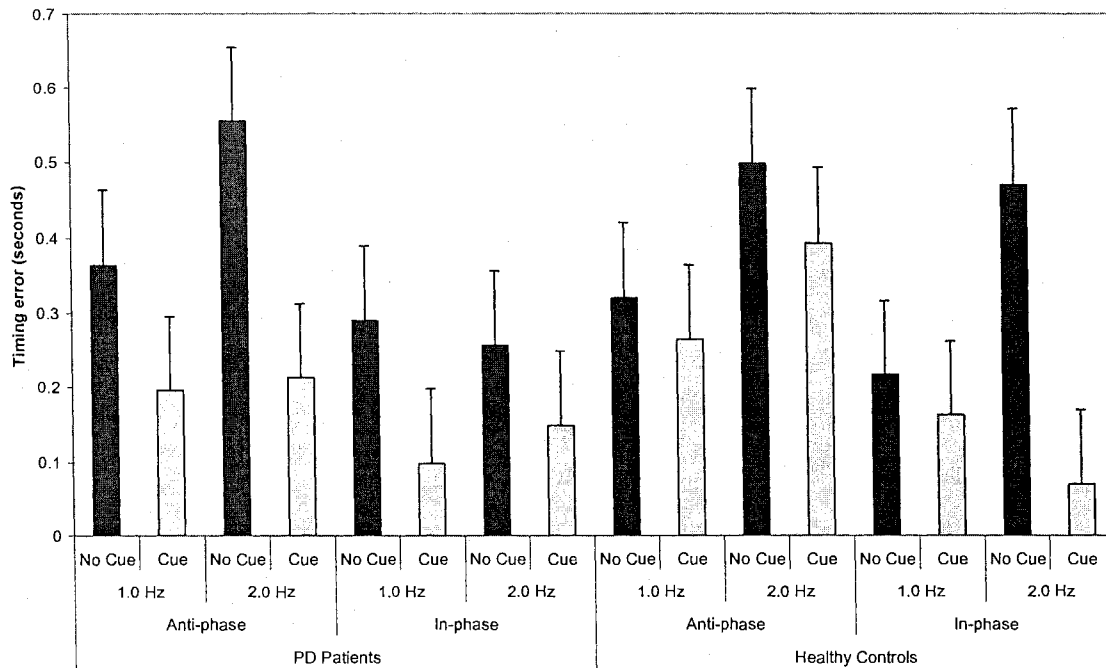


Figure 7. Standard deviation of timing error for the right finger

Figure 7. Significant main interactions for movement type [$F(1, 20) = 13.721, p < 0.01$] and cue [$F(1, 20) = 22.185, p < 0.01$] existed for the standard deviation of the timing error for the right finger. A paired samples t-test showed that there was significant difference for the continuation 1.0 Hz and 2.0 Hz condition [$t(27) = -2.161, p = 0.040$]. When frequency was increased, participants were more variable thus producing more timing errors. All participants performed with reduced timing variability during the synchronization condition; the addition of the external cue was able to decrease the amount of timing errors produced. When participants were engaged in the fast frequency

(2.0 Hz), the variability in the timing errors were increased as compared to when the slow frequency (1.0 Hz) was performed. Finally, the in-phase mode produced less timing variability than the anti-phase mode, which was expected since the in-phase mode is more stable.

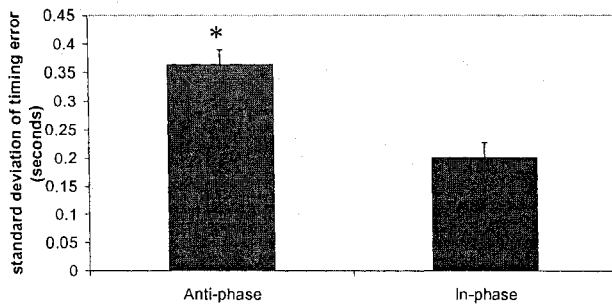


Figure 8a. The main effect of movement type on the standard deviation of the mean timing error of the left finger in a bimanual task

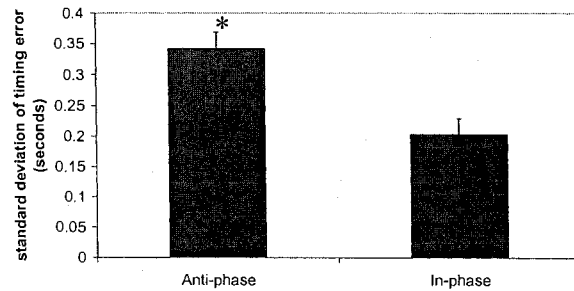


Figure 8b. The main effect of movement type on the standard deviation of the mean timing error of the right finger in a bimanual task

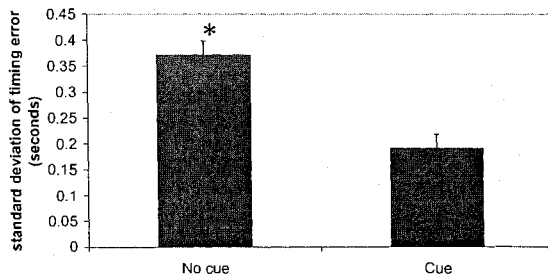


Figure 8c. The main effect of cue on the standard deviation of the mean timing error of the left finger in a bimanual task

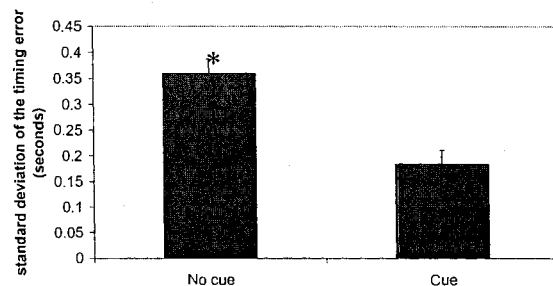


Figure 8d. The main effect of cue on the standard deviation of the mean timing error of the right finger in a bimanual task

The above figures depict the main interaction effects of movement type [$F(1, 20) = 17.706$, $p < 0.05$]; [$F(1, 20) = 13.721$, $p < 0.01$] and cue [$F(1, 20) = 21.761$, $p < 0.05$]; [$F(1, 20) = 22.185$, $p < 0.01$] on the standard deviation of the mean timing error of the left and right fingers respectively. For both fingers, the standard deviation of the mean timing errors was more variable during the anti-phase movement type compared to the in-phase movement type. Variability also increased when the cue was turned off as compared to when the cue was present for the whole duration of the trial.

Huntington's Disease Patients

Only two HD patients were found and able to complete the experimental task, therefore these patients will be looked at separately in two case studies. The MATLAB® program that was used to analyze the data for the PD patients and healthy controls was not able to successfully analyze the trajectories of the HD patients. Movement for the HD patients was so variable that consistent accurate phase relationships and timing errors were not able to be extracted from the program to draw inferences. Figures for timing error will be shown for only condition.

Patient DM

DM was a 46 year old man who had been diagnosed with HD 4 years prior to the experimental session. DM was on several medications to control his HD symptoms. Medications included Novo Mirtazapine, Novo Venlafaxine, Strattera, apo-pimozide, Strattera, Effexor, Ratio-citalopram and Ativan Sublingual. Recall, DM scored a 28/30 on the MMSE and a 14 on the UHDRS. When assessed, it was found that symptoms seemed to be worse on the right side of DM's body. Saccade initiation and velocity were found to be normal for this patient. Chorea in the face, mouth, trunk and extremities was common for the patient. When the retropulsion pull test was performed, DM could not recover spontaneously, and would fall if he was not caught. Finger tapping was also assessed prior to testing and it was found that DM was moderately impaired in this task with occasional arrests in his movement when asked to complete the taps. While assessing gait it was clear that DM walked with difficulty although no assistance was needed.

Patient DM performed the same bimanual finger tapping task as the PD patients however the frequency of the movements were set at a slower speed; the slow frequency was set at

0.83 Hz and the fast frequency was set at 1.53 Hz. Additionally, DM was only able to perform 2 trials for each condition.

Healthy Control Time Series Plot – Anti-phase 1.0 Hz Cue Condition:

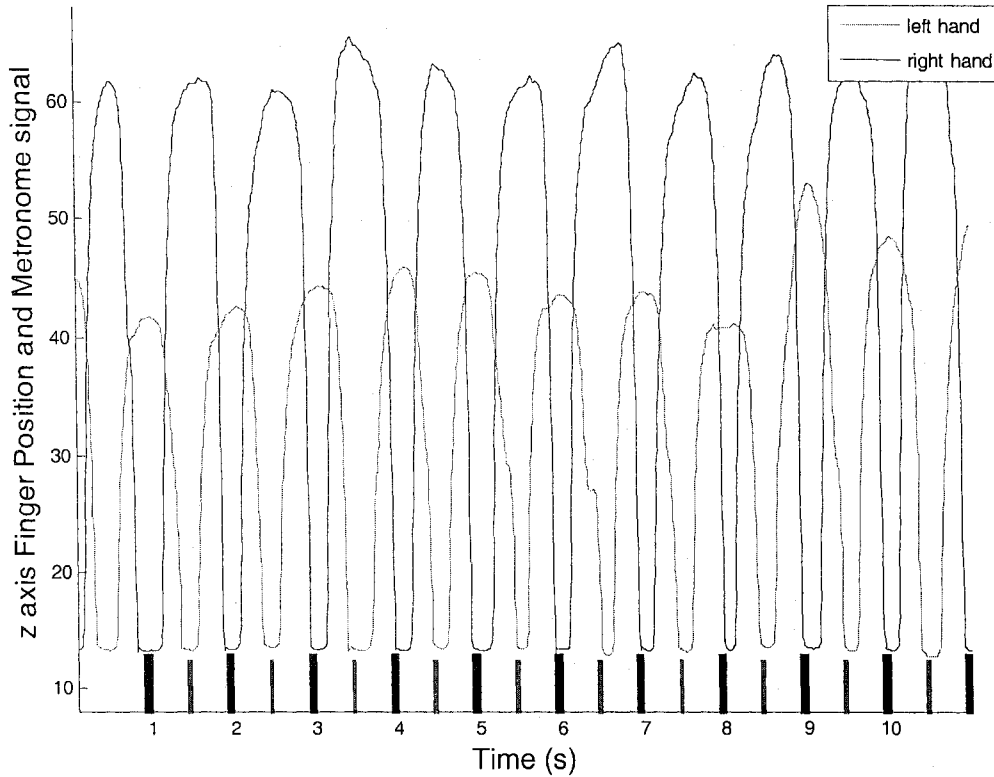


Figure 9. Finger trajectories for a single trial for a healthy control in the 1.0 Hz Anti-phase cue condition.

Figure 9 depicts the time series plot for the finger trajectories for a healthy control. The subject was able to coordinate their fingers successfully to the metronome beat and can achieve the anti-phase movement pattern (Mean relative phase = 181.9° ; Standard deviation of relative phase = 29° ; Mean timing error right finger = 0.67, left finger = 0.69; Standard deviation of mean timing error right finger = 0.55, left finger = 0.58). Time series plots for HD patients differ considerably from the above figure (HD plots will be shown in the present section).

Anti-phase 0.83 Hz No cue condition:

For this condition, the average velocity of the finger for the patient was 0.62 Hz. Between the two trials, the velocities differed by almost a third (velocity of trial 1 was 0.75 Hz, compared to 0.48 Hz for trial 2). Figures 11 and 12 depict the timing errors of the right and left fingers for a single 30 second trial. Mean timing error values were 1.45 and 0.79 seconds for the right and left fingers respectively.

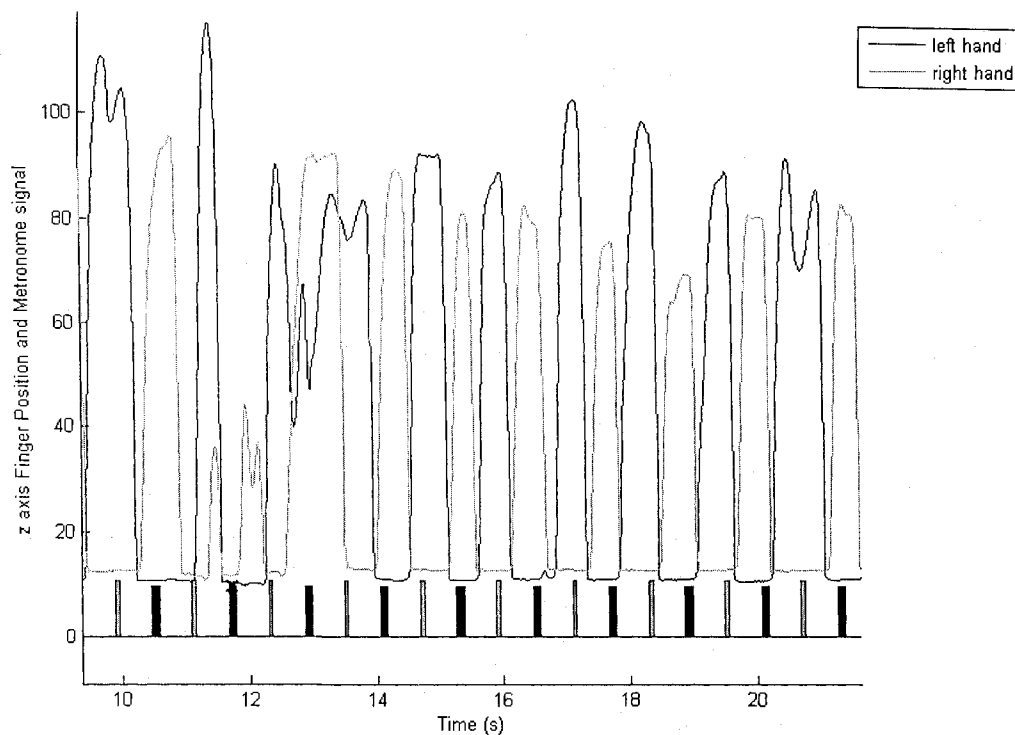


Figure 10. Finger trajectories for a single trial for patient DM in the 0.83 Hz Anti-phase no cue condition.

Figure 10 shows that for patient DM finger movements for the left finger contained more tremor than that of the right finger. The trajectories show that the fingers seem to be coordinated in an anti-phase movement type successfully. (See Figure 13 to view the polar plot for the mean relative phase for this trial).

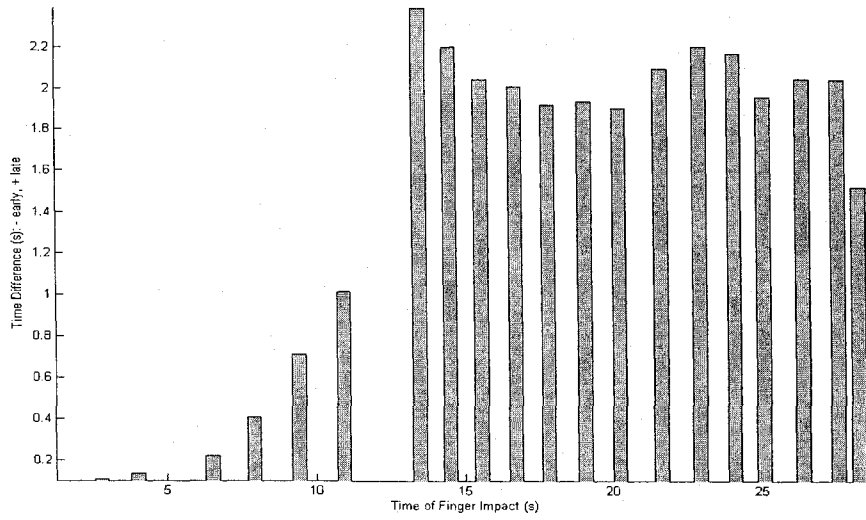


Figure 11. Timing error of the right finger

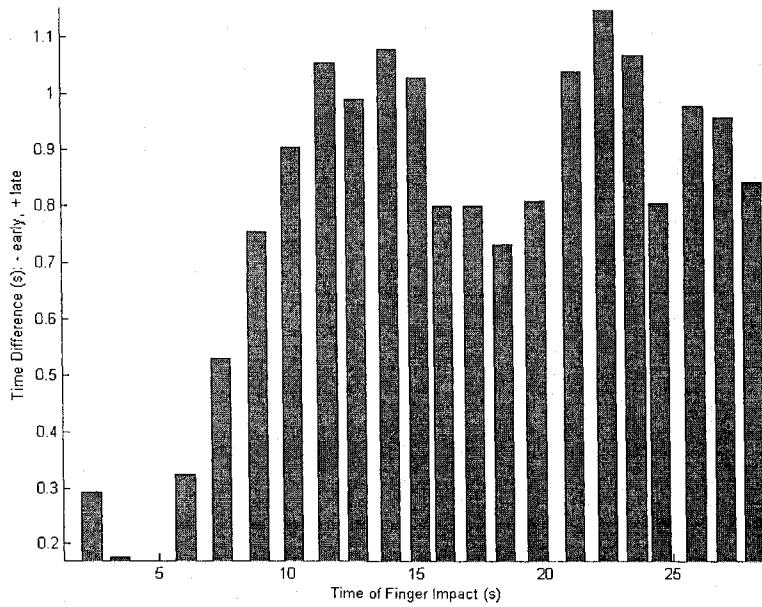


Figure 12. Timing error of the right finger

Timing errors for the second trial were not able to be computed due to the variability of the trajectories of the fingers for the patient.

When relative phase angle was computed using the MATLAB® program, mean values for the two trials were 168 and 181 degrees with the standard deviation 103 and 403.

Figure 13 and 14 depict the polar plot of the mean relative phase for the 2 trials for this condition. The mean on the polar plots of phase differences are indicated by an arrow.

(All future figures will depict the mean with the arrow). The distribution of the relative phase position between the two trials was differed significantly from one another.

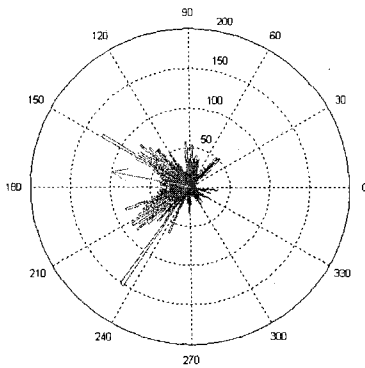


Figure 13. Distribution of Relative Phase Position for a single trial in the Anti-phase no cue 0.83 Hz condition

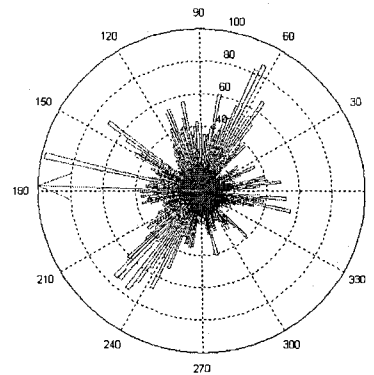


Figure 14. Distribution of Relative Phase Position for a single trial in the Anti-phase no cue 0.83 Hz condition

Anti-phase 1.53 Hz No cue condition

Timing errors were not able to be extracted from the 1.53 Hz conditions. Figure 15 depicts the raw trajectories for a section of a trial. Figure 16 shows the relative phase positions for a single trial. Mean relative phase was found at 176.4 degrees (standard

deviation of 280.0).

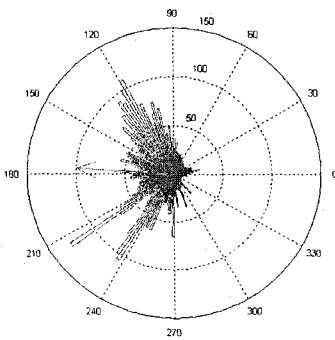
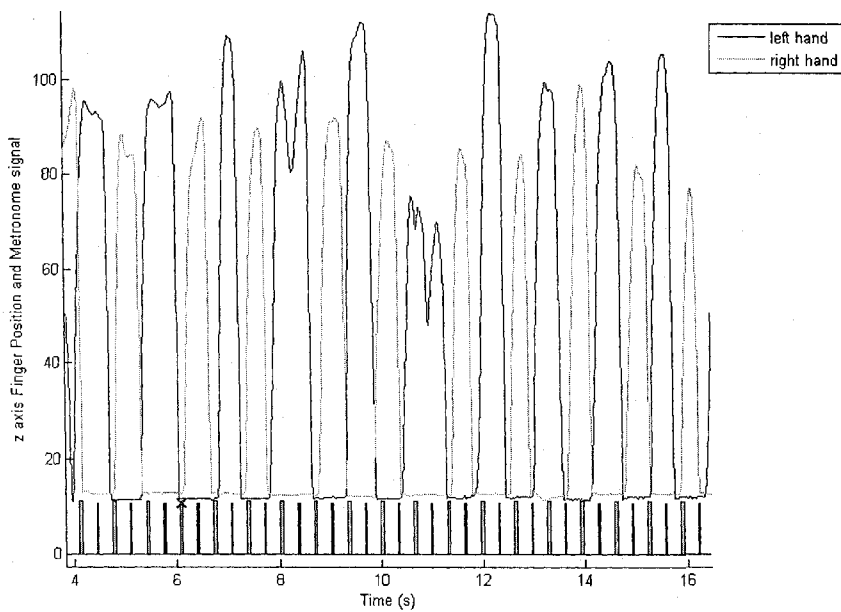


Figure 16. Distribution of Relative Phase Position for a single trial in the Anti-phase no cue 1.53 Hz condition

In-phase No cue condition (0.83 and 1.53 Hz)

Compared to the anti-phase no cue conditions (0.83 and 1.53 Hz), mean timing errors for the in-phase condition appear to be more stable. The average mean timing error for both the right and left fingers was 0.41 and 0.55 seconds respectively for the 0.83 Hz

condition. Regarding relative phase position, only one trial could be analyzed for both the slow and fast frequencies. The mean value was 7.64 degrees (standard deviation of 12.2) for the slow condition and 77.1 degrees (standard deviation of 151.1).

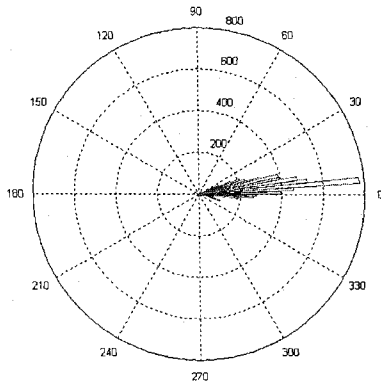


Figure 17. Distribution of Relative Phase Position for a single trial in the In-phase no cue 0.83 Hz condition

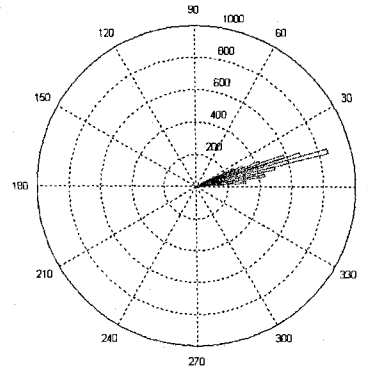


Figure 18. Distribution of Relative Phase Position for a single trial in the In-phase no cue 1.53 Hz condition

Since timing error could not be extracted for all conditions, comparison between the no cue and cue trials could not be performed. Relative phase positions for the cue trials were similar to those for the no cue trials; therefore relative phase positions seemed to be less variable during the in-phase conditions as compared to the anti-phase conditions at both slow and fast frequencies.

In-phase Cue condition (0.83 Hz).

Compared to the *no cue* conditions, mean timing error for the *cue* condition was decreased. Specifically, for one trial timing error was 0.0208 seconds and 0.0498 seconds for the right and left fingers respectively. Figure 19 shows the relative phase position indicating that relative phase was similar to the no cue condition with a mean value of 7.87 degrees (standard deviation of 12.4919).

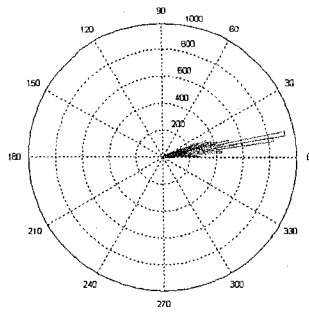


Figure 19 Distribution of Relative Phase Position for a single trial in the In-phase cue 0.83 Hz condition

Patient NN

NN was a 44 year old woman who had been diagnosed with HD 2 years prior to the experimental session. NN was taking the medications Nitoman, Novo Mirtazapine and Novo Venlafaxine to control her HD symptoms. When assessed, it was found that symptoms were worse on the right side of her body. Recall, NN scored a 29/30 on the MMSE and a 25 on the UHDRS. When asked to perform an ocular tracking pursuit task the patient was able to perform the full range of horizontal and vertical movements however the pursuits were interrupted. Chorea in the face, mouth, trunk and extremities was prolonged for the patient. Similar to patient DM, when the retropulsion pull test was performed NN would have fallen if she was not caught. NN was also moderately impaired in finger tapping. Tandem walking could not be attempted for patient NN. Regarding gait, NN adopted a wide based and slow stance and walked with difficulty. Patient NN performed the same bimanual finger tapping task as the PD patients and DM however the frequency of the movements were set at a slower speed. The slow frequency was set at 0.67 Hz and the fast frequency was set at 1.53 Hz. NN completed 5 trials for each condition trials started off as 30 seconds but were cut to 20 seconds.

Anti-phase 0.67 Hz No cue condition:

Timing errors varied from trial to trial (left finger 0.25 seconds to 3.22 seconds; right finger 0.39seconds to 3.43 seconds). The below figures show finger trajectories for 2 separate trials for this condition. (The “x” depicts the time at which the metronome beat was turned off during the trial. The large bar indicates when the metronome was discharged). For this subject relative phase positioning could not be computed due to variability of the movement. [For example, relative phase was computed at 824.7 degrees (standard deviation of 570.2), see Figure 20].shows the relative phase positioning was not able to be computed

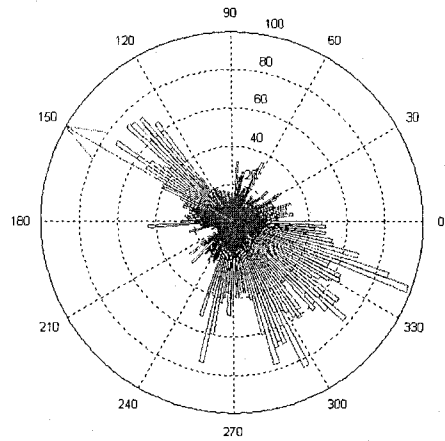


Figure 20. Distribution of Relative Phase Position for a single trial in the Anti-phase no cue 0.67 Hz condition

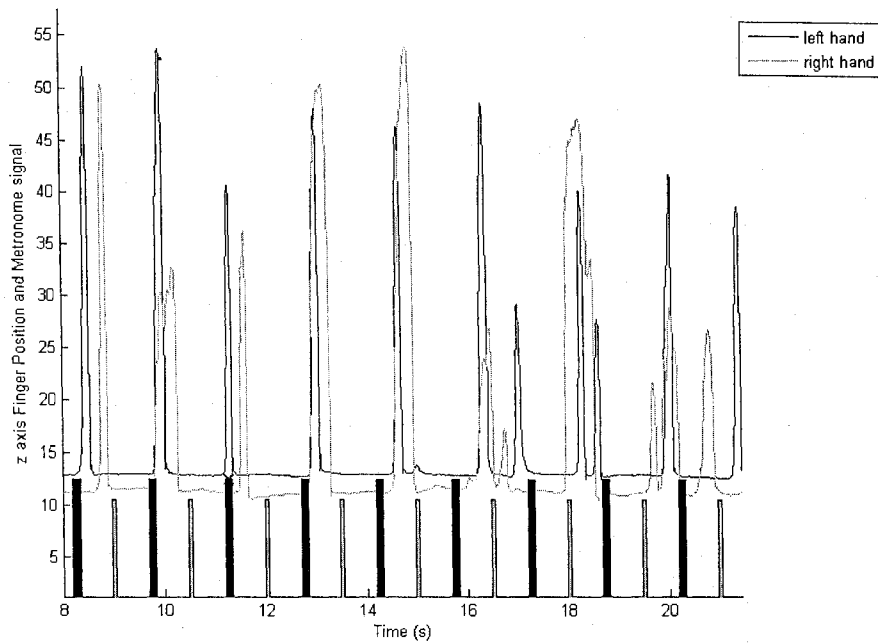


Figure 21a. Finger trajectories for a single trial for patient NN in the 0.67 Hz Anti-phase no cue condition.

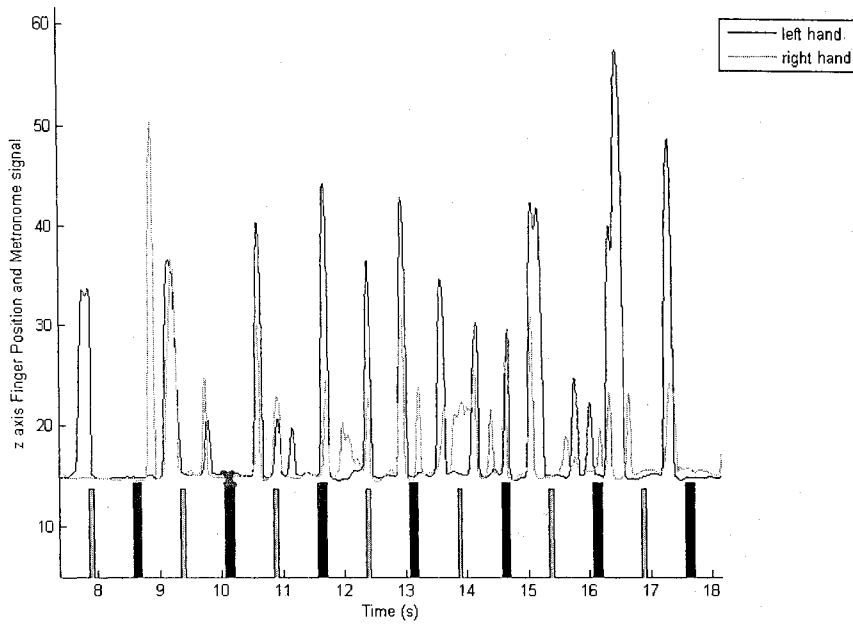


Figure 21b. Finger trajectories for a single trial for patient NN in the 0.67 Hz Anti-phase no cue condition.

Figures 21 a and b show the right and left finger trajectories. From these two figures it is evident that the right finger displayed more tremor than that of the left. Also once the cue

was turned off the fingers seem to be coupled together more in-phase than anti-phase movement pattern (however, since relative phase was not able to be computed it cannot be confirmed).

Anti-phase 1.53 Hz No cue condition:

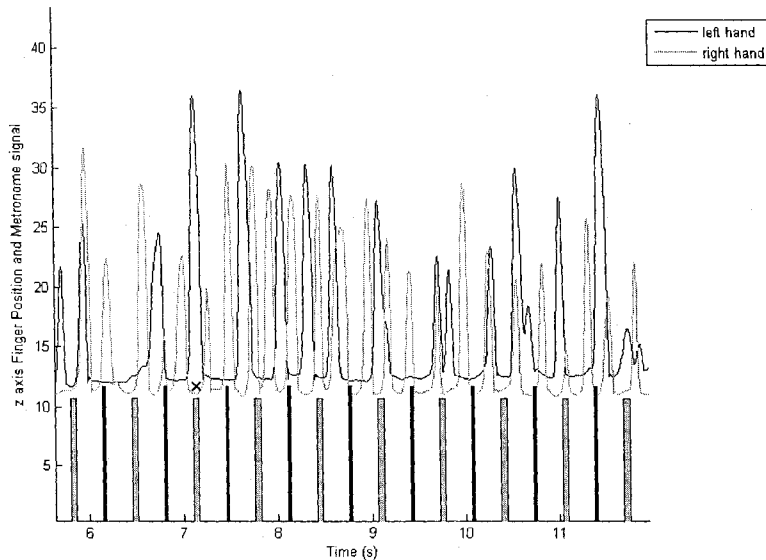


Figure 22. Finger trajectories for a single trial for patient NN in the 1.53 Hz Anti-phase no cue condition.

When frequency was increased to 1.53 Hz, finger tapping of the patient seemed to be more erratic than what was produced at the slower frequency. From Figure 22, it is evident that the right finger exhibited more finger taps than that of the left finger for the duration of the 30 second trial. The finger frequency achieved for this trial was for the left finger and for the right finger.

In-phase 0.67 No Cue Condition

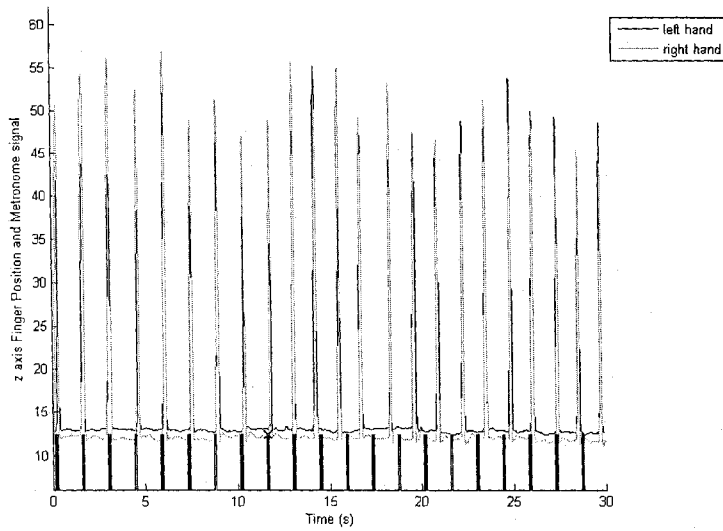


Figure 23. Finger trajectories for a single trial for patient NN in the 0.67 Hz In-phase no cue condition.

In-phase 1.53 No Cue Condition

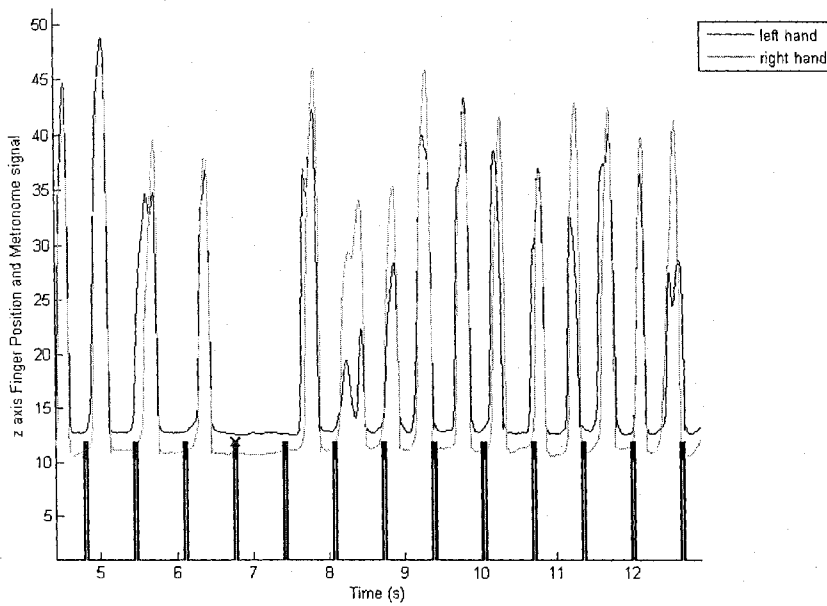


Figure 24. Finger trajectories for a single trial for patient NN in the 1.53 Hz In-phase no cue condition.

Figure 23 and 24 depict the finger trajectories for the in-phase no cue condition. Figure 21a and b displays trials in which the 0.67 Hz was performed while the 1.53 Hz trial is shown in figure 22. The patient was able to perform the in-phase movement pattern at the slower frequency without any problems. Timing of the metronome beat and the finger taps seem to generally coincide with one another as well. Additionally, the right and left fingers were tightly coupled together. When the speed was increased to 1.53 Hz frequency, coupling was not as strong as with the slower frequency. The right finger tended to move more frequently than that of the left side. Movement frequency achieved by the fingers was higher than what was set by the metronome. (Frequency was 2.37 Hz and 2.45 Hz for the right and left fingers respectively).

Anti-phase 0.67 Hz Cue Condition

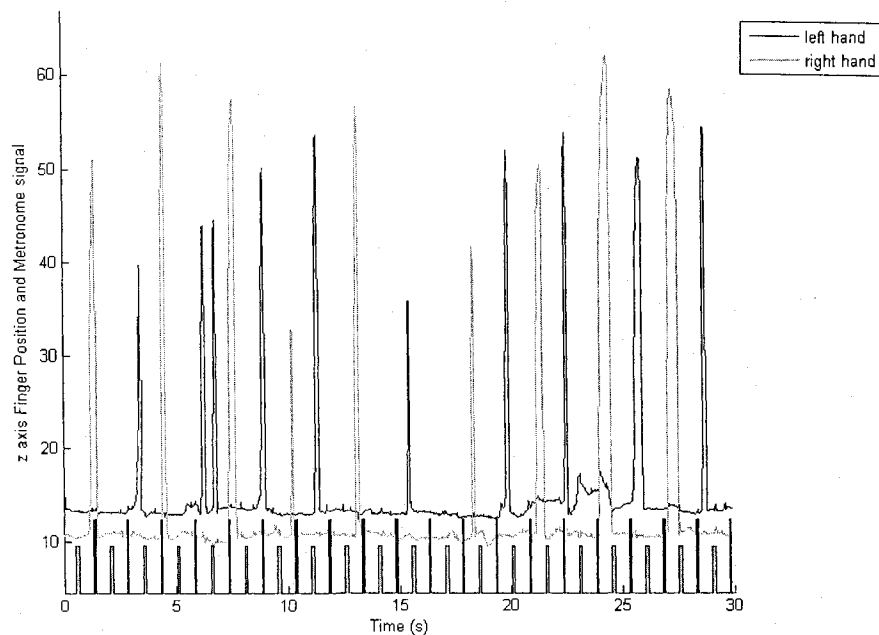


Figure 25. Finger trajectories for a single trial for patient NN in the 1.53 Hz Anti-phase cue condition.

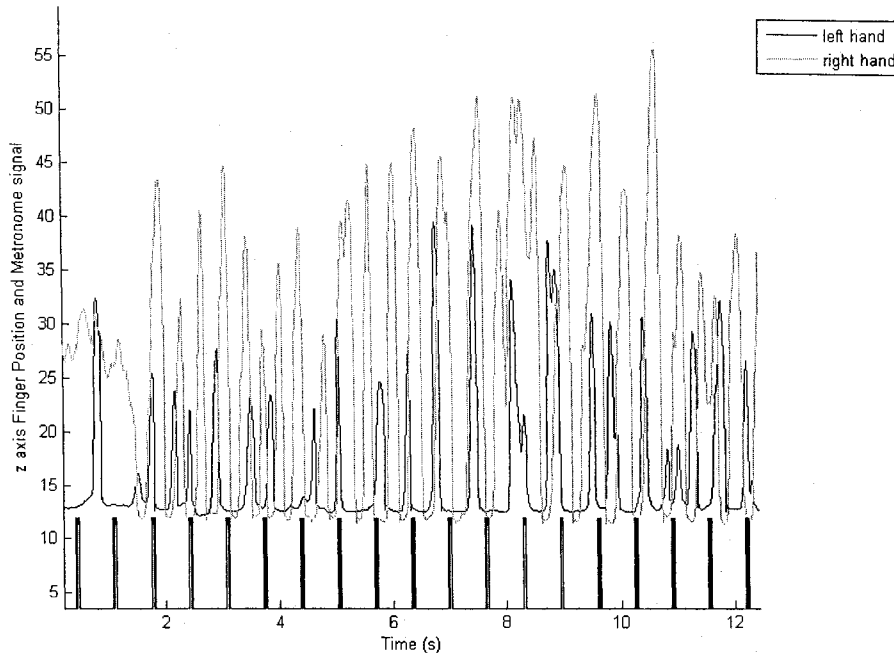
Anti-phase 1.53 Hz Cue Condition

Figure 26. Finger trajectories for a single trial for patient NN in the 1.53 Hz Anti-phase cue condition.

In Figure 25 and 26 it is clear that the patient is not able to achieve the anti-phase movement pattern with their fingers. In figure 21 it is clear that there is a large amount of timing error as the taps are not performed when the metronome was discharged and there are times when there are arrests in the finger tapping movement. When the faster frequency was performed, there was a large amount of movement displayed for both fingers which was not seen at the slower frequency. Finger frequency during the slow condition was 0.6 Hz and 0.1 Hz for the left and right fingers, and 1.93 Hz and 2.00 Hz for the fast condition.

In-phase 0.67 Cue Condition

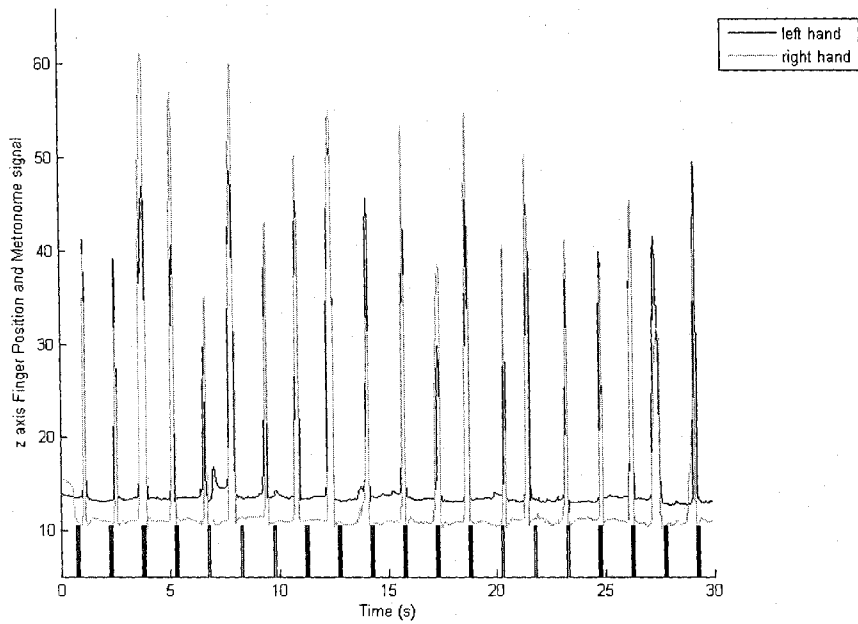


Figure 27. Finger trajectories for a single trial for patient NN in the 0.67Hz In-phase cue condition.

In-phase 1.53 Cue Condition

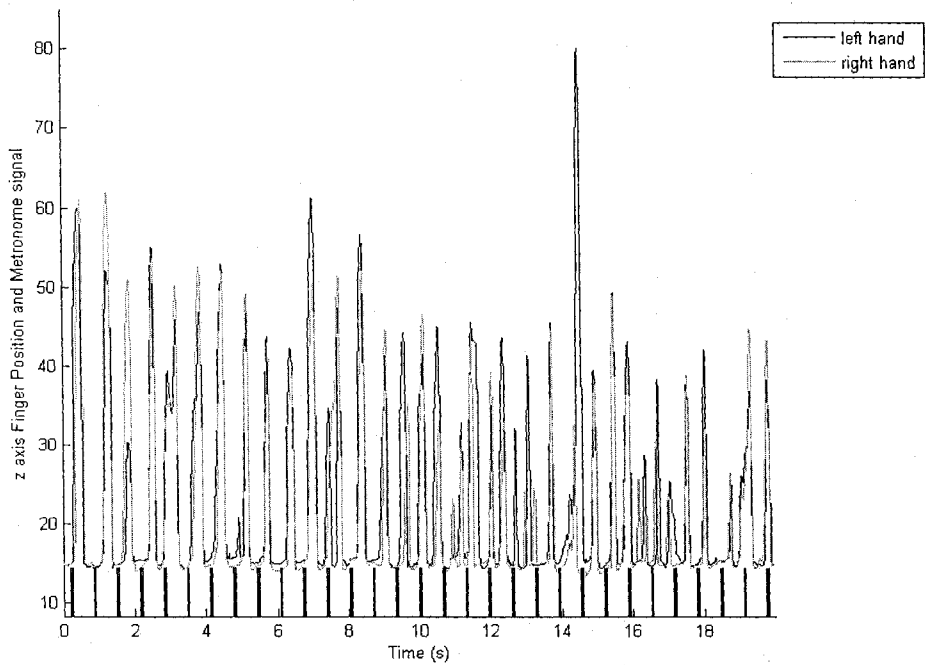


Figure 28. Finger trajectories for a single trial for patient NN in the 1.53 Hz In-phase cue condition.

For the in-phase cue condition the fingers were coupled in their movements for the two different speed conditions. Movement was more variable in the 1.53 Hz condition and there seemed to be more tremor in the right finger. As compared to the anti-phase cue conditions, the in-phase pattern seemed to be much more stable. Additionally, finger frequency was 0.65 and 0.72 Hz for the left and right fingers in the slow condition and was 1.53 and 1.55 Hz for the fast condition. Therefore, subjects were able to produce the desired frequency for this bimanual movement type (which was not observed in the anti-phase movement pattern).

Chapter V

Discussion

The performance of bimanual tasks has been examined in HD and PD, however, current literature has not been able to provide a consensus in determining if an external cue can facilitate timing for these special populations. The present study investigated if the use of an external cue (metronome beat) can stabilize movements for patients with PD and HD. It was hypothesized that patient populations would be more variable than healthy controls when performing the task on all dependent variables (mean relative phase, standard deviation of relative phase, mean timing errors for the right and left fingers and the standard deviation of the timing error for the right and left fingers). It was also hypothesized that the cue would benefit and therefore stabilize the movement pattern for patients with PD although not be able to facilitate those with HD. Studies conducted by Johnson et al (1998) and Johnson and et al (2000) were able to determine that the presence of an external cue is useful for both patient types, however it has also been that found that cues were of no benefit (Almeida, Wishart & Lee, 2002).

5.1 Parkinson's Disease Patients

In PD, the natural balance of the thalamocortical circuit is lost due to the depletion of dopamine in the striatum (Gazzaniga & Mangun 2002). Both the direct and indirect pathways operate through the GPi/SNr output nuclei and their influence is inhibitory on the thalamus. The relative degree of activation is changed in the brain of PD patients. Thus, increased activity in the output nuclei leads to increased inhibition on the glutamatergic excitation of the motor cortex and a subsequent reduction in movement,

observed in patients as bradykinesia (which was seen in all patients) (Gazzaniga & Mangun, 2002). Even though inhibition of the motor cortex arises in PD, amelioration of the task was seen by patients when an external cue was provided. Patients were able to perform the task with decreased variability in the *cue* trials similar to healthy controls. Healthy controls were able to produce the anti-phase movement pattern with more efficacy than PD patients. The anti-phase movement pattern is a more complex sequence involving sequential movement of the fingers 180 ° out of phase. PD patients were worse at performing this task to do compromised function of the basal ganglia. Unlike healthy controls, PD patients have an impaired ability to internally regulate movement. This causes the increase in variability of their movement pattern which can be decreased with cueing and the use of the external pathway to guide movement (Johnson et al, 1998). The cerebellum is a brain structure involved in the pathway of externally guided movements and is not compromised in PD (Swinnen & Wenderoth, 2004). The external cue was able to provide stability to the PD patients through utilization of this pathway. It is therefore likely that cueing was able to bypass the compromised internal rhythm of the basal ganglia by using the alternate external pathway which is directly cortically controlled (Johnson et al, 1998). Additionally, one may conclude that the cue provided additional temporal information to facilitate finger tapping in the bimanual task even though thalamocortical circuit balance is disrupted.

5.2 Mean Relative Phase and Standard Deviation of Relative Phase

There were no significant differences or interactions found when mean relative phase was investigated. This is not surprising since it has been shown that PD patients are able to perform in-phase and anti-phase movement patterns (Johnson et al, 1998). PD

patients can perform the two different movement types however they are usually more variable at performing the different phase relationships task than healthy controls. In the present study the differences were found in the standard deviation of the mean relative phase. PD patients were found to be significantly more variable than healthy controls regarding this dependent variable.

It has been established in the literature that the anti-phase movement pattern is less stable than the in-phase movement type (Amazeen, 1998). In the present experiment, the in-phase movement type was found to be significantly less variable for the standard deviation of the mean relative phase as compared to the anti-phase movement pattern. The in-phase movement is quite simple to perform since both fingers are moving at the same time and are making mirror symmetrical movements; there is therefore only one timing pattern that is used. In order to produce successful anti-phase movements sequential timing of muscle activation is required. For the anti-phase movement pattern, timing is faster than the in-phase movement type since both fingers need to tap every metronome beat cycle (but are not tapping simultaneously). In the Johnson et al study (1998), it was found that healthy controls could perform the anti-phase movement type for the 1.0 Hz no cue condition but not at the 2.0 Hz no cue condition, whereas the PD patients could not perform the anti-phase pattern at either of the frequencies. Interestingly, in the present study it was found that both groups were significantly more variable when they were performing the task at the slower 1 Hz speed. One would have expected that the opposite effect would have been found. The standard deviation of the relative phase for PD patients was also more variable than healthy controls when the 1.0 Hz frequency was performed.

5.3 Absolute mean timing error

The right and left fingers followed the same pattern of results for the dependent measurement of absolute mean timing error. When no cue was provided it was found that timing errors for both fingers was higher. This highlights the importance of the external cue (this will be discussed later). The frequency of the condition was found to play an important role in the accuracy of the timed movements. When the frequency was increased from 1.0 Hz to 2.0 Hz mean timing errors were found to be significantly more variable for both subject groups. Timing errors were also increased when the anti-phase movement type was performed as compared to the in-phase movement type. Both PD and healthy patients could perform and maintain the anti-phase movement type however they were more variable at producing this phase relationship. A significant 2-way interaction between cue and frequency were found showing that the timing errors at the *2.0 Hz no cue* condition were significantly more variable than the *1.0 Hz no cue* condition. One may speculate that due to the increase of the inhibitory GABA neurotransmitter to the motor cortex, movements made by PD patients are much slower than healthy controls (recall bradykinesia is the major clinical symptom of PD) (Gazzaniga & Mangun, 2002). Therefore, the 2.0 Hz no cue condition may have also been harder for PD patients since it is likely it is more difficult for this population to achieve faster frequencies (Johnson et al, 1998). Absolute mean timing performance was generally worse for PD patients across conditions however no significant differences were found between the two groups.

5.4 Standard deviation of the timing error

Similar to the measurement of absolute mean timing errors, significant differences were found for the fingers during the *no cue* trials as compared to the *cue* trials. Additionally, the anti-phase movement type was more variable than the in-phase movement type. Once again, no group differences were found. Across all conditions for both right and left fingers it was found that the PD patients were more variable than healthy controls during *no cue* trials. The greater variability in timing performance during the *no cue* trials indicates that PD patients were less consistent in their movement pattern for this measurement. Although PD patients were more variable than healthy controls no significant difference was found between the groups. For the *cue* trials PD and healthy controls performed similarly and during some conditions PD patients showed less variability in the distribution of timing errors.

5.5 The role of external cueing

The effects of external cueing were found to be important for PD and healthy controls in the experiment. Across all conditions the mean timing error of both fingers was decreased when the subjects (both PD and healthy) were provided with a cue. A significant main effect for cue for the right and left fingers were found regarding absolute mean timing error. When the external auditory cue was provided, timing performance in both the right and left fingers were significantly decreased than when the cue was not provided for the whole length of the trial. The increase in stability when the cue was provided highlights the role of the basal ganglia when internally guided movements are performed and shows the importance of utilizing the external pathway for

populations with basal ganglia disorders (Swinnen & Wenderoth, 2004). When the metronome cue was given, patients were able to maintain the in-phase and anti-phase movement patterns more accurately and with better stability which enhanced the coordination of the movement executed. Previous findings showed when an external cue was given during anti-phase movement type; PD patients reverted back to the more stable in-phase movement type (Johnson et al, 1998). In the present study, PD patients were able to perform and maintain the anti-phase movement pattern when the cue was provided. Differences between the current study and the one conducted by Johnson and colleagues can most likely be attributed to the fact that a multi-joint was used (shoulder, elbow, wrist) whereas the current study used a simple single-joint repetitive timing task. Findings from this study have shown that external cues can be used to stabilize movements (both phase and timing) for populations with PD.

5.6 Huntington's Disease

In HD, nerve cells in the striatum die causing a decrease of neurotransmitters to the GPi. This renders the GPi less inhibited causing the thalamus to become disinhibited which leads to an increased excitation of the motor cortex (caused by an increase of the neurotransmitter glutamate). Along with motor impairments, cognitive impairments are observed within this special population. The addition of using external cues to facilitate performance has been conflicting. It has been suggested that the addition of a cue may place additional attentional demands on these patients making the cue ineffective (Johnson et al, 2000). Within the current study the two HD patients were examined separately since the progression of their symptoms was different (NN portrayed more motor impairments than DM).

5.7 Huntington's Disease patient DM

Timing errors for patient DM were not able to be computed due to the variability of the patient's movement. During the performance of the task the patient would miss many of the movement cycles which rendered the algorithms that were computed by the MATLAB® program erroneous. Some relative phase polar plots were able to be extracted from the data. Regarding the in-phase condition DM was able to perform this movement type and was able to do so at both the slow and fast frequency (0.83 Hz and 0.153 Hz).

Additionally, based on these plots it was found that the relative phase measurements for DM varied considerable between trials within the same anti-phase conditions. The anti-phase movement is more complex than that of the in-phase movement as one finger must maintain a 180° phase difference with the other finger. The erratic movements and involuntary tics make it more difficult for patient DM to perform the anti-phase trials due to the complex sequential nature of the movement.

5.8 Huntington's Disease Patient NN

Similar to HD patient DM, timing errors were not able to be computed by the MATLAB® program for patient NN. NN's movement was extremely variable and relative phase angles were also not able to be computed for this subject. Inferences on the subject's movement will be made based upon the examination of the raw trajectories for the trials for this patient. Coupling during the in-phase conditions for the task seemed to be achieved for the patient and was more effective at the slower frequency. In the study conducted by Johnson et al (2000) when a cue was present the HD patients were able

maintain the in-phase movement type at the slower speed. When NN performed the anti-phase movement type was performed the subject did not seem to be in any particular phase relationship (these findings are similar to Johnson et al, 2000). It does not seem that the use of an external cue was able to stabilize the movement patterns or timing error for this particular HD patient. NN was cognitively aware that for successful completion of the trial the finger taps needed to coincide with the metronome beats but the involuntarily tics that are associated with HD was unable to aid the performance of the task. Symptoms associated with HD were too severe for this particular patient that the use of an external cue does not seem to be effective.

5.9 Comparison of PD and HD

The ability of HD patients to coordinate bimanual movements has not been looked at extensively. Due to low incidence rates and differing degrees of disease severity between the two patients in the present study, generalisations for the rehabilitative strategies cannot be made for HD populations. However it seems that for patient NN the cue was not able to stabilize the movement which could be attributed to the additional attentional demands the cue may have placed on the subject similar to what was seen in the peg purdue task conducted by Brown et al (1993). The study was able to show that both HD patients were more accurate while performing in-phase movements compared to the anti-phase movements. Regarding external cueing, it does not seem that metronome beat was able to decrease variability in timing errors or relative phase position. Dysfunctions of the thalamocortical loop and decreased attentional capacity are likely the causes for the failure of cue to provide stabilization to the patients' movement. PD and HD are both basal ganglia disorders, however the compromised output pathway

in both diseases affect movement coordination differently between the groups (Guberman, 1994). In PD, the increased inhibition on the thalamus leads to decreased excitation on the motor cortex (Gazzaniga & Mangun, 2002). Consequently, movements made by PD patients are bradykinetic yet predictable. In HD there is increased excitation from the thalamus to the motor cortex making movements erratic and unpredictable (Gazzaniga & Mangun, 2002). The involuntary movements made by the HD patients in the study were very irregular thus making it impossible to group the data during analysis.

5.11 Limitations and future directions

The main limitation of this study is the low subject sample for the HD patients since generalisations for the results could not be made. Between the two subjects there was also a great amount of variability which is why their results had to be interpreted separately. Drift cycles for the HD group was greater than healthy controls and PD patients rendering the computing program incapable of producing meaningful timing errors.

With the advancement of technology, the use of traditional imaging techniques and the combination of transcranial magnetic stimulation (TMS) may provide further insight into cortical activity during movement and timing (Carson & Swinnen, 2002). Virtual lesions can be created through repetitive TMS and may provide information into the contribution of cortical activity by comparing the activation patterns of the cortical sites in normal subjects to those in which a virtual lesion has been created. Another area which may be explored in the domain of external perceptual cues are the benefits of this type of cueing once the external cue has been taken away. The previous mentioned studies have shown that external cues benefit performance, however, upon complete

withdrawal or moderate to high reductions of the cue performance is affected. Therefore, the utilization of a set of strategies needs to be developed in order to improve memory consolidation in external cueing. These possible rehabilitation techniques can be explored once the extent to which external cues aid performance are uncovered.

5.12 Conclusion

In conclusion, does the use of an external cue aid the stability of movements produced in special populations with basal ganglia disorders? Through examination of the results it seems that an external cue is beneficial for patients with PD as the cue was able to reduce timing errors and benefit relative phase positioning that was produced by the fingers. PD patients performed generally similar to healthy controls, although as hypothesized their movements were more variable. While looking at the movement of HD patients, it seems as though an external cue is of no benefit for these patients groups due to in great amount of variability in their movement arising from involuntary tics and tremors. Therefore, although dysfunction and compromised output of the basal ganglia is found in patients with PD and HD, the neuropathology is quite distinct and rehabilitative strategies should be considered separately.

References

- Almeida, Q.J., Wishart, L.R., & Lee, T.D. (2002). Bimanual coordination deficits with Parkinson's Disease: The influence of movement speed and external cueing. *Movement Disorders*. 17: 30-37.
- Amazeen, P., Amazeen, E., & Turvey, M.T. (1998). Dynamics of intersegmental coordination: Theory and research. In D. Rosenbaum & C. Collier (Eds.), Timing of Behavior: Neural, computational, and psychological perspectives (pp. 237-259). Boston: MIT Press.
- Bilney, B., Morris, M.E., Churchyard A., Chiu, A.M., & Georgiou-Karistianis, N. (2005). Evidence for a disorder of locomotor timing in Huntington's Disease. *Movement Disorders*. 20: 51-57.
- Brown, R.G., Jahanshahi, M., & Marsden C.D. (1993). The execution of bimanual movements in patients with Parkinson's, Huntington's and cerebellar disease. *Journal of Neurology, Neurosurgery and Psychiatry*. 56:295-7.
- Cardoso de Oliveira S. (2002). The neuronal basis of bimanual coordination: recent neurophysiological evidence and functional models. *Acta Psychologica*. 110:139-159.
- Carson, R.G., & Swinnen, S.P. (2002). Coordination and movement pathology: models of structure and function. *Acta Psychologica*. 110: 357-364.
- Cunnington, R., Iansek, R., Johnson, K.S., & Bradshaw, J.L. (1997). Movement-related potentials in Parkinson's disease: Motor imagery and movement preparation. *Brain*. 120: 1339-1353
- Folstein, M.F., Folstein, S.E. & McHugh, P.R. (1975). "Mini-Mental State" A practical method for grading the cognitive state of patients for the clinician. *Journal of psychiatric research*. 12:189-198.
- Gazzaniga, M.S., Ivry, R.B. & Mangun, G.R. (2002). *Cognitive Neuroscience: The biology of the mind*. (2nd Ed). New York: W.W. Norton & Company.
- Georgiou, N., Bradshaw, J.L., Phillips, J.G., Chiu, E., & Bradshaw, J.A. (1995). Reliance on advance information and movement sequencing in Huntington's disease. *Movement Disorders*. 10: 472-481.
- Georgiou, N., Phillips, J.G., Bradshaw, J.L., Cunnington, R., & Chiu, E. (1997). Impairments of movement kinematics in patients with Huntington's disease: a comparison with and without a concurrent task. *Movement Disorders*. 12:386-396.

Guberman, A. (1994). *An Introduction to Clinical Neurology*. Boston: Little, Brown and Company.

Franz, E.A., & Ramachandran, V.S. (1998). Bimanual coupling in amputees with phantom limbs. *Nature Neuroscience*. 1: 443-444.

Franz, E.A., Waldie K.E., & Smith, M.J. (2000). The effect of callosotomy on novel versus familiar bimanual actions: A neural dissociation between controlled and automatic processes? *Psychological Science*. 11: 82-85.

Hefter, H., Homberg, V., Lange, H.W & Freund, H.J. (1987). Impairment of rapid movement in Huntington's disease. *Brain*. 110: 585-612.

Huntington Study Group (1996). Unified Huntington's Disease Rating Scale: reliability and consistency. *Movement Disorders*. 11: 136-142.

Johnson, K.A., Cunnington, R., Bradshaw, J.L., Phillips, J.G., Iansek, R., & Rogers, M. (1998) Bimanual co-ordination in Parkinson's disease. *Brain* 121: 743-753.

Johnson, K.A., Bennett, J.E., Georgiou, N., Bradshaw, J.L., Chiu, E., Cunnington, R., & Iansek, R. (2000). Bimanual co-ordination in Huntington's disease. *Experimental Brain Research*. Oct;134:483-489.

Johnson, K.A., Cunnington, R., Iansek, R., Georgiou, N., & Chiu, E. (2001) Movement-related potentials in Huntington's disease: movement preparation and execution. *Experimental Brain Research*. 138: 492-499.

Lee, T.D., Wishart, L.R., & Murdoch, E. (2002). Aging, attention and bimanual coordination. *Canadian Journal on Aging*. 21: 549-557.

Leis, B.C., Rand, M.K., Van Gemmert, A.W., Longstall, M.G., Lou, J.S., & Stelmach, G.E. (2005). Movement precues in planning and execution of aiming movements in Parkinson's disease. *Experimental Neurology*. 194:393-409.

Mechsner, F., Kerzel, D., Knoblich, G., & Prinz, W. (2001). Perceptual basis of bimanual coordination. *Nature*. 414:69-73.

Martinez-Martin, P., Gil-Nagel, A., Morlfin Gracia, L., Balseiro Gomez, J., Martinez- Sarries, J., & The cooperative multicentric group. (1994). Unified Parkinson's Disease Rating Scale Characteristics and Structure. *Movement Disorders*. 9: 76-83.

Parkinson's Society of Canada. (2005). What is Parkinson's Disease. Retrieved December 10, 2005 from, <http://www.parkinson.ca/pd/parkinson.html>.

Rosenblum, M. & Kurths, J. (1998). Analysing Synchronization Phenomena from Bivariate Data by Means of the Hilbert Transform. In H. Kantz, J. Kurths & G. Mayer-Kress. Nonlinear Analysis of Physiological Data. (p.91-99). Berlin: Springer Press.

Serrien, D.J., Burgunder, J.M & Wiesendanger, M. (2002). Control of manipulative forces during unimanual and bimanual tasks in patients with Huntington's disease. *Experimental Brain Research*. 143:328-34

Swinnen, S.P. (2002). Intermanual coordination: from behavioural principles to neural-network interactions. *Nature*. 3: 350-360.

Swinnen, S.P., & Wenderoth, N. (2004). Two hands, one brain:cognitive neuroscience of bimanual skill. *Trends Cognitive Science*. 8:18-25.

Thaut, M.H., Miltner, R., Lange, H.W., Hurt, C.P., & Hoemberg V. (1999). Velocity modulation and rhythmic synchronization of gait in Huntington's Disease. *Movement Disorders*. 14: 808-819.

Verbessem, P., Op't Eijnde, B., Swinnen, S.P., Vangheluwe, S., Hespel, P., Dom, R. (2002). Unimanual and bimanual voluntary movement in Huntington's disease. *Experimental Brain Research*. 147:529-37

Appendix I: Ethics Certificate



Université d'Ottawa University of Ottawa

Service de subventions de recherche et d'éthologie Research Grants and Ethics Services

February 12, 2007

**Object: Bimanual coordination in Huntington's and Parkinson's Disease
(file H 10-05-03)**

Dear Professor Balasubramaniam,

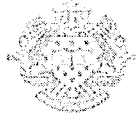
You will find enclosed the Health Sciences and Science Research Ethics Board renewal certification for your research project above-mentioned.

During the course of the study, any modifications to the protocol or forms may not be initiated without prior written approval from the REB. You must also promptly report to the REB all adverse events or experiences encountered by participants.

The renewal certification is retroactive to January 24, 2007 and valid until January 24, 2008. Please submit an annual status report to the Protocol Officer in January, 2008 to either close the file or request a renewal of ethics approval. This document can be found at:
http://www.rges.uottawa.ca/ethics/application_dwn.asp

A copy of this renewal approval will be sent to Research Services, if necessary.

Please do not hesitate to contact me at extension 5387 if you should have any questions.



Université d'Ottawa University of Ottawa

Service de subventions de recherche et deontologie Research Grants and Ethics Services

HEALTH SCIENCES AND SCIENCE RESEARCH ETHICS BOARD

CERTIFICATION OF ETHICS APPROVAL

This is to certify that the University of Ottawa Health Sciences and Science Research Ethics Board (REB) examined the application for extension of ethics approval for the research project **Bimanual coordination in Huntington's and Parkinson's Disease (file H 10-05-03)** submitted by Ramesh Balasubramaniam of the School of Human Kinetics. This project received initial ethics approval on January 24, 2006 by the REB as meeting appropriate ethical standards set out in the Tri-Council Policy Statement and in the Procedures of the University of Ottawa Research Ethics Boards. The University of Ottawa REB members accordingly gave it a one-year extension of ethics approval. This ethics renewal certification is retroactive to January 24, 2007 and valid until January 24, 2008.

550, rue Cumberland 550 Cumberland Street
Ottawa (Ontario) K1N 6N5 Canada Ottawa, Ontario K1N 6N5 Canada

(613) 562-5841 • Téléc./Fax (613) 562-5358
<http://www.uottawa.ca/services/research/ige/index.html>

Appendix II: Standardized Tests

Mini Mental State Examination

ÉCHELLE DE STATUT MENTAL DE FOLSTEIN (MMSE)**

Tang, E.L., Chu H.C. - The Modified Mini-Mental State (3 MS) examination. *J. Clin. Psychiatry*, 48: 314-317, 1987.
Folstein, M.F., Folstein, S.E., McHugh, P.R. - "Mini-Mental State": A practical method for grading the clinician. *J. Psychiatry Res.*, 12: 129-136, 1975.

Watch, pen, sheet

	3MS	MMSE	3MS	MMSE	3MS	MMSE	3MS	MMSE
	5				10			
					6			
To repeat To remember	3	3						
	7	5						
	9	3			5	1		
	15	5			5	1		
					10	1		
	5	3			3	3		
	5	2			9			

DATE _____

COTATION TOTALE :

3MS MMSE

100 30

Consignes et pointage spécifique au MMSE

Unified Parkinson's Disease Rating Scale

UNIFIED PARKINSON'S DISEASE RATING SCALE

I. MENTATION, BEHAVIOR AND MOOD

1. Intellectual Impairment

0 = None.

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

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

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

4 = Severe memory loss with orientation preserved to person only. Unable to make judgements or solve problems.

Requires much help with personal care. Cannot be left alone at all.

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

0 = None.

1 = Vivid dreaming.

2 = "Benign" hallucinations with insight retained.

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

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

3. Depression

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

2 = Sustained depression (1 week or more).

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

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

4. Motivation/Initiative

0 = Normal.

1 = Less assertive than usual; more passive.

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

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

4 = Withdrawn, complete loss of motivation.

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

5. Speech

0 = Normal.

1 = Mildly affected. No difficulty being understood.

2 = Moderately affected. Sometimes asked to repeat statements.

3 = Severely affected. Frequently asked to repeat statements.

4 = Unintelligible most of the time.

6. Salivation

0 = Normal.

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

2 = Moderately excessive saliva; may have minimal drooling.

3 = Marked excess of saliva with some drooling.

4 = Marked drooling, requires constant tissue or handkerchief.

7. Swallowing

0 = Normal.

1 = Rare choking.

2 = Occasional choking.

3 = Requires soft food.

4 = Requires NG tube or gastrostomy feeding.

8. Handwriting

0 = Normal.

1 = Slightly slow or small.

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

3 = Severely affected; not all words are legible.

4 = The majority of words are not legible.

9. Cutting food and handling utensils

0 = Normal.

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

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

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

4 = Needs to be fed.

10. Dressing

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

11. Hygiene

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

12. Turning in bed and adjusting bed clothes

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

13. Falling (unrelated to freezing)

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

14. Freezing when walking

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

15. Walking

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

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

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

17. Sensory complaints related to parkinsonism

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

III. MOTOR EXAMINATION**18. Speech**

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

19. Facial Expression

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

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

0 = Absent.

1 = Slight and infrequently present.

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

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

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

21. Action or Postural Tremor of hands

0 = Absent.

1 = Slight; present with action.

2 = Moderate in amplitude, present with action.

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

4 = Marked in amplitude; interferes with feeding.

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

0 = Absent.

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

2 = Mild to moderate.

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

4 = Severe, range of motion achieved with difficulty.

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

0 = Normal.

1 = Mild slowing and/or reduction in amplitude.

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

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

4 = Can barely perform the task.

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

0 = Normal.

1 = Mild slowing and/or reduction in amplitude.

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

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

4 = Can barely perform the task.

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

0 = Normal.

1 = Mild slowing and/or reduction in amplitude.

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

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

4 = Can barely perform the task.

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

0 = Normal.

1 = Mild slowing and/or reduction in amplitude.

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

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

4 = Can barely perform the task.

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

0 = Normal.

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

2 = Pushes self up from arms of seat.

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

4 = Unable to arise without help.

28. Posture

0 = Normal erect.

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

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

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

4 = Marked flexion with extreme abnormality of posture.

29. Gait

0 = Normal.

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

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

3 = Severe disturbance of gait, requiring assistance.

4 = Cannot walk at all, even with assistance.

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

0 = Normal.

1 = Retropulsion, but recovers unaided.

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

3 = Very unstable, tends to lose balance spontaneously.

4 = Unable to stand without assistance.

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

0 = None.

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

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

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

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

IV. COMPLICATIONS OF THERAPY (In the past week)

A. DYSKINESIAS

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

0 = None

1 = 1-25% of day.

2 = 26-50% of day.

3 = 51-75% of day.

4 = 76-100% of day.

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

0 = Not disabling.

1 = Mildly disabling.

2 = Moderately disabling.

3 = Severely disabling.

4 = Completely disabled.

34. Painful Dyskinesias: How painful are the dyskinesias?

0 = No painful dyskinesias.

1 = Slight.

2 = Moderate.

3 = Severe.

4 = Marked.

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

0 = No

1 = Yes

B. CLINICAL FLUCTUATIONS

36. Are "off" periods predictable?

0 = No

1 = Yes

37. Are "off" periods unpredictable?

0 = No

1 = Yes

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

0 = No

1 = Yes

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

0 = None

1 = 1-25% of day.

2 = 26-50% of day.

3 = 51-75% of day.

4 = 76-100% of day.

C. OTHER COMPLICATIONS

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

0 = No

1 = Yes

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

0 = No
1 = Yes

42. Does the patient have symptomatic orthostasis?

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

0 = No
1 = Yes

V. MODIFIED HOEHN AND YAHR STAGING

STAGE 0 = No signs of disease.

STAGE 1 = Unilateral disease.

STAGE 1.5 = Unilateral plus axial involvement.

STAGE 2 = Bilateral disease, without impairment of balance.

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

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

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

STAGE 5 = Wheelchair bound or bedridden unless aided.

VI. SCHWAB AND ENGLAND ACTIVITIES OF DAILY LIVING SCALE

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

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

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

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

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

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

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

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

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

10% = Totally dependent, helpless. Complete invalid.

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

Unified Huntington's Disease Rating Scale

University of Calgary/Foothills Hospital, Calgary, Alberta, Canada: Oksana Suchowersky, M.D., Gina Rohs, R.N., Mary Lou Klinek, R.N.

Johns Hopkins University, Baltimore, Maryland, U.S.A.: Christopher Ross, M.D., Frederick W. Bylisma, Ph.D., Neal Ranen, MD, Meeia Sherr, BS, RN

University of British Columbia, Vancouver, British Columbia, Canada: Michael Hayden, M.D., Lynn Raymond, M.D., Ph.D., Campbell Clark, Ph.D., Berry Kremer, M.D., Ph.D.

**APPENDIX 2
HUNTINGTON STUDY GROUP
UNIFIED HUNTINGTON'S DISEASE
RATING SCALE**

MOTOR ASSESSMENT

OCULAR PURSUIT (horizontal and vertical)

- 0 = complete (normal)
- 1 = jerky movement
- 2 = interrupted pursuits/full range
- 3 = incomplete range
- 4 = cannot pursue

SACCADE INITIATION (horizontal and vertical)

- 0 = normal
- 1 = increased latency only
- 2 = suppressable blinks or head movements to initiate
- 3 = unsuppressable head movements
- 4 = cannot initiate saccades

SACCADE VELOCITY (horizontal and vertical)

- 0 = normal
- 1 = mild slowing
- 2 = moderate slowing
- 3 = severely slow, full range
- 4 = incomplete range

DYSARTHRIA

- 0 = normal
- 1 = unclear, no need to repeat
- 2 = must repeat to be understood
- 3 = mostly incomprehensible
- 4 = mute

TONGUE PROTRUSION

- 0 = can hold tongue fully protruded for 10 seconds
- 1 = cannot keep fully protruded for 10 seconds
- 2 = cannot keep fully protruded for 5 seconds
- 3 = cannot fully protrude tongue
- 4 = cannot protrude tongue beyond lips

MAXIMAL DYSTONIA (trunk and extremities)

- 0 = absent
- 1 = slight/intermittent
- 2 = mild/common or moderate/intermittent
- 3 = moderate/common
- 4 = marked/prolonged

MAXIMAL CHOREA (face, mouth, trunk and extremities)

- 0 = absent
- 1 = slight/intermittent
- 2 = mild/common or moderate/intermittent
- 3 = moderate/common
- 4 = marked/prolonged

RETROPULSION PULL TEST

- 0 = normal
- 1 = recovers spontaneously
- 2 = would fall if not caught
- 3 = tends to fall spontaneously
- 4 = cannot stand

FINGER TAPS (right and left)

- 0 = normal ($\geq 15/5$ sec.)
- 1 = mild slowing and or reduction in amplitude (11-14/5 sec.)
- 2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement (7-10/5 sec.).
- 3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movements (3-6/5 sec.)
- 4 = Can barely perform the task (0-2/5 sec.)

PRONATE/SUPINATE-HANDS (right and left)

- 0 = normal
- 1 = mild slowing and/or irregular
- 2 = moderate slowing and irregular
- 3 = severe slowing and irregular
- 4 = cannot perform

LURIA (fist-hand-palm test)

- 0 = ≥ 4 in 10 seconds, no cue
- 1 = < 4 in 10 seconds, no cue
- 2 = ≥ 4 in 10 seconds, with cues
- 3 = < 4 in 10 seconds with cues
- 4 = cannot perform

RIGIDITY-ARMS (right and left)

- 0 = absent
- 1 = slight or present only with activation
- 2 = mild to moderate
- 3 = severe, full range of motion
- 4 = severe with limited range

BRADYKINESIA-BODY

- 0 = normal
- 1 = minimally slow (? normal)
- 2 = mildly but clearly slow
- 3 = moderately slow, some hesitation
- 4 = markedly slow, long delays in initiation

GAIT

- 0 = normal gait, narrow base
- 1 = wide base and/or slow
- 2 = wide base and walks with difficulty
- 3 = walks only with assistance
- 4 = cannot attempt

TANDEM WALKING

- 0 = normal for 10 steps
- 1 = 1 to 3 deviations from straight line
- 2 = > 3 deviations
- 3 = cannot complete
- 4 = cannot attempt

COGNITIVE ASSESSMENT

VERBAL FLUENCY TEST (raw score)

SYMBOL DIGIT MODALITIES TEST (raw score)

STROOP INTERFERENCE TEST

- Color Naming (number correct)
- Word Reading (number correct)
- Interference (number correct)