A Study of Motor Control in Healthy Subjects and in Parkinson's Disease Patients

by

Shelly Levy-Tzedek

B.S. Bioengineering
University of California, Berkeley, 2002

M.S. Biological Engineering
Massachusetts Institute of Technology, 2004

SUBMITTED TO THE DEPARTMENT OF BIOLOGICAL ENGINEERING IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY IN BIOLOGICAL ENGINEERING
AT THE
MASSACHUSETTS INSTITUTE OF TECHNOLOGY

JUNE 2008

Signature of Author:_____
Department of Biological Engineering
March 28, 2008

Certified by:_____
Douglas A. Lauffenburger
Professor of Biology, Chemical Engineering and Biological Engineering
Head, Department of Biological Engineering – Thesis Supervisor

Accepted by:_____
Alan J. Grodzinsky
Professor of Electrical, Mechanical, and Biological Engineering
Chair, Graduate Program Committee

Thesis Committee:

Douglas A. Lauffenburger, PhD, Thesis Advisor, MIT

Alan J. Grodzinsky, PhD, Committee Chair, MIT

Jeffrey E. Arle, MD, PhD, Lahey Clinic

Dennis M. Freeman, PhD, MIT

A Study of Motor Control in Healthy Subjects and in Parkinson's Disease Patients

by

Shelly Levy-Tzedek

Submitted to the Department of Biological Engineering
at the Massachusetts Institute of Technology on March 28, 2008
in partial fulfillment of the requirements for the degree of Doctor of Philosophy

ABSTRACT

Parkinson's disease (PD) is a primarily motor disorder which affects at least half a million people in the US alone. Deep brain stimulation (DBS) is a neurosurgical intervention by which neural structures are stimulated electrically by an implanted pacemaker. It has become the treatment of choice for PD, when not adequately controlled by drug therapy. We introduced a novel robotic platform for the study of the effects of DBS on motor control in PD. Subjects performed discrete wrist movements with and without a force field. We found preliminary indication that motor learning may be taking place with stimulation, and demonstrated how robotic testing can augment existing clinical tools in evaluation of the disease.

To study the effect of stimulation on movement frequency, we employed a rhythmic task that required movements of the elbow to remain within a closed shape on a phase plane. Three closed shapes required varying frequency/amplitude combinations of elbow movement. The task was performed with and without visual feedback. Analysis of data from the healthy control subjects revealed a non-monotonic relation between accuracy on the phase plane and movement speed. Further kinematic analyses, including movement intermittency and harmonicity, number and type of submovements (movement primitives) fit per movement cycle, and the effects of vision on intermittency were used to support the model we propose, whereby there exist two subtypes of rhythmic movement; small-amplitude, high-frequency movements are nearly maximally harmonic, and harness the elastic properties of the limb to achieve smoothness and accuracy, and large-amplitude, low-frequency movements share characteristics with a string of discrete movements, and make use of visual feedback to achieve smoothness and accuracy.

Bradykinesia (slowness of movement) is one of the hallmarks of PD. We examined the effects of visual feedback on bradykinesia. PD patients off dopaminergic medication and healthy age-matched controls performed significantly faster movements when visual feedback was withdrawn. For the bradykinetic subjects, this increase in movement speed meant either a mitigation or an elimination of bradykinesia. Our results support a role of the basal ganglia in sensorimotor integration, and argue for the integration of non-vision exercises into patients' physical therapy regime.

Thesis Supervisor: Douglas A. Lauffenburger
Title: Professor of Biology, Chemical Engineering and Biological Engineering
Head, Department of Biological Engineering

ACKNOWLEDGEMENTS

Dr. H.I. Krebs was the principal investigator for this work and provided partial financial support for the work. Data for the discrete reaching task were collected in collaboration with Dr. J.E. Arle at the Lahey Clinic. Data for the rhythmic task were collected in collaboration with Dr. H. Poizner at the University of California, San Diego.

I am gratefully indebted to my advisor, Prof. Doug Lauffenburger, my committee Chair, Prof. Alan Grodzinsky, and my committee members, Dr. J.E. Arle and Prof. Dennis Freeman. Their incredible support has been a column of smoke by day and a column of fire by night, leading me forward. Words fail me as I attempt to describe the gratitude I feel to Dr. J.E. Arle. With infinite kindness, he shared his non-existing time and his vast knowledge. His commitment to academic rigor coupled with clinical relevance, which he wove into our discussions throughout, has been a model for me to follow.

Co-authors for Chapter 2, which was published in Advanced Robotics (2007) are: H.I. Krebs, J.L. Shils, D. Apetauerova, and J.E. Arle.

I am grateful to Prof. N. Hogan and Prof. D. Sternad for insightful comments on previous drafts of Chapter 3 and for engaging discussions that helped shape it into its current form. Many thanks to Dr. J. Shils for helpful comments on Chapter 2.

Warm thanks go to Brandon Rohrer for all his help with the submovement analysis – for freely sharing his time, knowledge and code.

I want to thank the Howard Hughes Medical Institute and the MIT Presidential Fellowship Program for awarding me a pre-doctoral fellowship and a Presidential fellowship, respectively, thus giving me immense freedom during my time at MIT. Special thanks to Dr. Maryrose Franko of HHMI, with whom it was always a pleasure to interact.

I want to thank the lab members that made a real difference in my experience, and with whom I so enjoyed learning – Maxim Shusteff, Thomas Burg, Peter Russo, Emily Cooper, George Popescu, Josh Young, Sarah Mendelowitz, Lorenzo Masia, Nevan Hanumara, Kate Bosecker, Jooeun Ahn, Yun Seong Sun, Benedetta Cesqui, and very special thanks to Steven K. Charles – a real friend and an exemplary colleague. Thank you Marj!

Thanks go out to Nicola Tan and Melissa Kaufman whom I had the pleasure to mentor through MIT's UROP program: our experience together taught me a lot. The students of Bioengineering and Technology were such a great team to TA – and Professor J. Essigmann (at whose office I always felt welcome to just drop by for a quick chat – thank you, John!) a privilege to work with.

Thank you Neil Gershenfeld for the most FABulous experience at MIT – I know I can make almost anything!

Finally, I want to thank my guarding angels – whether in official uniform, in lab coats, in home-made sweaters or in worn-out sweatshirts – you have made all the difference.

This thesis is dedicated in loving memory of Prof. Ted E. Cohn of Berkeley, California. I wish I would be as inspiring a mentor to at least one person as he had been to many.

CHAPTER 1

INTRODUCTION AND BACKGROUND

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disease, often characterized by tremor, slowness of movement and rigidity. The degeneration of neurons in the substantia nigra – one of the four main nuclei in the basal ganglia (BG) – creates a shortage in the neurotransmitter dopamine, resulting in movement impairments that characterize the disease.

In the US, at least 500,000 people are thought to suffer from PD and about 50,000 new cases are reported annually; the average age at onset is around 60, and the incidence rate increases significantly with advancing age (OCPL/NINDS 2006). Aging of the society will likely lead to a larger prevalence of the disease in the population (Dorsey et al. 2007). In fact, it has been suggested that PD is a form of accelerated aging, since some of the key PD symptoms share characteristics with manifestations of normal aging (Pahwa 2006).

The two most common treatments for the disease, dopaminergic medication and deep-brain stimulation (DBS) target the BG: dopaminergic therapy aims to replace the dopamine lost with the death of dopaminergic cells of the substantia nigra, whereas electric stimulation of the subthalamic nucleus (STN) or the globus pallidus (GPi) is presumed to alter the temporal firing patterns within the basal ganglia (Arle et al. 2008), as well as the output signals from the BG (Meissner et al. 2005).

Since PD is primarily a motor disorder, we were interested in using objective metrics of motor performance to evaluate the benefit gained with treatment. More specifically, the initial goal of this work was to correlate specific aspects of movement (such as accuracy, curvature of the path taken to a target, etc.) with stimulation parameters of STN DBS (i.e., frequency, amplitude and pulse width), such that a model of the relation among those parameters can serve to tune stimulation parameters in a closed-loop fashion to gain optimal motor benefit.

Accordingly, we planned to run a series of experiments involving PD patients with implanted stimulators, as well as age-matched controls. In the first phase of experiments, we tested patients with stimulation turned 'on' and 'off', as they performed a reaching task with their wrist, and compared it to age-matched controls. We had subjects perform the task in the presence and in the absence of a force field, so that we could study their ability to adapt to the new motor environment; motor learning has been shown to be impaired in Essential Tremor (ET) patients following thalamic deep-brain stimulation (Chen et al. 2006), and we were interested in the corresponding effects of STN DBS.

Through this first set of experiments we introduced a novel platform for the study of deep-brain stimulation in PD: the "wrist robot", a device able to measure and to perturb wrist movements. Furthermore, through our experience in the first phase of the experiment, we were able to identify a case where the robotic testing was

able to identify an impairment in motor control that was not otherwise captured in a neurological examination, and another where the change in robotic scores with stimulation was opposite in direction to that in the clinical scores. These suggest that the robotic testing can serve as a tool to complement existing clinical tools. These data, together with preliminary evidence that motor learning may be taking place in the presence of stimulation were published in (Levy-Tzedek et al. 2007a), and are included here as **Chapter 2**.

Despite the demonstrated potential for benefit from employing the robotic testing alongside the existing clinical tools, the resolution of the data was not such that merited continuation into more advanced phases of this approach.

In parallel, we were also exploring the effects of deep-brain stimulation on the generation of rhythmic movement.

Pacemaking cells were found in the BG (Plenz and Kital 1999; Surmeier et al. 2005), which could potentially drive rhythmic muscle activity (Goulding and Pfaff 2005; Harris-Warrick 2002). Activation of specific components of the BG has been correlated with particular aspects of rhythmic movement control: the activity of the anterior putamen was found to correlate with increased frequency of finger tapping (Lehericy et al. 2006). Finally, PD patients were found to exhibit an aberrant pattern of rhythm generation (Freeman et al. 1993; Nakamura et al.

1978), and significantly larger fluctuations in gait timing than healthy age-matched controls (Bartsch et al. 2007).

These findings support a role for the BG in control of rhythmic movement, and a natural extension to previous work would be to study the effects of DBS on rhythmic movement generation. The DBS electrodes are implanted within the BG and are thought to modify the aberrant firing rates recorded in PD (Gale et al. 2008; Meissner et al. 2005) and the regularity of the firing (Shils et al. 2008). As such, it would be plausible to expect DBS to have an effect on rhythmic movement generation if indeed it is a function in whose control the BG participate.

To test the hypothesis that generation of rhythmic movement is altered with DBS, we employed a unique experimental paradigm used by (Doeringer and Hogan 1998). In this paradigm, subjects were asked to perform cyclic elbow movements, such that the trace of their movement would remain within a closed shape on a phase plane (velocity vs. position), which was displayed on a computer screen. Subjects performed the task at three different speed ranges, as dictated by three closed shapes on the phase plane, both with and without visual feedback.

Using this approach to studying rhythmic movement generation we were well-poised to investigate the ability of PD patients to coordinate movement – in this

case – to co-modulate speed and position throughout the task. Finally, administering both vision and non-vision trials allowed us to study the role of visual feedback on one of the hallmarks of PD – bradykinesia, or slowness of movement.

We tested four experimental subject groups on this task: PD patients with DBS (tested on and off stimulation), PD patients without stimulators (tested on and off medication), age-matched healthy control subjects, and young healthy control subjects.

In studying the ability of PD patients to coordinate movement, and the effects of treatment on this ability – PD medication has been suggested to affect "intensive" aspects of movement (such as movement extent), but not "coordinative" aspects of movement, when patients performed a discrete reaching task (Schettino et al. 2006); some preliminary results were presented in (Levy-Tzedek et al. 2007b) – we expected that, for all experimental groups, the ability to coordinate movement – or movement accuracy – would be a monotonic function of movement speed. We found this not to be the case. In **Chapter 3** we present the data from the healthy control subjects and the smoothness and harmonicity analyses performed on them, supporting a conclusion that there are two "subtypes" of movement within rhythmic movement. In **Chapter 4** we bolster this conclusion with further kinematic analyses demonstrating different types and numbers of

submovements employed for each rhythmic-movement subtype, as well as a differential effect of vision on either subtype.

In **Chapter 5** we present data showing that both PD patients off medication and age-matched controls perform significantly faster movements in the non-vision trials than in the vision trials. For bradykinetic PD patients, that meant that their bradykinetic symptoms were either mitigated or altogether eliminated, suggesting that visual feedback plays a role in the process leading to bradykinesia, and supporting a role for the BG in sensorimotor integration.

In **Chapter 6** we examine the frequencies, and the ranges of frequencies, at which subjects from all four experimental groups perform the task, and the effects of treatment on the PD groups.

We conclude with **Chapter 7**, where we summarize our findings, draw conclusions and discuss suggestions for future work.

But first, in the remainder of this chapter, we survey the literature on PD, the BG, and the major forms of available treatment.

Background

Parkinson's disease

Parkinson's disease (PD) is the second most common age-related disease. It is a chronically progressive neurodegenerative disease, characterized most prominently by tremor at rest, rigidity, slowness of movement (bradykinesia), paucity of movement, and inability to begin a voluntary movement ("freezing"; akinesia). Other symptoms include impaired balance, reduction in movement amplitude (hypokinesia), in voice volume (hypophonia), in facial expressions (hypomimia), in size (micrographia) and speed of handwriting, and in stride length when walking. Affect and cognition may also be affected. These symptoms are brought about following a loss of neurons in the zona compacta of the substantia nigra (Calne 2005). These neurons form the nigrostriatal dopaminergic pathway, and their loss leads to a deficiency of the neurotransmitter dopamine in the striatum (Dauer and Przedborski 2003). It is estimated that 80 percent of dopamine content in the motor pathways is lost before people develop symptoms of PD. This is equivalent to losing approximately 50 percent of the dopamine-producing neurons in the substantia nigra (Stoessl et al. 2005).

Recent data suggest that the pathophysiologic changes in PD include aberrations in the overall firing rates, decreased neuronal selectivity, and increased neuronal oscillation and synchronization in the basal ganglia (BG;

(Gale et al. 2008). The BG form a part of neural networks that are implicated in aspects of motor planning (Mehler-Wex et al. 2006), control of rhythmic movements (Freeman et al. 1993; Takakusaki et al. 2004), and processing of visual information (Sil'kis 2007).

It has been suggested that PD is a form of accelerated aging, since some of the key PD symptoms are similar to signs of normal aging (Pahwa 2006); however, there is currently no sound support for this view (Hawkes 2008; Sandyk 1997).

Causes

It is not clear what brings about Parkinson's disease. Environmental and genetic causes have been researched, but these explain only a minority of the cases, and a clear link has yet to be established. While some environmental factors are associated with a higher risk of developing parkinsonian symptoms (such as pesticides (Chade et al. 2006)), others (e.g., cigarette smoking and coffee drinking) are associated with a reduced risk of developing PD (Hernan et al. 2002; Scott et al. 2005). Certain occupations are associated with increased incidence of PD – namely, healthcare, teaching and farming (Goldman et al. 2005). Further hypotheses for possible causes include a self-generated toxin, such as the result of a normal metabolism of dopamine, which generates harmful reactive oxygen species (Cohen 1984).

The specific molecular events that provoke neurodegeneration in PD have not yet been elucidated. There exist, however, several models that aid in the study of the disease and its symptoms.

Models

Genetic

An important pathological feature of PD is the presence of Lewy bodies – 15-μm-diameter filamentous, cytoplasmic inclusions, found mainly in the cells of the substantia nigra in PD patients. A major component of a Lewy body is a protein called α-synuclein (Spillantini et al. 1997). Mutations in the α-synuclein gene have been associated with rare familial cases of PD, and this discovery led to the development of genetically engineered flies and mice that overexpress the mutant human gene (Betarbet et al. 2002). However, α-synuclein is found in all Lewy bodies, including the vast majority of PD cases, where there is no α-synuclein-gene mutation. Other implicated genes are: parkin, DJ-1, PINK1, LRRK2 and UCH-L1; as with α-synuclein, the proteins parkin and ubiquitin (the protein product of UCH-L1) have been identified as components of Lewy bodies (Bonifati 2005). DJ-1 knockout *Drosophila* flies have been created and are now being studied (Meulener et al. 2005).

Chemical

Pharmacological agents and environmental toxins have been used to develop experimental PD models. Most notable among those is MPTP.

MPTP

In 1983, researchers reported that parkinsonian symptoms were observed in a group of drug users, and were caused by MPTP (1-methyl-4- phenyl-1,2,3,6-tetrahydropyridine). Subsequently, MPTP was shown to be an effective neurotoxin that selectively destroys nigrostriatal cells. It is a thermal-breakdown product of a narcotic used by drug abusers as a heroin substitute (Singer et al. 1986). As consumption of this substance results in clinical symptoms that are remarkably similar to idiopathic PD - also referred to as sporadic PD, is without a known cause, and accounts for 95% of the cases (Dauer and Przedborski 2003) – researchers have used it to develop animal models of the disease in susceptible species, including mice, cats and primates (Betarbet et al. 2002). It is often used as the gold-standard model for preclinical evaluations of new therapies aimed at treating PD symptoms (Dauer and Przedborski 2003).

Several other animal models exist that target specific species, exhibit certain subsets of the parkinsonian symptom range and/or seek to prove or disprove specific hypotheses, such as the respective roles of, and interactions between,

oxidative stress, mitochondrial respiration defect, and abnormal protein aggregation in PD pathogenesis. For reviews of some of these models, see (Betarbet et al. 2002; Dauer and Przedborski 2003).

Treatments over the years

Medicine

Replenishment of striatal dopamine through oral administration of levodopa, a dopamine precursor, initially alleviates most of the disease symptoms. However, after several years of treatment, its effect wears off, and patients develop dyskinesia (involuntary movements), which may become quite disabling. There is currently an open debate in the field as to whether levodopa may even accelerate the progression of the disease (Fahn 2005; Walton-Hadlock et al. 2005). Some researchers claim that levodopa impairs learning, but not generalization, for certain tasks (Shohamy et al. 2006). Other dopamine agonists are also used, such as pramipexole (Moller and Oertel 2005). Often, dopaminergic therapy is combined with pharmacological agents that either inhibit the metabolism of levodopa in circulation, or ones that inhibit the breakdown of dopamine in the brain (Pahwa 2006), thus making the dopaminergic therapeutic agent potent for longer periods. At this time, no treatment actually halts dopaminergic neuron degeneration; rather, existing treatments alleviate some of the symptoms.

Neuroablation

Lesioning of the globus pallidus pars interna (GPi), the ventral intermediate nucleus (VIM) of the thalamus, and the subthalamic nucleus (STN) were performed in the 1950s-1960s. With the introduction of levodopa in 1967, this surgical approach was mostly abandoned (Ashkan et al. 2004). The long-term complications associated with levodopa and improved surgical procedures brought pallidotomy, thalamotomy and subthalamotomy back to the foreground of therapy in the 1980s-1990s (Thobois et al. 2005a).

Deep Brain Stimulation

In 1987, the first deep-brain stimulation (DBS) procedure was performed to treat tremor (Benabid et al. 2005). The target of the stimulation was the thalamic VIM region, and the treatment proved efficient in reducing tremor. In 1993, the procedure was applied to the STN (Benabid et al. 2005), and in 1994 to the GPi (Breit et al. 2004) to treat PD. Stimulation has several advantages over neuroablation (Thobois et al. 2005a): it can be done bilaterally, has fewer side effects, can be adjusted , or turned off altogether. Note that once the stimulator is implanted, patients may still consume medication. Usually, the amount required for optimal performance is much reduced compared to pre-operation dosages (Ashkan et al. 2004). DBS is also extensively used to treat patients with dystonia

(Tagliati et al. 2004). It is currently explored as a possible treatment for obsessive-compulsive disorder (Lipsman et al. 2007), Tourette syndrome (Temel and Visser-Vandewalle 2004), chronic pain, depression and other disorders (Shils et al. 2008).

Deep brain stimulation

DBS targets

Initially, DBS was performed in the VIM of the thalamus, to replace thalamotomy in the treatment of tremor. Bilateral high-frequency stimulation of the STN and of the GPi for the treatment of PD followed in 1993 and 1994, respectively (Breit et al. 2004). DBS of either of these two sites within the BG addresses not only tremor, but also rigidity, akinesia and drug-induced dyskinesia (Ashkan et al. 2004). Few studies compared these two targets for relative efficacy. The main tool for evaluation of the disease progression, and hence for the comparison among treatments, is the Unified Parkinson's Disease Rating Scale (UPDRS). It is an overall assessment rating scale that quantifies all the motor and behavioral aspects of PD. It includes: mentation, activites of daily living (ADL) and a motor examination. Obeso et al. found STN as a target to give more improvement on the UPDRS motor scores than GPi (Obeso et al. 2001), and others found it to be associated with decreased levodopa requirements and longer stimulator half-life (Ashkan et al. 2004). In a 69-participant study, which followed patients 3-4 years

post-operatively, these results were duplicated, and STN was found to be a superior target also in terms of better ADL scores and prolonged periods with good mobility and no dyskinesia. Both groups showed deterioration in performance in motor function and ADL (when in the 'on medication' state) over time. The STN group also showed deterioration in speech and postural stability. More commonly, those with STN DBS experienced cognitive decline, speech difficulty, instability, gait disorders and depression (Rodriguez-Oroz et al. 2005). For both targets, a comparison between pre-operative, off-medication, performance and 4-years post-operative, off-stimulation, performance showed no difference as regards the UPDRS motor score (tremor, rigidity and hypokinesia), but a significant worsening in gait, postural stability and speech, suggesting that the disease progresses outside the dopaminergic system in its late stages (Freund 2005).

Effects and side effects

Studies reporting the postoperative results of bilateral STN DBS implantation are generally favorable (see, for example, (Kawakami et al. 2005; Lezcano et al. 2004)). Summary of several such results, presented in (Ashkan et al. 2004), shows 38-68% improvement in motor function[1], 32-68% improvement in ADL[2], 64-93% improvement in levodopa-induced dyskinesia, and 32-77% reduction in levodopa dose. Freezing of gait has also been shown to significantly improve

[1] defined by the UPDRS, part 3
[2] defined by the UPDRS, part 2

with STN DBS when comparing "off medication" state pre-operatively and postoperatively; no significant change observed between "on medication" states (Davis et al. 2006).

Reports of negative side effects exist, but are more sporadic. First and foremost is the risk during the implantation surgery itself, where an inadvertent hemorrhage may cause a debilitating stroke, or death. Otherwise, there have been anecdotal reports of post-surgery: (1) transient acute depression (Bejjani et al. 1999); this has been reported for pallidotomy (lesioning of the GPi) as well (Bezerra et al. 1999); (2) laughter (when stimulation settings were set to 50% over therapeutic values) (Krack et al. 2001); (3) pseudobulbar crying[3] (Okun et al. 2004); (4) tremor, which did not exist pre-operatively (Thobois et al. 2005b); and (5) reversible worsening in stuttering (Burghaus et al. 2006).

Cortical stimulation

Stimulation of the cortex is emerging as a new treatment for pain management. Stimulation is delivered either via an epidurally implanted electrode array, or non-invasively, using transcranial magnetic stimulation (TMS). Transcranial stimulation frequencies are relatively low, typically in the range 0.2-10 Hz; stimulation lasts seconds to minutes, and its (progressively fading) effect may last up to 1 month. This approach is very much in the exploratory stage, and

[3] Pseudobulbar crying is a term used for patients who cry, but show no other evidence of subjective feelings of depression such as dysphoria, anhedonia, or vegetative signs; this side effect was reported for a single case, where the patient had previously undergone pallidotomy

although some patients greatly benefit from the treatment, many experience very slight improvement or none at all. For a review on the current state of this treatment, see (Pridmore et al. 2005). Recently, cortical stimulation has been proposed as a less risky alternative to deep brain stimulation for treatment of Parkinson's disease. The rationale being, as the motor cortex is affected by corrupt signals from the basal ganglia in PD, stimulating it may have a positive outcome on PD symptoms. Whether this approach is successful remains to be seen (Arle and Shils 2008).

So far, one study reported a 1-month improvement in gait and bradykinesia following motor- and prefrontal-cortex repetitive TMS (rTMS) (Lomarev et al. 2006).

Another study, using extradural motor cortex stimulation (EMCS) in 6 patients, with stimulation parameters ranging between: 2.5-6 v, 150-180 μsec, 25-40 Hz, reports a 42-62% decrease in overall UPDRS score, and a reduction of 11-73% in levodopa prescribed. Patient follow-up in this study was done 4 months to 2.5 years post-operatively. The researchers assert that the treatment affects the entire spectrum of PD symptoms (Pagni et al. 2005).

Basal ganglia

The BG consist of four subcortical nuclei – the striatum, the substantia nigra, the globus pallidus, and the subthalamic nucleus (see figure 1) – and play a major

role in voluntary movement control. They receive input from the cerebral cortex and send output to the brain stem, and through the thalamus back to the prefrontal, premotor and motor cortices (Kandel et al. 2000).

Substantia nigra

The substantia nigra is comprised of two parts: the reticular (pars reticulata, SNr) and the compact (pars compacta, SNpc). The cells of the pars compacta are dopaminergic (dopamine-producing) and also contain neuromelanin, a dark pigment derived from dopamine. Neuromelanin accumulates with age in lysosomal granules of the cells and accounts for the dark color of this structure as well as for its ensuing name. Degeneration of these dopaminergic neurons in PD causes a depletion of dopamine in the striatum, most notably in the putamen.

Striatum

The striatum – comprised of the putamen, the caudate nucleus, and the ventral striatum – is the major recipient of inputs to the BG from the cerebral cortex, the thalamus and the brain stem. Its neurons project to the globus pallidus and to the reticular portion of the substantia nigra.

Globus pallidus

The globus pallidus is also comprised of two parts: the internal (GPi) and the external (GPe). The cells of the GPi, like the cells of SNr, use the inhibitory neurotransmitter GABA (γ-aminobutyric acid). The GPi plays a part in sensorimotor processing (Deletis and Shils 2002) and is one of the targets for deep brain stimulation.

Subthalamic nucleus

The STN lies just below the thalamus, and its glutamatergic cells are the only excitatory projections in the BG. Based on microelectrode recording studies, it is thought that tonic activity is abnormally increased in the STN of patients with Parkinson's disease, and is responsible for the parkinsonian symptoms. Further support for this view comes from the amelioration in parkinsonism observed after lesioning of the STN (Kandel et al. 2000). STN is currently the main target for DBS for PD. Researchers using deep brain stimulation as a tool to study the STN concluded that the STN, especially in the left hemisphere, is involved in visuospatial orientation (Witt et al. 2006). Others assert that the STN serves as a regulator of the associative[4] and limbic[5] circuits (Temel et al. 2005).

[4] The prefrontal association cortex is involved with creating a working memory, an active maintenance of information relevant to an ongoing behavior
[5] The limbic system is associated with emotion, learning, and memory

Inter-BG circuitry

Output from the BG to the thalamus and the brain stem, in the form of tonic inhibition, comes from SNr and GPi. This inhibitory output is thought to be modulated by two parallel pathways coming down from the striatum: the 'direct' and the 'indirect' pathways (Alexander and Crutcher 1990) (see figure 2).
In the **indirect pathway**, striatal signals pass to the GPe, and from there to the STN, both interactions mediated by inhibitory GABA. The STN then sends excitatory signals to the GPi and SNr. In the **direct pathway**, inhibitory GABA striatal signals pass directly to the GPi and SNr.

On the one hand, then, the output nuclei, GPi and SNr, receive excitatory input from the indirect pathway, and on the other hand, they receive inhibitory input through the direct pathway. These opposing signals are not fired constantly, but their relative timing is used to modulate the output of the basal ganglia. In other words, the neurons in the output nuclei discharge inhibitory signals tonically at high frequency. When (phasic) input arrives from the direct pathway, the output nuclei are transiently suppressed, the thalamus and, ultimately, the cortex, are activated, and movement is facilitated. Alternatively, input from the indirect pathway is excitatory to the output nuclei, which then further suppress thalamic activation, and inhibits movement. Recently, it has been suggested that there exist yet two more pathways: a 'hyperdirect' one, with faster conduction velocities

than the two others, in which the STN receives input from the cortex, and it sends its output to the BG output nuclei GPi/SNr (Nambu 2005); and one where striatal neurons are directly connecting to forebrain and control or modulate cortical activity (Furuta and Kaneko 2006).

Extra-BG circuitry

The inter-BG pathways are a part of a cortical-subcortical neuronal circuit. Cortical neurons input into the caudate-putamen in the striatum, the signals pass through either the direct or the indirect pathway to the output nuclei, which project into the thalamus, which in turn, sends input back to the cortex (e.g., Graybiel 2001). Topographic projections from the cortex – primary motor (MC) and premotor[6] areas – enter the putamen. Movement-related neurons in the putamen are organized somatotopically. This topographic organization propagates down through the GPi to the thalamus. The skeletomusclar loop is then closed when projections from the thalamus reach the cortex[7] (Kandel et al. 2000).

The direct pathway is driven by the dopaminergic D1 receptors in the striatum, and removes the inhibition of the BG output nuclei on the ventrolateral (VL) thalamus with the result of a facilitatory influence on the motor cortex. The indirect pathway, driven by dopaminergic D2 receptors in the striatum, exerts an

[6] including the arcuate and the supplementary motor area (SMA)
[7] SMA, premotor cortex, and precentral motor fields

inhibitory influence (Kaji et al. 2005). The parallel functional architecture of the two parallel pathways, with opposing influences on the BG output nuclei, was described by (Alexander and Crutcher 1990).

Why are there two pathways

Little is known about the interaction between the direct and the indirect pathway. One possibility is that the direct pathway is in charge of facilitating a movement, while the indirect pathway is responsible for putting the breaks on that movement, smoothing it out. This reciprocity is consistent with the view that the BG play a role in scaling movement amplitude/velocity. Another possibility is that the two project into different cell populations in the GPi/SNr, and while the direct pathway reinforces a selected pathway, the indirect pathway suppresses potentially conflicting patterns. This focusing of neural activity is similar to the inhibitory surround described for various sensory systems (Kandel et al. 2000).

BG in PD

Because the dopaminergic input from the SNc to the striatum acts as inhibitory input to the indirect pathway (D2 receptor), and as excitatory input to the direct pathway (D1 receptor), its absence leads to an overactive indirect pathway, and hypoactive direct pathway. The overall effect is excessive inhibitory influence on the motor cortex, which underlies bradykinesia and akinesia (Kaji et al. 2005).

Recently, a modeling approach has been employed as a powerful technique for the study of the mechanisms whereby DBS achieves its clinical benefits in PD (Arle et al. 2008; McIntyre et al. 2007; Shils et al. 2008).

Learning in the BG

Cells of several regions in the BG are autonomously active and possibly act as 'pacemakers'. Such dopaminergic neurons in the SNpc, when their firing rate is accelerated, cause a pause in cholinergic interneuron activity in the striatum. That pause in their activity is thought to generate a learning signal in the striatum (Surmeier et al. 2005). One reason for this hypothesis is that all synapses in the BG, apart from those of the STN, are GABA-ergic, and so a pause in activity brings about increased activity of the target neuron.

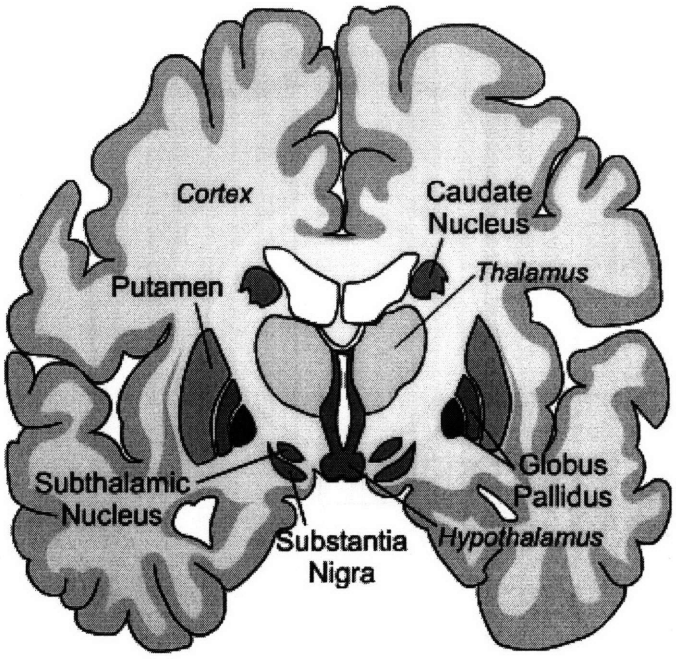

Figure 1. A schematic of the basal ganglia and the thalamus (HOPES 2008).

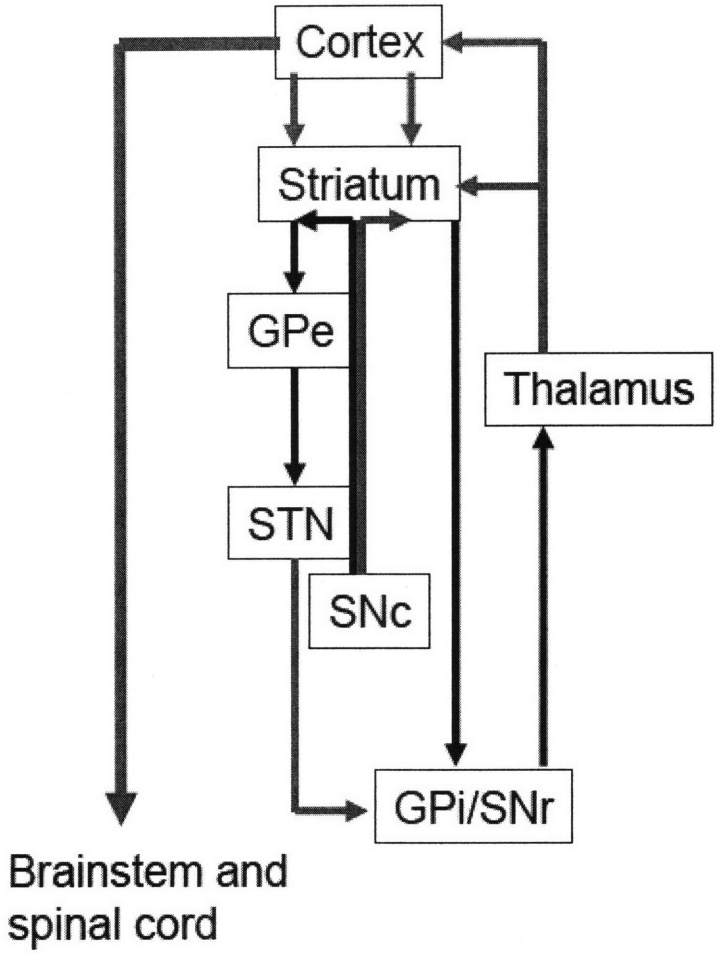

Figure 2. Alexander, Crutcher and Delong's model of the BG (Alexander et al. 1990):gray connections represent the inhibitory connections and the black connections represent excitatory ones. Modified from (Shils et al. 2008); See same for a schematic of the stimulated PD state.

REFERENCES

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

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

Arle JE, Mei LZ, and Shils JL. Modeling parkinsonian circuitry and the DBS electrode. I. Biophysical background and software. *Stereotact Funct Neurosurg* 86: 1-15, 2008.

Arle JE, and Shils JL. Motor cortex stimulation for pain and movement disorders. *Neurotherapeutics* 5: 37-49, 2008.

Ashkan K, Wallace B, Bell BA, and Benabid AL. Deep brain stimulation of the subthalamic nucleus in Parkinson's disease 1993-2003: where are we 10 years on? *Br J Neurosurg* 18: 19-34, 2004.

Bartsch R, Plotnik M, Kantelhardt JW, Havlin S, Giladi N, and Hausdorff JM. Fluctuation and synchronization of gait intervals and gait force profiles distinguish stages of Parkinson's disease. *Physica A* 383: 455-465, 2007.

Bejjani BP, Damier P, Arnulf I, Thivard L, Bonnet AM, Dormont D, Cornu P, Pidoux B, Samson Y, and Agid Y. Transient acute depression induced by high-frequency deep-brain stimulation. *N Engl J Med* 340: 1476-1480, 1999.

Benabid AL, Chabardes S, and Seigneuret E. Deep-brain stimulation in Parkinson's disease: long-term efficacy and safety - What happened this year? *Curr Opin Neurol* 18: 623-630, 2005.

Betarbet R, Sherer TB, and Greenamyre JT. Animal models of Parkinson's disease. *Bioessays* 24: 308-318, 2002.

Bezerra ML, Martinez JV, and Nasser JA. Transient acute depression induced by high-frequency deep-brain stimulation. *N Engl J Med* 341: 1003; author reply 1004, 1999.

Bonifati V. Genetics of Parkinson's disease. *Minerva Med* 96: 175-186, 2005.

Breit S, Schulz JB, and Benabid AL. Deep brain stimulation. *Cell Tissue Res* 318: 275-288, 2004.

Burghaus L, Hilker R, Thiel A, Galldiks N, Lehnhardt FG, Zaro-Weber O, Sturm V, and Heiss WD. Deep brain stimulation of the subthalamic nucleus reversibly deteriorates stuttering in advanced Parkinson's disease. *J Neural Transm* 113: 625-631, 2006.

Calne D. A definition of Parkinson's disease. *Parkinsonism Relat Disord* 11 Suppl 1: S39-40, 2005.

Chade AR, Kasten M, and Tanner CM. Nongenetic causes of Parkinson's disease. *J Neural Transm Suppl* 147-151, 2006.

Chen H, Hua SE, Smith MA, Lenz FA, and Shadmehr R. Effects of human cerebellar thalamus disruption on adaptive control of reaching. *Cereb Cortex* 16: 1462-1473, 2006.

Cohen G. Oxy-radical toxicity in catecholamine neurons. *Neurotoxicology* 5: 77-82, 1984.

Dauer W, and Przedborski S. Parkinson's disease: mechanisms and models. *Neuron* 39: 889-909, 2003.

Davis JT, Lyons KE, and Pahwa R. Freezing of gait after bilateral subthalamic nucleus stimulation for Parkinson's disease. *Clin Neurol Neurosurg* 108: 461-464, 2006.

Deletis V, and Shils JL. *Neurophysiology in Neurosurgery: A Modern Intraoperative Approach*. Academic Press, 2002.

Doeringer JA, and Hogan N. Intermittency in preplanned elbow movements persists in the absence of visual feedback. *J Neurophysiol* 80: 1787-1799, 1998.

Dorsey ER, Constantinescu R, Thompson JP, Biglan KM, Holloway RG, Kieburtz K, Marshall FJ, Ravina BM, Schifitto G, Siderowf A, and Tanner CM. Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. *Neurology* 68: 384-386, 2007.

Fahn S. Does levodopa slow or hasten the rate of progression of Parkinson's disease? *J Neurol* 252 Suppl 4: IV37-IV42, 2005.

Freeman JS, Cody FW, and Schady W. The influence of external timing cues upon the rhythm of voluntary movements in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 56: 1078-1084, 1993.

Freund HJ. Long-term effects of deep brain stimulation in Parkinson's disease. *Brain* 128: 2222-2223, 2005.

Furuta T, and Kaneko T. Third pathway in the cortico-basal ganglia loop: Neurokinin B-producing striatal neurons modulate cortical activity via striato-innominato-cortical projection. *Neurosci Res* 54: 1-10, 2006.

Gale JT, Amirnovin R, Williams ZM, Flaherty AW, and Eskandar EN. From symphony to cacophony: Pathophysiology of the human basal ganglia in Parkinson disease. *Neurosci Biobehav Rev* 32: 378-387, 2008.

Goldman SM, Tanner CM, Olanow CW, Watts RL, Field RD, and Langston JW. Occupation and parkinsonism in three movement disorders clinics. *Neurology* 65: 1430-1435, 2005.

Goulding M, and Pfaff SL. Development of circuits that generate simple rhythmic behaviors in vertebrates. *Curr Opin Neurobiol* 15: 14-20, 2005.

Graybiel AM. Neural networks: neural systems V: basal ganglia. *Am J Psychiatry* 158: 21, 2001.

Harris-Warrick RM. Voltage-sensitive ion channels in rhythmic motor systems. *Curr Opin Neurobiol* 12: 646-651, 2002.

Hawkes CH. Parkinson's disease and aging: Same or different process? *Mov Disord* 23: 47-53, 2008.

Hernan MA, Takkouche B, Caamano-Isorna F, and Gestal-Otero JJ. A meta-analysis of coffee drinking, cigarette smoking, and the risk of Parkinson's disease. *Ann Neurol* 52: 276-284, 2002.

HOPES. Basal Ganglia. [Online image] Available http://www.stanford.edu/group/hopes/basics/braintut/ab6.html. *The Huntington's Disease Outreach Project for Education, at Stanford* Figure AB-18, 2008.

Kaji R, Urushihara R, Murase N, Shimazu H, and Goto S. Abnormal sensory gating in basal ganglia disorders. *J Neurol* 252 Suppl 4: IV13-IV16, 2005.

Kandel E, Schwartz JH, and Jessel T. Principles of neuroscience. McGraw-Hill, 2000.

Kawakami N, Jessen H, Bordini B, Gallagher C, Klootwyk J, and Garell CP. Deep brain stimulation of the subthalamic nucleus in Parkinson's disease. *WMJ* 104: 35-38, 2005.

Krack P, Kumar R, Ardouin C, Dowsey PL, McVicker JM, Benabid AL, and Pollak P. Mirthful laughter induced by subthalamic nucleus stimulation. *Mov Disord* 16: 867-875, 2001.

Lehericy S, Bardinet E, Tremblay L, Van de Moortele PF, Pochon JB, Dormont D, Kim DS, Yelnik J, and Ugurbil K. Motor control in basal ganglia circuits using fMRI and brain atlas approaches. *Cereb Cortex* 16: 149-161, 2006.

Levy-Tzedek S, Krebs HI, Shils JL, Apetauerova D, and Arle JE. Parkinson's disease: a motor control study using a wrist robot. *Advanced Robotics* 21: 1201-1213, 2007a.

Levy-Tzedek S, Poizner H, Song D, and Krebs HI. Dopamine-replacement therapy acts to alleviate hypokinesia in Parkinson's disease but fails to normalize coordinative aspects of movement when performing a rhythmic task. In: *Society for Neuroscience Abstracts* 2007b, p. 818.819.

Lezcano E, Gomez-Esteban JC, Zarranz JJ, Lambarri I, Madoz P, Bilbao G, Pomposo I, and Garibi J. Improvement in quality of life in patients with advanced Parkinson's disease following bilateral deep-brain stimulation in subthalamic nucleus. *Eur J Neurol* 11: 451-454, 2004.

Lipsman N, Neimat JS, and Lozano AM. Deep brain stimulation for treatment-refractory obsessive-compulsive disorder: the search for a valid target. *Neurosurgery* 61: 1-11; discussion 11-13, 2007.

Lomarev MP, Kanchana S, Bara-Jimenez W, Iyer M, Wassermann EM, and Hallett M. Placebo-controlled study of rTMS for the treatment of Parkinson's disease. *Mov Disord* 21: 325-331, 2006.

McIntyre CC, Miocinovic S, and Butson CR. Computational analysis of deep brain stimulation. *Expert Rev Med Devices* 4: 615-622, 2007.

Mehler-Wex C, Riederer P, and Gerlach M. Dopaminergic dysbalance in distinct basal ganglia neurocircuits: implications for the pathophysiology of Parkinson's disease, schizophrenia and attention deficit hyperactivity disorder. *Neurotox Res* 10: 167-179, 2006.

Meissner W, Leblois A, Hansel D, Bioulac B, Gross CE, Benazzouz A, and Boraud T. Subthalamic high frequency stimulation resets subthalamic firing and reduces abnormal oscillations. *Brain* 128: 2372-2382, 2005.

Meulener M, Whitworth AJ, Armstrong-Gold CE, Rizzu P, Heutink P, Wes PD, Pallanck LJ, and Bonini NM. Drosophila DJ-1 mutants are selectively sensitive to environmental toxins associated with Parkinson's disease. *Curr Biol* 15: 1572-1577, 2005.

Moller JC, and Oertel WH. Pramipexole in the treatment of Parkinson's disease: new developments. *Expert Rev Neurother* 5: 581-586, 2005.

Nakamura R, Nagasaki H, and Narabayashi H. Disturbances of rhythm formation in patients with Parkinson's disease: part I. Characteristics of tapping response to the periodic signals. *Percept Mot Skills* 46: 63-75, 1978.

Nambu A. A new approach to understand the pathophysiology of Parkinson's disease. *J Neurol* 252 Suppl 4: IV1-IV4, 2005.

Obeso JA, Olanow CW, Rodriguez-Oroz MC, Krack P, Kumar R, and Lang AE. Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease. *N Engl J Med* 345: 956-963, 2001.

OCPL/NINDS. Parkinson's Disease: Hope Through Research. *National Institute of Neurological Disorders and Stroke, National Institutes of Health* 2006.

Okun MS, Raju DV, Walter BL, Juncos JL, DeLong MR, Heilman K, McDonald WM, and Vitek JL. Pseudobulbar crying induced by stimulation in the region of the subthalamic nucleus. *J Neurol Neurosurg Psychiatry* 75: 921-923, 2004.

Pagni CA, Zeme S, Zenga F, and Maina R. Extradural motor cortex stimulation in advanced Parkinson's disease: the Turin experience: technical case report. *Neurosurgery* 57: E402; discussion E402, 2005.

Pahwa R. Understanding Parkinson's disease: an update on current diagnostic and treatment strategies. *J Am Med Dir Assoc* 7: 4-10, 2006.

Plenz D, and Kital ST. A basal ganglia pacemaker formed by the subthalamic nucleus and external globus pallidus. *Nature* 400: 677-682, 1999.

Pridmore S, Oberoi G, Marcolin M, and George M. Transcranial magnetic stimulation and chronic pain: current status. *Australas Psychiatry* 13: 258-265, 2005.

Rodriguez-Oroz MC, Obeso JA, Lang AE, Houeto JL, Pollak P, Rehncrona S, Kulisevsky J, Albanese A, Volkmann J, Hariz MI, Quinn NP, Speelman JD, Guridi J, Zamarbide I, Gironell A, Molet J, Pascual-Sedano B, Pidoux B, Bonnet AM, Agid Y, Xie J, Benabid AL, Lozano AM, Saint-Cyr J, Romito L, Contarino MF, Scerrati M, Fraix V, and Van Blercom N. Bilateral deep brain stimulation in Parkinson's disease: a multicentre study with 4 years follow-up. *Brain* 128: 2240-2249, 2005.

Sandyk R. The accelerated aging hypothesis of Parkinson's disease is not supported by the pattern of circadian melatonin secretion. *Int J Neurosci* 90: 271-275, 1997.

Schettino LF, Adamovich SV, Hening W, Tunik E, Sage J, and Poizner H. Hand preshaping in Parkinson's disease: effects of visual feedback and medication state. *Exp Brain Res* 168: 186-202, 2006.

Scott WK, Zhang F, Stajich JM, Scott BL, Stacy MA, and Vance JM. Family-based case-control study of cigarette smoking and Parkinson disease. *Neurology* 64: 442-447, 2005.

Shils JL, Mei LZ, and Arle JE. Modeling parkinsonian circuitry and the DBS electrode. II. Evaluation of a computer simulation model of the basal ganglia with and without subthalamic nucleus stimulation. *Stereotact Funct Neurosurg* 86: 16-29, 2008.

Shohamy D, Myers CE, Geghman KD, Sage J, and Gluck MA. L-dopa impairs learning, but spares generalization, in Parkinson's disease. *Neuropsychologia* 44: 774-784, 2006.

Sil'kis IG. The contribution of synaptic plasticity in the basal ganglia to the processing of visual information. *Neuroscience and Behavioral Physiology* 37: 779-790, 2007.

Singer TP, Salach JI, Castagnoli N, Jr., and Trevor A. Interactions of the neurotoxic amine 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine with monoamine oxidases. *Biochem J* 235: 785-789, 1986.

Spillantini MG, Schmidt ML, Lee VM, Trojanowski JQ, Jakes R, and Goedert M. Alpha-synuclein in Lewy bodies. *Nature* 388: 839-840, 1997.

Stoessl AJ, Adams JR, and Wszolek ZK. Functional imaging in inherited Parkinson's. *Parkinson Report* 16: 14-18, 2005.

Surmeier DJ, Mercer JN, and Chan CS. Autonomous pacemakers in the basal ganglia: who needs excitatory synapses anyway? *Curr Opin Neurobiol* 15: 312-318, 2005.

Tagliati M, Shils J, Sun C, and Alterman R. Deep brain stimulation for dystonia. *Expert Rev Med Devices* 1: 33-41, 2004.

Takakusaki K, Saitoh K, Harada H, and Kashiwayanagi M. Role of basal ganglia-brainstem pathways in the control of motor behaviors. *Neurosci Res* 50: 137-151, 2004.

Temel Y, Blokland A, Steinbusch HW, and Visser-Vandewalle V. The functional role of the subthalamic nucleus in cognitive and limbic circuits. *Prog Neurobiol* 76: 393-413, 2005.

Temel Y, and Visser-Vandewalle V. Surgery in Tourette syndrome. *Mov Disord* 19: 3-14, 2004.

Thobois S, Delamarre-Damier F, and Derkinderen P. Treatment of motor dysfunction in Parkinson's disease: an overview. *Clin Neurol Neurosurg* 107: 269-281, 2005a.

Thobois S, Tisch S, Xie-Brustolin J, Mertens P, Hariz MI, Benatru I, Broussolle E, and Limousin-Dowsey P. Can chronic subthalamic nucleus stimulation induce de novo tremor in Parkinson's disease? *Mov Disord* 20: 1066-1069, 2005b.

Walton-Hadlock JL, Fahn S, Keiburtz K, and Tanner CM. Levodopa and the Progression of Parkinson's Disease. *New England Journal of Medicine* 352: 1386-1386, 2005.

Witt K, Kopper F, Deuschl G, and Krack P. Subthalamic nucleus influences spatial orientation in extra-personal space. *Mov Disord* 21: 354-361, 2006.

CHAPTER 2

PARKINSON'S DISEASE: A MOTOR CONTROL STUDY USING A WRIST ROBOT

Advanced Robotics, Vol. 21, No. 10, pp. 1201–1213 (2007)

Also available online - www.brill.nl/ar

Short paper

Parkinson's disease: a motor control study using a wrist robot

S. LEVY-TZEDEK [1,*], H. I. KREBS [1], J. L. SHILS [2], D. APETAUEROVA [2] and J. E. ARLE [2]

[1] *Massachusetts Institute of Technology, Cambridge, MA 02139, USA*
[2] *Lahey Clinic, Burlington, MA 01805, USA*

Received 24 October 2006; accepted 30 December 2006

Abstract—Deep brain stimulation (DBS) is the most common surgical procedure for patients with Parkinson's disease (PD). DBS has been shown to have a positive effect on PD symptoms; however, its specific effects on motor control are not yet understood. We introduce the novel use of a wrist robot in studying the effects of stimulation on motor performance and learning. We present results from patients performing reaching movements in a null field and in a force field with and without stimulation. We discuss special cases where robotic testing reveals otherwise undiagnosed impairments, and where clinical scores and robot-based scores display opposing trends.

Keywords: Wrist robot; Parkinson's disease; deep brain stimulation; motor control; motor learning.

1. INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disease, often characterized by tremor, slowness of movement and rigidity. The degeneration of neurons in the substantia nigra creates a shortage in the neurotransmitter dopamine, resulting in movement impairments that characterize the disease. In the US, at least 500 000 people are thought to suffer from PD and about 50 000 new cases are reported annually; the average age of onset is around 60 [1]. Aging of the society will likely lead to a larger prevalence of the disease in the population. At this time, there is no cure for PD. After initial diagnosis, many patients have only a mild manifestation of the symptoms and need no treatment for several years. When the severity of symptoms increases, doctors usually prescribe levodopa to help replace the brain's lost dopamine [1]. For those patients for whom pharmacological treatment loses efficacy, the most common therapeutic surgical procedure is deep brain stimula-

*To whom correspondece should be addressed. E-mail: shellyle@mit.edu

tion (DBS) of the subthalamic nucleus (STN). In 1987 the first deep-brain high-frequency stimulation of the thalamus was performed to treat tremor and in 1993 the technique was applied to the subthalamic nucleus for treatment of advanced PD [2].

STN DBS has been demonstrated to be effective in mitigating the primary disease symptoms. An average improvement of about 52% over baseline is reported, using the unified PD rating scale (UPDRS) motor score, in the 'off medication' condition. However, the literature suggests an incidence of adverse effects related to the surgery in approximately 11% of the cases [3].

While DBS demonstrates a high rate of success as a PD treatment, its mechanism of action is not yet well understood. Robotic technology has been used extensively in studying unimpaired subjects (e.g., Refs [4–7]). It has also been employed in studying stroke [8–10], Huntington disease [11] and PD [12]. It has been used in combination with imaging techniques [13], and may similarly assist in elucidating specific effects of stimulation on motor performance and motor learning.

To investigate motor learning, we used an implicit learning task: explicit learning refers to the acquisition of information accompanied by awareness of the learned information and its influence; implicit learning refers to similar acquisition without awareness of the learned information and its influence. In particular, we are investigating procedural learning, which is a form of implicit learning where skill improves over repetitive trials. Imaging results with healthy young males showed an increase in activation of the striatum during early phases of implicit motor learning and decreased activation during the skill-transfer phase [12, 13]. As the striatum is a component of the basal ganglia, which are affected in PD, we set out to test PD patients in the 'off medication' state on the same task and compare them with age-matched controls [12].

Here, we expand upon our previous studies, and employ a novel wrist robot to study motor performance and motor learning in PD patients with DBS, comparing the stimulation 'on' and stimulation 'off' conditions, in the 'on medication' state. While significant contributions to the study of motor control and to neuroscience were achieved *via* studies involving more proximal limb segments, i.e., shoulder-and-elbow, devices that allow similar kinds of studies with more distal limb segments such as the wrist and hand offer certain advantages as these areas have larger cortical representation, which are more lateralized and thus will facilitate our future tests with cortical stimulators.

To test motor performance, we examine the characteristics of subjects' movements in a null force field (see Methods)—we evaluate their point-to-point wrist movements, and score the movements based on their accuracy, smoothness and timing. We compare the scores of PD patients with DBS turned on to their score when the DBS is turned off. We also compare those scores to those of age-matched controls. After performing the point-to-point movements in the null force field, subjects' movements are examined in the presence of a force field. Their rate of adaptation to the field is assessed and compared among the groups. As mentioned

earlier, one goal of the research is to evaluate the effect of stimulation on motor learning. Another goal is to use the wrist robot as a patient-evaluation device to provide a non-invasive, objective, accurate and reproducible method of scoring patients' performance, based on which adjustments to stimulation parameters could be made.

2. METHODS

2.1. Wrist robot

The wrist robot is configured for safe, stable and compliant operation in close physical contact with humans. This is achieved using backdrivable hardware and impedance control—a key feature of the robot control system. The robot can move, guide or perturb movements of a subject's limb, and can record motions and mechanical quantities such as the position, velocity and torques applied. It is designed with 3 d.o.f., corresponding to those of the human wrist: abduction–adduction (AA), flexion–extension (FE) and pronation–supination (PS). A curved rail sits between four guide wheels, which allow it to rotate. Figure 1 shows the wrist robot.

AA and FE motions are accomplished by a differential mechanism with a total speed reduction of 8:1, while PS movement is accomplished by a curved rail geared to 10:1. A key aspect of the design is combining these speed-reduction ratios in a compact, low-friction transmission, as it permits the use of smaller and lighter actuators than a direct-drive design of comparable performance, while maintaining a low robot output impedance (i.e., the device is highly 'backdrivable'). Ideally, a subject attempting to move the robot at speeds from 0 to 38 rad/s should encounter

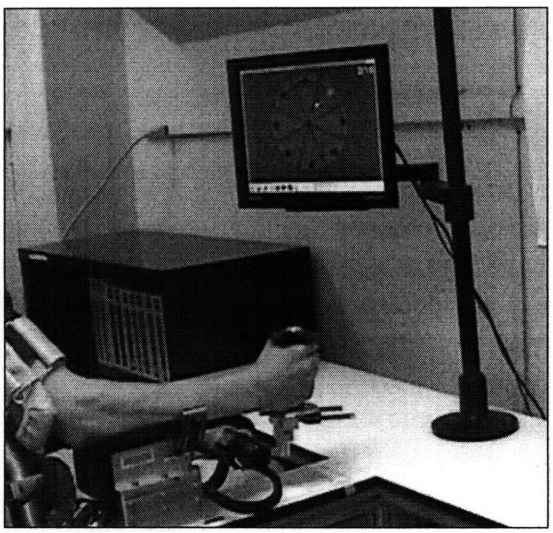

Figure 1. The wrist robot. Here, used to control a cursor on the screen and move it to a presented target.

no significant friction, inertia or stiffness. In this design, the apparent stiffness is zero, the maximum apparent inertia for each wrist d.o.f. is estimated to be (30–45) $\times$ 10^{-4} kg m^2 and the maximum apparent static friction torque is 0.29 N m for PS, 0.075 N m for FE and 0.075 N m for AA. The device accommodates the range of motion of everyday tasks: FE 60°/60°, AA 30°/45° and PS 70°/70°. The torque output from the device is capable of lifting the person's hand against gravity, accelerating the inertia and appears to be able to overcome most forms of hypertonicity. The device can produce a range of continuous stall torques with no cogging (1.85 N m for PS, 1.43 N m for FE and 1.43 N m for AA), impedances (0 to 60 N m/rad for PS, 0 to 40 N m/rad for FE and 0 to 40 N m/rad for AA) and damping (0 to 1 N m s/rad for PS, 0 to 0.45 N m s/rad for FE and 0 to 0.45 N m s/rad for AA). For more details on the device, see Refs [14–16].

2.2. Protocol

Ten subjects diagnosed with PD and with bilaterally implanted DBS participated in the experiment after giving their informed consent. Subjects were seated in a chair, resting their arm on an armrest, while holding the robotic manipulandum's end-effector in their hand. They used the end-effector to control a cursor on a computer screen positioned in front of them. They were presented with one center target and eight peripheral ones (see Fig. 1). A different target was highlighted every 1.6 s, alternating between a randomly selected peripheral target and the center target. This duration was chosen to allow enough time for subjects who may have a long reaction time and move at a slow speed to complete the movement. We asked the subjects to reach the targets with the cursor as they changed color. Each set of 80 movements out to the periphery and back to the center is termed a block. Some of the blocks were performed in a null force field and some in the presence of a curl force field. The forces used are proportional to the subject's wrist velocity, and are perpendicular to it:

$$\begin{bmatrix} \tau_{FE} \\ \tau_{AA} \end{bmatrix} = \begin{bmatrix} 0 & 0.15 \\ -0.15 & 0 \end{bmatrix} \begin{bmatrix} \dot{\theta}_{FE} \\ \dot{\theta}_{AA} \end{bmatrix}, \tag{1}$$

where τ is the torque vector (Nm), $\dot{\theta}$ is the wrist velocity vector (rad/s) multiplied by constant matrix representing the imposed viscosity (Nm s/rad).

After an initial practice block (null perturbation forces), subjects performed one block in the absence of perturbation forces (null), six blocks within a curl force field (A), two blocks with a curl field in the opposite direction (B) and, finally, one more block in a null force field. The null block is used to study baseline performance. The set of blocks in the A field is used to study motor learning. The set of blocks in the B field is used to study skill transfer, i.e., the effect that learning one task (compensating for force field A) has on the rate of learning of another task (compensating for force field B). The final null block is used to verify that no effects of fatigue are present. Subjects performed the entire set of null–A–B–null blocks

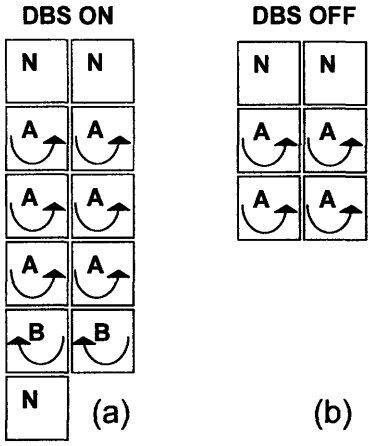

Figure 2. Order of blocks in the DBS ON (a) and DBS OFF (b) conditions. Each block comprises a set of 80 movements to a peripheral target and back to the center target. N = null field, A = force field in one direction (clockwise or counter clockwise; controlled by the sign of the B matrix in (1) and B = force field in the opposite direction to A. Half of the subjects experienced a clockwise force field in A and half experienced a counterclockwise forced field in A.

with stimulation on (DBS ON; see Fig. 2a). After a 1-h break, their stimulators were turned off bilaterally and testing resumed 15 min later. With stimulation off (DBS OFF) patients performed only the practice block, the baseline null block and four blocks of the A field (see Fig. 2b). Subjects continued to follow their normal medication regimen throughout the experiment. When in the stimulation 'on' state, patients were evaluated using a battery of neuropsychological tests, including the UPDRS and the modified Hoehn and Yahr scale (H&Y). When in the stimulation 'off' state, they were re-evaluated only on the H&Y scale and on Part 3 (Motor) of the UPDRS.

We analyzed the movement traces generated by the subjects and scored each movement based on parameters that reflect movement quality. Here, we present two of these measures of performance: path length and lateral deviation.

2.3. Robot-based performance metrics

Reaching movements involving the shoulder and elbow have been shown to follow a straight trajectory [4], and performance measures were developed based on this observation. Measuring total path length to a target and deviation from a straight line to the target as indicators of movement quality has been a common approach [12, 17]. Wrist movements have not yet been similarly characterized. However, we see a very clear pattern indicating these two measures are relevant for wrist movements: when healthy subjects are exposed to a force field which perturbs their movements, they suffer an increase in both path length and lateral deviation, but learn to compensate for the force field, which is manifested in a shorter path length and less deviation (unpublished observations).

We use the following equations for calculating these measures:

$$\text{Path length:} \quad S = \int_{s_0}^{s_N} ds, \tag{2}$$

where S is the total path length and s_0 and s_N are the first and last position points, respectively. We, thus, measure the total length of the subject's wrist movement as the subject reaches from the central target to a peripheral one. This value is assigned as the path length score for that movement. The score per block is the average score for the 80 individual movements in the block.

$$\text{Lateral deviation:} \quad D = \sqrt{\sum_{i=1}^{N} (s(i) - p(i))^2}, \tag{3}$$

where D is the total lateral deviation, N is the total number of samples, $s(i)$ is the wrist position at sample i and $p(i)$ is the point of intersection between the straight line connecting the targets and a normal to that line, passing through $s(i)$. That is, for each movement, we pass an imaginary line connecting the center point to the peripheral target and calculate by how much the subject's wrist deviated laterally from that line. This value is the assigned lateral deviation score for the movement.

3. RESULTS

We are currently pursuing our initial goal of recruiting and testing 40 subjects. Here, we present several cases that exemplify the versatility of the robotic apparatus in identifying various facets of the disease. We have so far encountered five distinct categories of patients in the experiment: one typical and four atypical; we discuss each separately below.

3.1. Patient A—typical

A 62-year-old right-handed male, diagnosed with PD 14 years prior to the experiment, had bilaterally implanted STN DBS 1.5 years earlier. The subject had no problem performing the task with stimulation on (see Fig. 3a). With stimulation off, the subject was still able to perform the task, although with less agility (see Fig. 3b). When forces were introduced in the DBS OFF state, performance deteriorated further (*cf.*, Fig. 3c and d), yet improved over successive blocks (*cf.*, Fig. 3d and e). Five out of the 10 patients we tested so far fit this overall pattern.

3.2. Patient B—clinical scores and robotic scores do not agree

A 65-year-old left-handed male, diagnosed with PD 17 years prior to the experiment, had bilaterally implanted STN DBS 2.5 years earlier. The patient had been

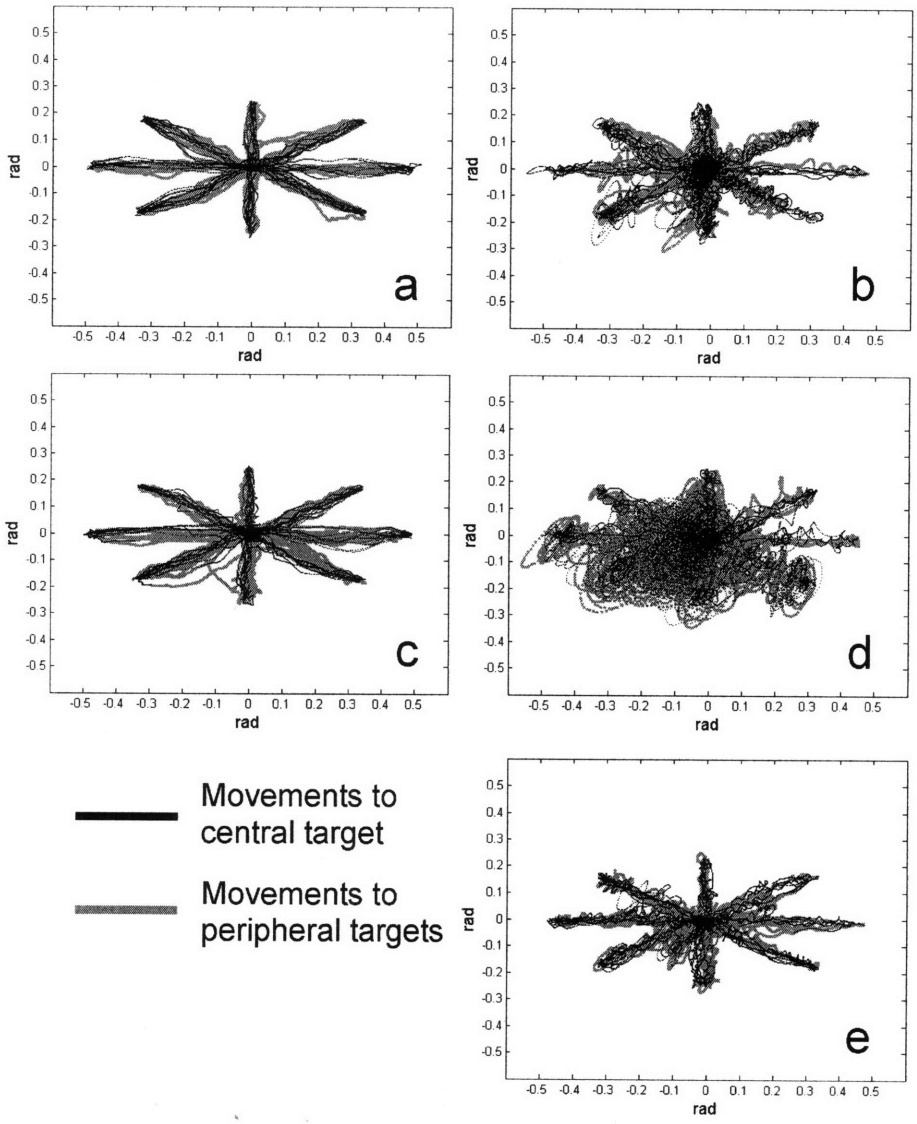

Figure 3. Movement traces of patient A in the DBS ON (left column) and DBS OFF (right column) conditions. (a) DBS ON, block 2 (null field); (b) DBS OFF, block 2 (null field); (c) DBS ON, block 3 (A field); (d) DBS OFF, block 3 (A field) and (e) DBS OFF, block 6 (A field).

suffering from a severe bipolar disorder when off stimulation. This subject's performance appeared to improve according to the robot-based measures when stimulation was turned off, yet his UPDRS Part 3 and H&Y scores indicated a decline (see Table 1 and Fig. 4).

3.3. Patient C—inability to perform task

A 62-year-old right-handed male, diagnosed with PD 15 years prior to the experiment, had bilaterally implanted STN DBS 1 year earlier. The subject's clinical scores were not abnormal for his condition (see Table 1). He verbally confirmed understanding the task, but was unable to execute it as required. The task can be de-

Table 1.
ON/OFF clinical scores

Patient	UPDRS On	UPDRS Off	H&Y On	H&Y Off
A	9	35	2	3
B	10	17	0	2
C	11	22	2.5	2.5
D	9	29	0	3
E	27	32	3	3

The Motor section (Part 3) of the UPDRS and the modified H&Y. Higher scores indicate increased impairment.

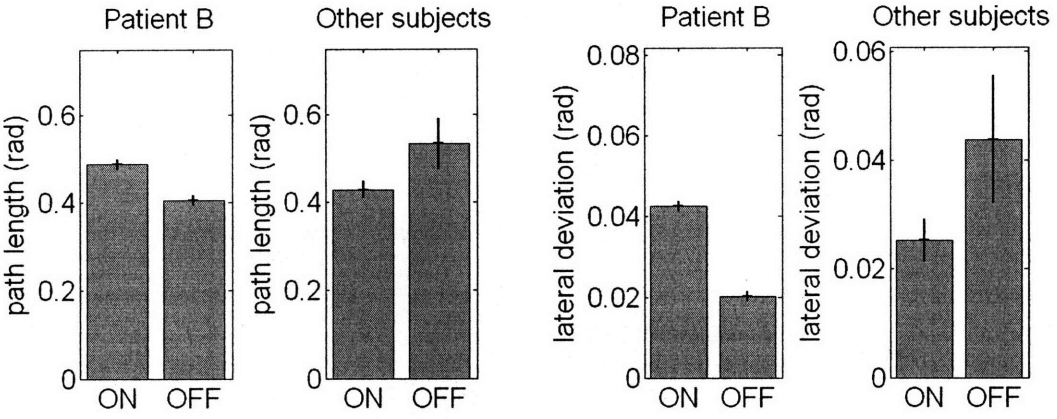

Figure 4. Robot-based performance measures demonstrating an improvement in patient B's performance when stimulation is turned off. Patient B's results are plotted next to the average performance of seven other PD patients.

composed into random and predictable movement directions. When the movement direction is random, the subject must wait for a visually displayed target before initiating movement. The predictable movement was the return back to the center target after each reach to a peripheral one. Cursor location was recorded during the 1.6 s allocated for each movement. Inspecting Fig. 5, one would notice that the patient was not moving the wrist at all during times that were allocated for 'back to the center' movements (black line), but only during times allocated for 'out to a peripheral target' movements (gray line). This pattern persisted in both the DBS ON and DBS OFF states. Inspection of Fig. 5 reveals the subject had no physical problem with reaching the targets or visual impairment that prevented him from detecting the highlighted target. It appears the presence or absence of a randomness component played a role in his ability to respond to stimuli. This impairment, readily evident using the robotic task, was not otherwise detected with the conventional clinical scales. We speculate that may be due to a difficulty with executing concatenated tasks.

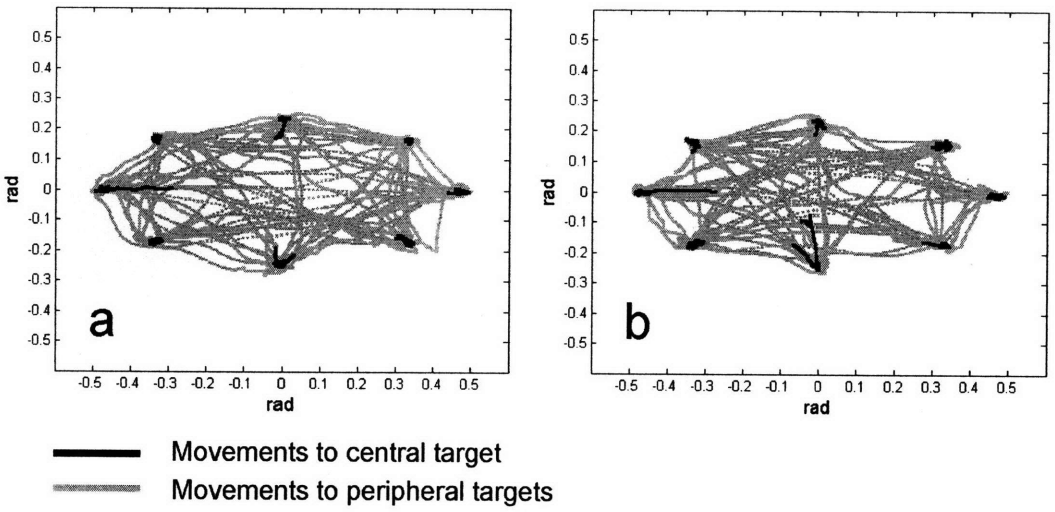

Figure 5. Movement traces of patient C, demonstrating his inability to perform the task in either the 'stimulation on' (a) or 'stimulation off' (b) state.

3.4. Patient D—inability to perform task only in the DBS OFF state

A 66-year-old left-handed male, diagnosed with PD 12 years prior to the experiment, had bilaterally implanted STN DBS 1.5 years earlier. The subject had no particular difficulty performing the task with stimulation on (see Fig. 6a). With stimulation off, the subject was unable to perform the task as required (see Fig. 6b).

3.5. Patient E—long wear-off period, mostly gait affected by PD

An 80-year-old right-handed male, diagnosed with PD 14 years prior to the experiment, had bilaterally implanted STN DBS 5 years earlier. This subject's PD symptoms manifested themselves mostly in the lower limbs. From DBS ON to DBS OFF, his UPDRS Part 3 score worsened by 3 points and his H&Y score did not change (see Table 1). We also found no statistically significant difference in his performance between the two conditions using the robot-based measures. The patient anecdotally mentioned days-long periods for the stimulation effects to wear off. This is a case where (i) evaluation shortly after turning the stimulation off may not be relevant and (ii) using the wrist robot for evaluation when symptoms manifest themselves mostly in the lower limb may be less relevant.

4. DISCUSSION

We introduce the use of a wrist robot, able to measure wrist position and exert forces on it, in evaluation of PD patients with implanted DBS. We test subjects in a null field to evaluate their baseline performance, and then in the presence of a force field to examine their capacity for motor learning and their rate of motor learning. We survey five distinct cases that exemplify the breadth of the patient spectrum that was

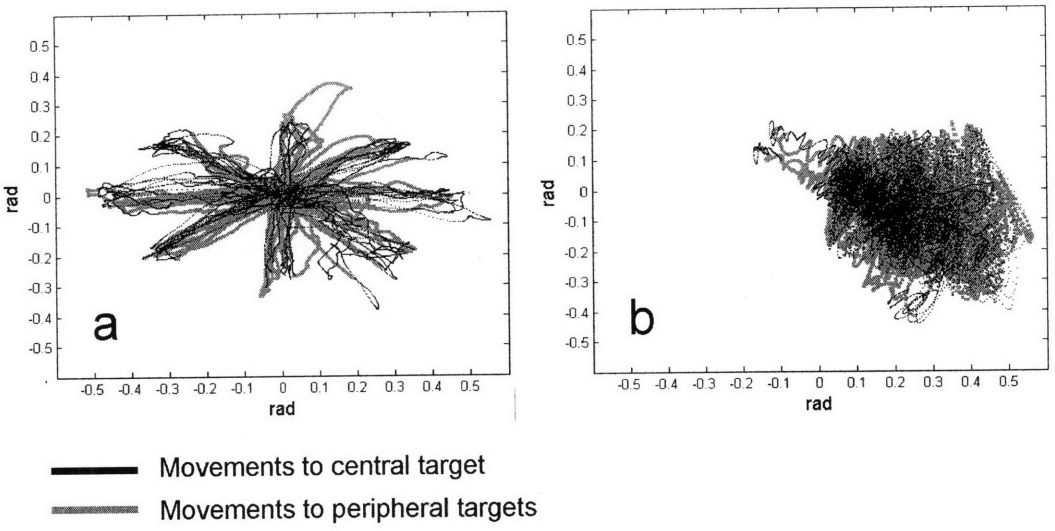

Figure 6. Movement traces of patient D, demonstrating his ability to perform the task in the 'stimulation on' (a) state, but not in the 'stimulation off' (b) state. Both figures depict the patient's movements in a null field.

tested: (i) one which displayed a 'typical' behavior when stimulation was turned off (five out of 10 subjects), (ii) one which scored better on robotic-based measures, but worse on clinical scales when stimulation was turned off, (iii) one who was unable to perform the task in either stimulation setting, (iv) one who was unable to perform the task only when in the stimulation 'off' setting, and (v) one who displayed no significant difference between the 'on' and the 'off' states, possibly due to a combination of factors—long stimulation-effects wear-off periods and primary symptom manifestation on the lower limbs. The initial results from these cases suggest that the wrist robot may serve as a complimentary tool to clinical scales—to detect different aspects of movement not covered by the clinical scales. To further investigate this possibility, we are currently testing more patients as well as healthy controls.

Our robotic technology opens the door to a variety of applications within the patient care realm. One such application that we are presently studying is the possibility of using the robot to update stimulation parameters: each patient's performance is evaluated at baseline before stimulators are implanted. After stimulators are implanted and turned on, as the patients perform reaching movements using the wrist robot, their trajectories are analyzed, and new stimulation settings are identified and transmitted to the pulse generator for optimized performance (gain scheduling).

5. CONCLUSIONS

We report the novel combination of two well-established and validated technologies, i.e. DBS and the wrist robot, to study the effects of stimulation on motor control in patients with PD. In particular, our goals are to evaluate specific parameters of

movement in a null field—timing, accuracy and smoothness—as well as rate of motor learning, manifested as adaptation to the presence of a force field. With stimulation parameters as the input and robot-based measures of performance as output, we might be better able to optimally adapt the DBS parameters to the patients' needs over time even as the neuro-degeneration process progresses. The wrist robot provides a novel platform for studying the effects of neurological diseases and their treatments on motor performance and motor learning.

Acknowledgment and disclosure

S. L.-T. is a Howard Hughes Medical Institute Predoctoral Fellow and is supported in part by the VA Veterans Affairs grants B3607R. H. I. K. is a co-inventor in the MIT-held patent for the robotic device used to test patients in this work. He holds equity positions in Interactive Motion Technologies, Inc., the company that manufactures this type of technology under license to MIT.

REFERENCES

1. National Institute of Health, National Institute of Neurological Disorders and Stroke, *Parkinson's Disease Backgrounder*. NIH, Bethesda, MD (2004).
2. A. L. Benabid, S. Chabardes and E. Seigneuret, Deep-brain stimulation in Parkinson's disease: long-term efficacy and safety—What happened this year?, *Curr. Opin. Neurol.* **18**, 623–630 (2005).
3. G. Kleiner-Fisman, J. Herzog, D. N. Fisman, F. Tamma, K. E. Lyons, R. Pahwa, A. E. Lang and G. Deuschl, Subthalamic nucleus deep brain stimulation: summary and meta-analysis of outcomes, *Mov. Disord.* **21**, S290–S304 (2006).
4. T. Flash and N. Hogan, The coordination of arm movements: an experimentally confirmed mathematical model, *J. Neurosci.* **5**, 1688–1703 (1985).
5. R. Shadmehr and F. A. Mussa-Ivaldi, Adaptive representation of dynamics during learning of a motor task, *J. Neurosci.* **14**, 3208–3224 (1994).
6. K. A. Thoroughman and R. Shadmehr, Learning of action through adaptive combination of motor primitives, *Nature* **407**, 742–747 (2000).
7. H. Gomi and M. Kawato, Human arm stiffness and equilibrium-point trajectory during multi-joint movement, *Biol. Cybern.* **76**, 163–171 (1997).
8. H. I. Krebs, N. Hogan, M. L. Aisen and B. T. Volpe, Robot-aided neurorehabilitation, *IEEE Trans. Rehabil. Eng.* **6**, 75–87 (1998).
9. H. I. Krebs, M. L. Aisen, B. T. Volpe and N. Hogan, Quantization of continuous arm movements in humans with brain injury, *Proc. Natl. Acad. Sci. USA* **96**, 4645–4649 (1999).
10. B. Rohrer, S. Fasoli, H. I. Krebs, R. Hughes, B. Volpe, W. R. Frontera, J. Stein and N. Hogan, Movement smoothness changes during stroke recovery, *J. Neurosci.* **22**, 8297–8304 (2002).
11. M. A. Smith and R. Shadmehr, Intact ability to learn internal models of arm dynamics in Huntington's disease but not cerebellar degeneration, *J. Neurophysiol.* **93**, 2809–2821 (2005).
12. H. I. Krebs, N. Hogan, W. Hening, S. V. Adamovich and H. Poizner, Procedural motor learning in Parkinson's disease, *Exp. Brain Res.* **141**, 425–437 (2001).
13. H. I. Krebs, T. Brashers-Krug, S. L. Rauch, C. R. Savage, N. Hogan, R. H. Rubin, A. J. Fischman and N. M. Alpert, Robot-aided functional imaging: application to a motor learning study, *Hum. Brain Mapp.* **6**, 59–72 (1998).

14. H. I. Krebs, J. Celestino, D. Williams, M. Ferraro, B. T. Volpe and N. Hogan, A wrist exten sion to MIT-MANUS, in: *Advances in Human-Friendly Robotic Technologies for Movement Assistance/Movement Restoration for People with Disabilities*, Z. Bien and D. Stefanov (Eds), pp. 377–390. Springer, Berlin (2004).
15. H. I. Krebs and N. Hogan, Therapeutic robotics: A technology push, *Robotics* **94**, 1727–1738 (2006).
16. H. I. Krebs, B. T. Volpe, D. Williams, J. Celestino, S. K. Charles, D. Lynch and N. Hogan, Robot-aided neurorehabilitation: a robot for wrist rehabilitation, *IEEE Trans. Neural Syst. Rehabil. Eng.*, in press (2007).
17. N. Malfait, D. M. Shiller and D. J. Ostry, Transfer of motor learning across arm configurations, *J. Neurosci.* **22**, 9656–9660 (2002).

CHAPTER 3

NON-MONOTONICITY ON A SPATIO-TEMPORALLY DEFINED CYCLIC TASK: EVIDENCE OF TWO MOVEMENT TYPES?

ABSTRACT

We tested 23 healthy subjects using a novel paradigm for the study of rhythmic movements. The required amplitude and frequency ranges of the elbow movements were specified to the subjects using a closed shape on a phase-plane display, showing velocity vs. position. We found that the combined accuracy in velocity and in position throughout the movement was not a monotonic function of movement speed. Our findings suggest that specific frequency/amplitude combinations give rise to two distinct types of movements – one of a more rhythmic nature, and the other of a more discrete nature.

INTRODUCTION

In healthy subjects, we have previously found the basal ganglia (BG) to play a role in motor control and motor learning when subjects performed a discrete motor task (Krebs et al. 1998). The BG are severely affected in Parkinson's disease, and our group has been involved with studying motor control – performance and learning – in Parkinson's disease (PD) on discrete tasks (Krebs et al. 2001; Levy-Tzedek et. al. 2007; Tunik et al. 2007; Messier et al. 2007; Krebs et. al. in press). The BG are also implicated in control of rhythmic limb movements (Takakusaki et al. 2004). In fact, activation of specific components of the BG has been correlated with particular aspects of rhythmic movement control, such as the frequency of finger tapping (Lehéricy et al. 2006).

Furthermore, the BG have been shown to be involved in pacemaking activity on the neuronal level (Plenz and Kital 1999; Surmeier et al. 2005), which could potentially drive rhythmic muscle activity (Harris-Warrick 2002).

We have expanded our studies to include rhythmic tasks to study the differences between control of rhythmic movement in healthy subjects and in their PD peers. To study the effects of vision on motor control in PD, we included both 'vision' and 'non-vision' trials, where visual feedback was present or absent, respectively. Here we report the results for the healthy control subjects.

The experimental paradigm was designed such that timing cues were not explicit, but rather, timing was implicitly dictated by a closed shape on a phase-plane display (where speed is plotted vs. position). The phase plane afforded a way to display target amplitude and frequency of movement to subjects without giving them any explicit timing cues (e.g., via a metronome). It is widely used to study dynamical systems, especially those that typically underlie the production of rhythmic behavior (e.g. limit-cycle oscillators; Kelso and Tuller 1984). A key feature of the phase plane is that it "suppresses time"; that is, a phase-plane plot fully characterizes the dynamics of a one-dimensional oscillator yet does not explicitly represent time. Therefore, by using a phase plane display we were able to give precise instructions about target amplitude and frequency while minimizing requirements for processing explicit timing information.

We evaluated the accuracy of subjects' movements under different amplitude and frequency conditions. That is, we evaluated how accurately they were able to

continuously modulate both speed and position of their elbow to stay within the specified ranges.

To our knowledge, the relation between speed and accuracy in a task that requires co-modulation of speed and position throughout the task, as opposed to tasks that are either spatially or temporally defined, has not been explored.

The relation between speed and accuracy has been extensively explored in the context of what has become known as the Fitts task, where task requirements are either spatially (Fitts 1954; Fitts and Peterson 1964) or temporally (Schmidt et al. 1979; Wright and Meyer 1983) defined. In the traditional paradigm, subjects either perform the task as fast as possible (e.g., Fitts 1954), or at a high frequency (movement time = 180-500 ms, Schmidt et al. 1979; Wright and Meyer 1983), and accuracy is measured at the endpoints of the movement only. In our task, by comparison, speed profiles are constrained to be within a particular range, either at slow, intermediate or fast speeds, and their spatial variation is dictated by a closed shape displayed on the phase plane.

In addition, Fitts was able to formulate a lawful relation between movement time (MT) and required accuracy, which has become known a Fitts' Law (Fitts 1954):

$$MT = a + b \cdot \log_2\left(\frac{2D}{W}\right) \qquad \text{(eq. 1)}$$

Where D is the distance to the target, W is the target width; a and b are empirically determined constants. The logarithmic term is termed the "index of difficulty" (ID):

$$ID = \log_2\left(\frac{2D}{W}\right) \qquad \text{(eq. 2)}$$

Our task does not lend itself to computation of an ID value, however, since accuracy is not required only at the endpoints, but along the entire path. In addition, the task required spatio-temporal accuracy, as opposed to strictly spatial accuracy.

Despite these important differences between the paradigms, we expected that the overall conclusion from research into the relation between speed and accuracy, which was found to be universally applicable in such a wide variety of situations (albeit with some modifications, depending on the specific task requirements, e.g., Schmidt et al. 1979), using different end effectors, limbs and subject populations (see table 1 in Plamondon and Alimi 1997) would hold in this case: that is, that faster movements, as they allow less opportunity for online error correction, would be less accurate than slower ones.

However, we found that accuracy on the task did not decrease monotonically with increasing speed. In an effort to provide an interpretation of this finding, we evaluated the relative smoothness and the level of harmonicity of subjects' movements across the different amplitude and frequency conditions. We found

smoothness and harmonicity to increase monotonically with increasing movement speed.

METHODS

Subjects

Twenty-three healthy adult subjects without any known neurological disorders or tremor were tested using their dominant hand in this experiment (Age: 52.7±22.3 years, range: 22-81 years; 10 females, 13 males). All subjects gave their informed consent to participate.

Equipment

The equipment used for this experiment consisted of a modified version of the elbow-angle measurement device described in Doeringer & Hogan 1998. A forearm support, consisting of a commercially available wrist splint (Futuro splint wrist brace) strapped to a flat aluminum plate atop a lightweight aluminum tube, was hinged via precision ball bearings to a stationary support, mounted on a table in front of the seated subject. The forearm support was deliberately designed to be as light as possible, to minimize its effect on the natural behavior of the limb. Its moment of inertia was ~0.0056 $kg \cdot m^2$, an order of magnitude less than the mean value of the subjects' forearm moment of inertia, ~0.075 $kg \cdot m^2$.

The forearm support was connected to the shaft of a rotary incremental encoder (Gurley Precision Instruments Model # R119). This provided a position resolution of 0.0003 radians per count. The encoder was in turn connected to a counter card inside a computer running the real-time Linux operating system. Using this angle sensor, we were able to display both the position and the velocity of the elbow directly to the subject in real time. The computer controlled the recording of the data, as well as the display, which was a 17-inch monitor, positioned ~80 cm from a subject's eyes. Data were recorded at 200Hz. A large, opaque plastic cover was placed parallel to the table, and above the apparatus, such that during the experiment, the subjects' forearm was occluded from view (see figure 1).

Protocol

The protocol consisted of 3 blocks of 20 trials each. Subjects were presented with a display of the phase plane of their elbow motion; the horizontal axis displayed angular position and the vertical axis displayed angular velocity. We kept the same dependence between the arm state variables (angular position and velocity) and display for all blocks because we wanted to minimize unnecessary relearning of the relationship. The target elbow behavior was indicated by a region of the phase plane; this region was a doughnut shape formed from two ellipses displayed on the screen. Each ellipse corresponds to a sinusoidal elbow motion, with the nonzero width of the doughnut shape allowing for a range of amplitudes and frequencies. The three blocks of trials were

differentiated by the shapes of their target regions; the shape displayed was either (i) a tall thin region (fast, small-amplitude sinusoid), (ii) a circular region, or (iii) a wide region (slow, large-amplitude sinusoid; see table 1 and figure 2). All of the target regions occupied equal amounts of display screen area. The order of presentation was altered and balanced across subjects, such that approximately half of the subjects were tested first on the 'fast' block and approximately half were tested first on the 'slow' one; the second block of trials always consisted of the medium-speed condition. Before each block of 20 trials, subjects were allowed to practice the movement until they felt comfortable with the task, which usually took about four 40-second practice trials. Each test trial lasted for 20 seconds. For each block of 20 trials, 5 of them (the 2^{nd}, the last, and 3 randomly selected) were blind; during these trials, subjects could see the doughnut-shaped target region, but not the trace corresponding to their own elbow motion. The instructions to the subjects were as follows:

> On the screen in front of you, you will see a cursor whose vertical position will depend on your elbow velocity, and whose horizontal position will depend on your elbow position. We ask that you move your elbow back and forth in cyclic movements (demonstrate) so that the cursor stays within the doughnut shape displayed on the screen. On some trials, the cursor will not be visible; you won't be able to see the trace of your movement on the screen. In those trials, continue to try and move within the guidelines even though you cannot see the trace (demonstrate).

The protocol was approved by the Institutional Review Boards of the Massachusetts Institute of Technology and of the University of California, San Diego.

Ellipse	Frequency (in Hz)		Amplitude (in degrees)	
	Center	Range	Center	Range
Tall, fast	2.3	1.3-5.5	6.7	3.3-10.2
Round, medium	0.55	0.36-0.85	16.3	12.9-19.8
Wide, slow	0.16	0.07-0.3	24.6	20.6-28.6

Table 1. Frequency and amplitude values for the center of each of the three ellipses, as well as the allowed ranges for those values.

Data analysis

Data were analyzed using MATLAB® (7.0.1, The MathWorks, Natick, MA). Trend was removed from the position data, so as to reduce the effects of drift. This was achieved by removing the best straight-line fit from the position data. Position and each of its three derivatives, were filtered using a zero-phase (bidirectional) digital filtering with a first order Butterworth filter (bidirectional filtering doubles the filter order) with a cutoff frequency of 20Hz. Velocity was calculated as the difference between every two consecutive points in the filtered position record,

multiplied by the sampling frequency and then filtered as described above. In a similar fashion, acceleration and jerk, were calculated.

Accuracy

Each 20-sec trial was given a numerical score that represents the percent of the total trial time that was spent inside the target zone on the phase plane.

Smoothness

The smoothest rhythmic movement can be defined using a "mean squared jerk" (MSJ) measure (Nelson 1983). Accordingly, to evaluate smoothness in each trial, we calculated the average of the rate of change of acceleration (jerk) squared, and divided it by the mean squared jerk of a corresponding maximally smooth rhythmic movement (Hogan and Sternad 2007), to obtain the mean squared jerk ratio (MSJR):

$$MSJ = \frac{1}{t_2 - t_1} \int_{t_1}^{t_2} \frac{1}{2} \left| d^3x / dt^3 \right|^2 dt \qquad \text{(eq. 3)}$$

$$MSJR = \frac{MSJ_{movement}}{MSJ_{ms}} \qquad \text{(eq. 4)}$$

Where MSJ_{ms} is the MSJ of the corresponding maximally smooth movement. As described in appendix II of Hogan and Sternad (2007), the minimum-MSJ movement is strictly periodic and essentially sinusoidal. Accordingly, we used a

sinusoid of the same duration, amplitude and number of peaks as the corresponding maximally smooth movement. Zero crossings in the velocity data were used to define peaks in the position data. Data points before the first and after the last velocity peak were discarded, so that a direct comparison can be made with the corresponding sinusoid. A ratio value approaching unity would indicate a mean-squared jerk value comparable to that of a maximally smooth movement.

Frequency

The average frequency for each trial was estimated by calculating the reciprocal of twice the average peak-trough horizontal distance in the position record.

Harmonicity

For every movement half-cycle, between two zero-crossings in the position record, harmonicity was calculated as follows: When a single peak in acceleration occurred in the half cycle, the harmonicity value was set to one; When an inflection occurred in the half-cycle acceleration trace, movement harmonicity was computed as the ratio of the minimum to the maximum absolute value of the acceleration within the given half cycle; Finally, if the acceleration trace within the half cycle changed its sign, the harmonicity value was set to zero (Guiard 1993; Buchanan et al. 2006).

Harmonicity values were then averaged across the entirety of each 20-second trial.

Statistical test

A non-parametric paired test, the sign test, was used to test the significance of differences between data sets. This nonparametric test was chosen to eliminate the need for assumptions regarding population distributions required in parametric tests.

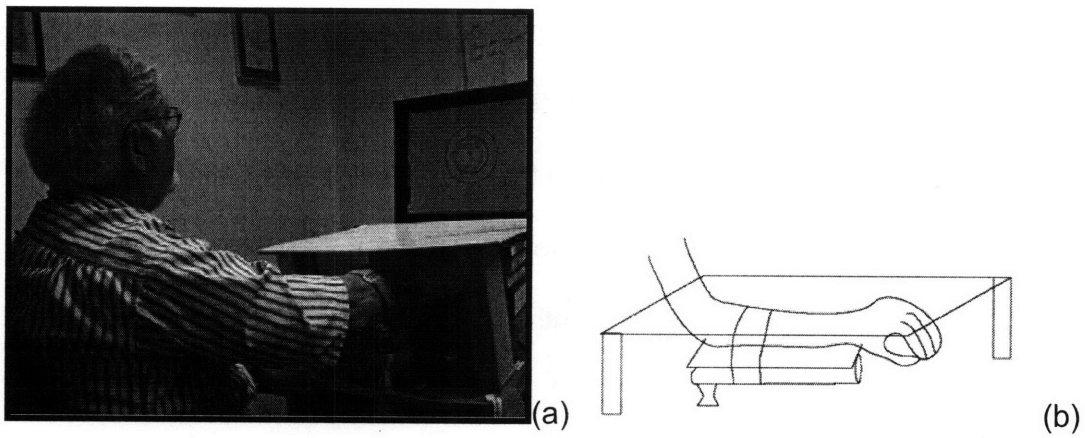

Figure 1. The experimental setup. (a) The forearm is strapped to the angle-measuring device, and is occluded from the subject's view by an opaque cover. The subject coordinates simultaneous modulation of both speed and position to control a cursor displayed on a phase plane. (b) An illustration of the arm's position below the cover.

RESULTS

Velocity traces from each of the three experimental blocks (slow, medium and fast) of one subject are shown in figure 2.

Figure 3 is showing accuracy of combined speed and position, measured throughout the entire trial, for the three different blocks, corresponding to the wide, circular and tall ellipses on the phase plane. As we expected, accuracy scores, expressed as the percent of the movement time spent inside the target zone on the phase plane, were lower (significantly, $p<0.005$) when subjects performed the medium block compared to the slower block. However, rather than a further drop in accuracy when tracing the tall ellipse on the phase plane, subjects' accuracy scores were significantly ($p<0.05$) higher in that block compared to the medium one.

This non-monotonic relation between the accuracy on the task and the speed at which the task is performed suggests that there may be multiple sources of movement accuracy, and that these become either more or less important depending on the movement speed. We explored the differences among the blocks in an effort to identify potential sources of accuracy.

From figure 2, it appears that the slower movements are more intermittent than the faster ones. Indeed, using the MSJR measure, we found that smoothness decreased with decreasing movement speed ($p<0.005$; see figure 4). We

employed a power-law model to represent the change in MSJR with the average frequency:

$$MSJR = a \cdot frequency^{b} \qquad \text{(eq. 5)}$$

For a = 0.02 sec^6 and b ≈ -6, this model accounts for 92% of the variation in the data. It is important to note that an MSJR value close to unity, as found for the fast block (MSJR = 1.21) indicates movement that is nearly maximally smooth. The smoothest back-to-back sequence of discrete movements was found to yield an MSJR value of 6 (Hogan and Sternad 2007); in the medium condition the mean MSJR value was 6.35, and in the slow condition it approached a value of 600[1].

The frequencies at which the subjects performed the three blocks (slow, medium, and fast) are plotted in figure 5. Figure 5 demonstrates that subjects did not perform the task at the entire range of allowed frequencies, but rather executed the task at a narrow range of frequencies.

Harmonicity values for the three blocks are shown in figure 6. Differences among all blocks were significant ($p<0.0001$; see figure 6). Of particular note is that the mean harmonicity value for the fast block was 0.95, indicating movements of harmonic nature, whereas the mean harmonicity values for the medium and slow

[1] It should be noted that the higher MSJR values are sensitive to the method of jerk calculation. Using an alternative, spline-fitting method, we obtained a value of ~3 for the medium block's MSJR.

blocks were 0.3 and 0.0008, respectively, supporting an interpretation that they are composed of a string of discrete action units (Guiard 1993; Buchanan et al. 2006).

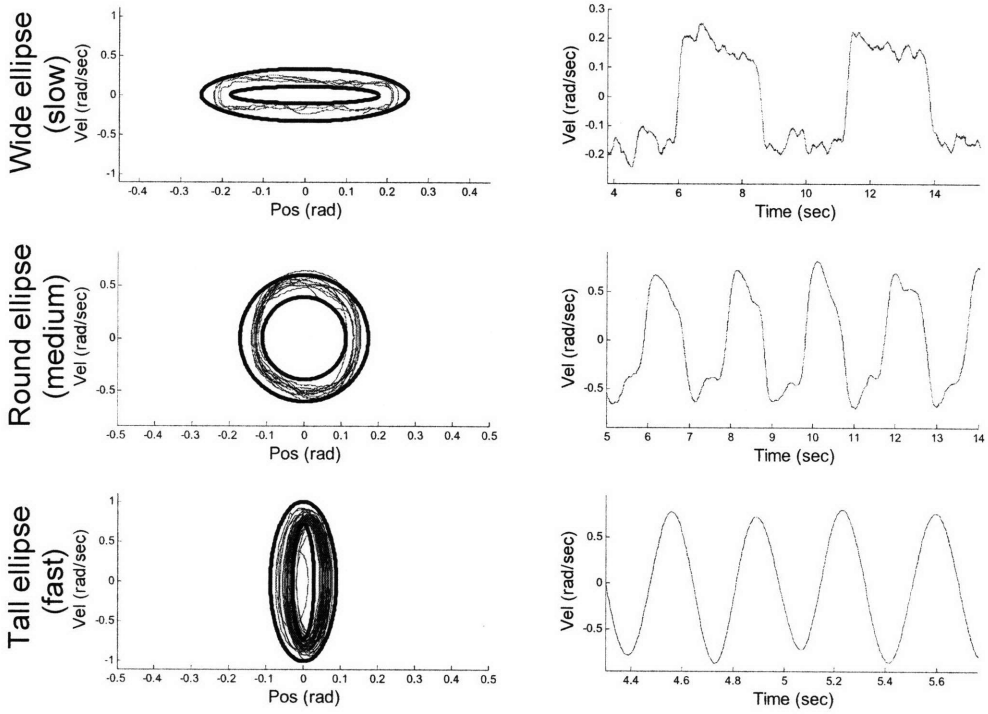

Figure 2. Left column: phase plane trajectories from one subject in the slow, medium and fast blocks. Y axis: angular velocity (rad/sec), x axis: position (rad). Right column: velocity traces from the same subject in the slow, medium and fast blocks. Y axis: angular velocity (rad/sec), x axis: time (sec).

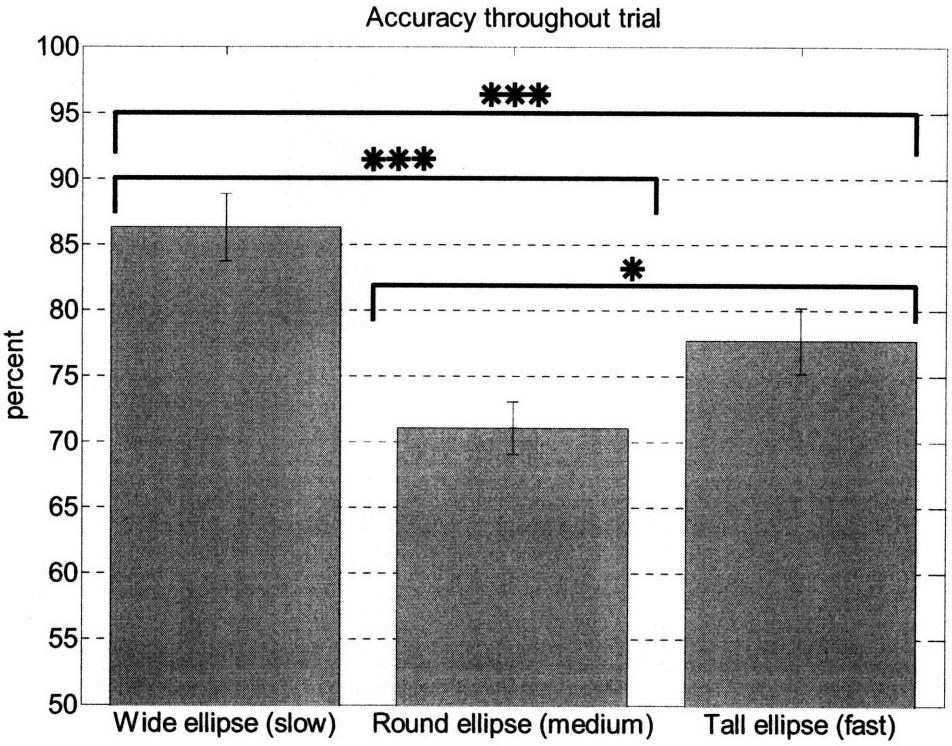

Figure 3. Accuracy (percent time in doughnut) values for the three vision blocks (slow, medium, fast). * - $p<0.05$, *** - $p<0.005$; error bars represent standard error.

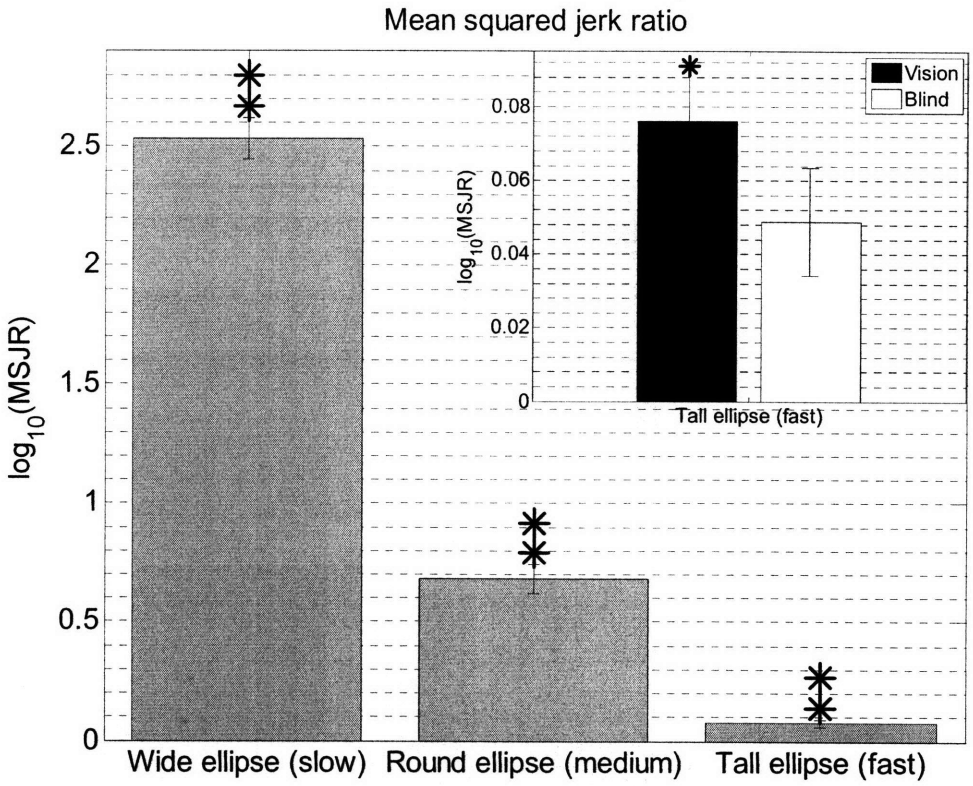

Figure 4. MSJR (relative smoothness) values for the three vision blocks (slow, medium, fast). The logarithm of the values is displayed, to facilitate comparison among the blocks. Inset: fast vision and blind MSJR values. A single asterisk denotes a significant difference between the vision and blind trials ($p<0.0005$); two vertical asterisks denote this block is significantly different from both others ($p<0.005$). Error bars represent standard error.

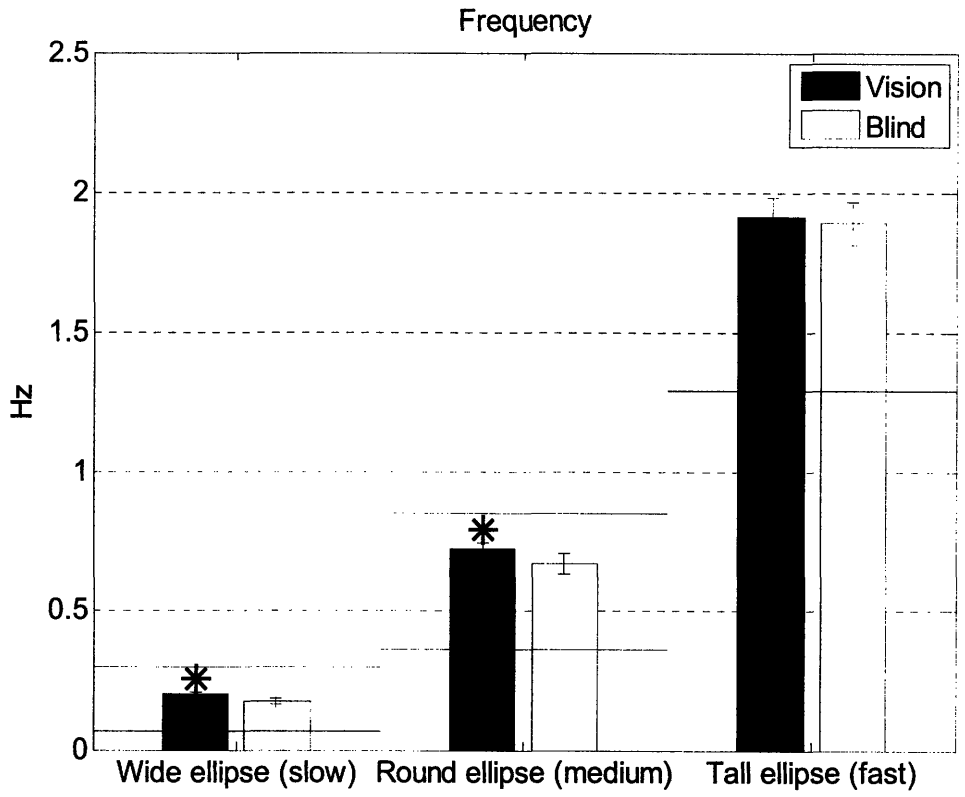

Figure 5. Frequency values for the vision and non-vision conditions in each of the three blocks (slow, medium, fast). An asterisk denotes a significant difference ($p<0.0005$) between the vision and the non-vision conditions in the block. The horizontal bars mark the allowed range for each block (only the lower end of the range is shown for the 'fast' block). Error bars represent standard error.

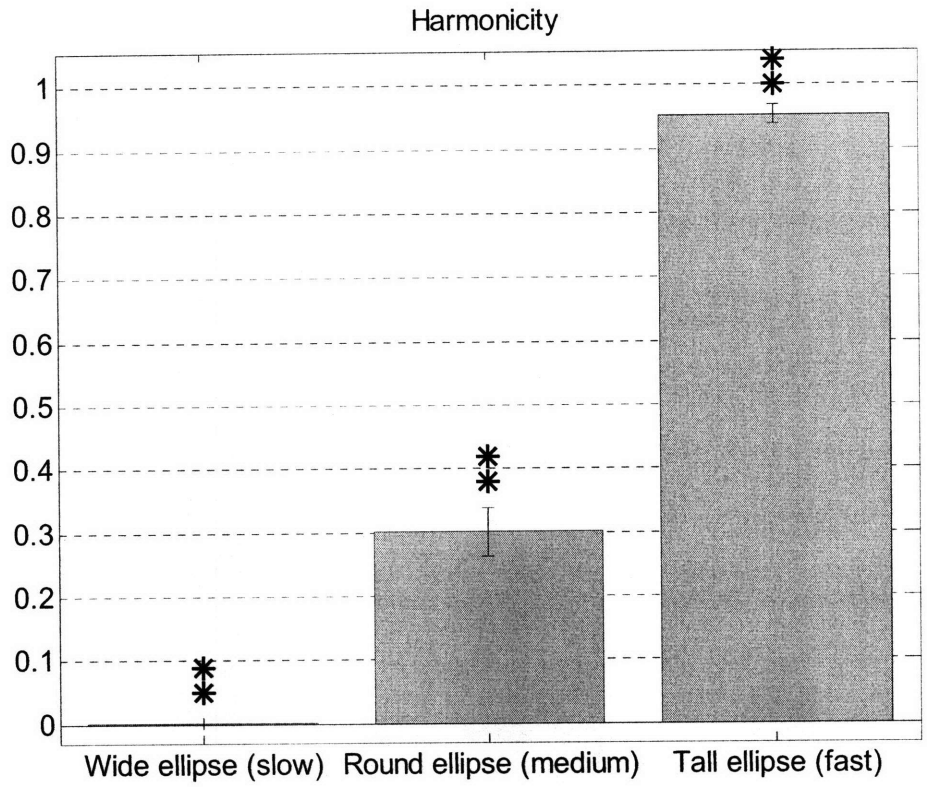

Figure 6. Harmonicity values for the three vision blocks (slow, medium, fast). Two vertical asterisks denote this block is significantly different from both others ($p<0.001$). Error bars represent standard error.

DISCUSSION

Summary of results

We found a non-monotonic relation between the speed of movement and the combined accuracy of speed and position. While accuracy scores dropped from the slow to the medium speed, they increased between the medium and the fast speeds. We explored potential indicators of different movement types in the three experimental blocks, which may point to utilization of alternative sources of movement accuracy. We found that movements in the fast block were nearly maximally smooth, and nearly maximally harmonic. In contrast, movements in the medium and slow blocks were approximately as smooth as the smoothest concatenation of discrete movements, or less, and had mean harmonicity values not greater than 0.3, supporting an interpretation that they are composed of a string of discrete action units.

These results suggest that movements in the fast block were of a more rhythmic nature, and subjects may have used the elastic properties of the limb to achieve not only high smoothness, and to conserve mechanical energy (Guiard 1997; Wisleder and Dounskaia 2007), but also to achieve repeatability (van Mourik and Beek 2004), and hence accuracy.

In contrast, in the medium and the slow blocks, subjects may have made use of visual feedback to achieve movement accuracy, and within these blocks, slower

movements afford more time for visual corrections, and are therefore at once more accurate and less smooth.

The finding that movements performed at the fastest speed required by the experimental paradigm were more accurate, in terms of co-modulation of speed and position throughout the movement, was surprising because we expected the broadly applicable principle that there is a tradeoff between movement speed and accuracy to apply here as well.

Speed-accuracy relations

In a highly influential article in 1954, Fitts formulated a logarithmic relation between the duration and the required spatial precision of repetitive aimed upper limb movements, basing his theoretical model on information theory. A decade later, together with Peterson (1964) he demonstrated that a logarithmic relation exists for discrete movements as well. This relationship was shown in later experiments to hold for different subject populations, end-effectors and experimental paradigms (Wallace and Newell 1983; Meyer et al. 1988; Plamondon and Alimi 1997). Whereas some researchers anchored the logarithmic relationship in a different theoretical basis than that of Fitts (e.g., Crossman and Goodeve 1963/1983), others found an altogether different tradeoff relation; for example, Schmidt et al. (1979), described a linear speed-accuracy tradeoff using a modified Fitts paradigm. Wright and Meyer (1983) concluded that

a logarithmic trade-off was present when the task was spatially defined, and a linear relation came through when the task was temporally constrained.

There has been evidence of models' breakdown on tasks of a low index of difficulty (ID) (Beamish et al. 2006), of high frequency (e.g., Crossman and Goodeve 1963/1983; Schmidt et al. 1979), of slow speeds (e.g., Schmidt et al. 1979), when switching from one type of task to another (e.g., discrete to rhythmic; Smits- Engelsman et al. 2002) or when performing two-handed movements of disparate difficulty (Kelso et al. 1979) but, to our knowledge, it has never been demonstrated that the relation may be non-monotonic. It is important to stress, as we did in the introduction, that our task is different from the traditional Fitts task in several respects. Still, we were able to identify a situation under which the speed-accuracy relation takes a non-monotonic shape.

Movement amplitude

It may be argued that in the fast block subjects had the benefit of smaller-amplitude movements, which may have contributed to the increased accuracy. While we believe movement amplitude plays an important role, it is not likely to be the sole reason for the increased accuracy observed in the fast block compared with the medium block; When comparing the slow and the medium blocks, movement accuracy declines in the medium compared with the slow,

despite a decrease in amplitude, suggesting that the smaller amplitude in the fast block is not uniquely responsible for the increased accuracy.

Movement Speed

Alternatively, the differences between the fast block on the one hand and the medium and slow blocks on the other, could result from the speed of the movement. Crossman and Goodeve (1963/1983) noted that single rapid (200-300 msec) motions were more accurate, that is, had less endpoint variability than predicted by Fitts' 10 bits/sec information processing (IP) rate (Fitts 1954). The accuracy of ballistic movement had been previously described by Woodworth (1899). That is, ballistic primitives may be preprogrammed with the result of being highly accurate; since the movements in the "fast" block are performed at a high frequency and with a small amplitude, they may require only a single ballistic movement in each half-cycle, which may underlie the observed increase in accuracy in the fast condition. This explanation, however, would not account for the MSJR value for the fast movements, which approaches unity. Back-to-back discrete movements would involve breaking twice in each cycle (acceleration equals zero), which would be manifested in decreased smoothness and harmonicity values.

Mechanical filtering?

It may be that "mechanical filtering" due to (1) the inertial properties of the moving limb or (2) the increase in stiffness with speed (Nagasaki 1991; van Galen and de Jong 1995) account for the smoothing of the movement at high frequencies. We demonstrate that this is not the case, as evidenced by a small, yet significant, increase in intermittency with vision in the fast block, compared to the non-vision condition (1.21±0.05 vs. 1.13±0.04 (mean±SE); see figure 4 inset), despite a nonsignificant change in frequency (see figure 5 inset). In other words, the smoothness is found to be significantly different between two conditions where the limb moves at essentially indistinguishable frequencies. The observation that movements at the highest frequency were approaching maximal smoothness cannot, therefore, be dismissed as a mere artifact of biomechanics. That does not, however, exclude the possibility that the mechanical properties of the limb were being harnessed to produce a highly smooth movement. This is a subtle, yet important point: while we argue that mechanical filtering is not the reason for high smoothness values at high frequencies, the mechanical properties of the limb are likely exploited, such that all that needs to be set for a movement is the neutral position and muscle stiffness, thereby pre-programming the amplitude and frequency of the movement (Nelson 1983), and intervention is only in the form of an escapement – a mechanism whereby energy is released at exactly the amount needed to compensate for dissipative losses (Kelso et al. 1981) thereby operating as a limit-cycle oscillator.

Discrete vs. rhythmic movements

Whereas most researchers focused on tasks of a discrete nature, some studied and compared both discrete and repetitive movements (Fitts 1954; Fitts and Peterson 1964; Crossman and Goodeve 1963/1983; Schmidt et al. 1979; Guiard 1997; Smits-Engelsman et al. 2002, Buchanan et al. 2003). Their findings were not always in agreement. Fitts and Peterson (1964) concluded that both types of movement follow the same type of behavior, later known as Fitts' Law, with different slopes. Fitts' law describes a dependence between the time to complete a movement and the distance and size of the target. It is interesting to note that Fitts and Peterson found cyclic movements to take longer to complete than discrete movements of the same index of difficulty (Fitts and Peterson 1964). Crossman and Goodeve (1963/1983) and Guiard (1997) also found Fitts' Law to apply to both types of movement, at least approximately.

In contrast, Schmidt et al., (1979) found that when movements are temporally constrained, while in discrete-aiming tasks the endpoint error is directly related to the amplitude and inversely related to the movement time, for reciprocal movements, the endpoint error is directly related to the amplitude and independent of the movement time.

Smits-Engelsman et al. (2002) demonstrated that, contrary to Fitts and Peterson's (1964) results, when subjects performed the same task in a discrete, and in a cyclic manner, for the same index of difficulty, the latter allows subjects to reach twice the speed of the former. They posited that had cyclic movements

been but a concatenation of discrete ones, there should have been little difference in the performance between the two. Their results are in line with the view that discrete and cyclic movements are governed by different control principles. Further support for the idea that cyclic and discrete movements are separately controlled comes from a brain-imaging study (Schaal et al. 2004), as well as from theoretical considerations (Guiard 1993).

Finally, Buchanan and colleagues performed a series of studies exploring the use of two different units of action – rhythmic and discrete – both separately and within the same movement, and found that as subjects approach targets of higher ID, their movements become more discrete in nature, while they are more harmonic in nature when approaching a target of low ID (Buchanan et al. 2003, 2004, 2006). As Guiard pointed out earlier, such a correlation between harmonicity and task ID may in fact be a secondary effect, and the result of the slowing down of movement as one reaches to a target of higher ID, as predicted by Fitts' law (Guiard 1997).

Information processing vs. energy-saving considerations

Many of the theories that were brought forth to describe the reasons for the speed-accuracy dependence, though successful in describing the kinematic aspects of the movement, do not consider the biomechanical muscle properties and their role in controlling endpoint accuracy (cf. van Galen and de Jong 1995; Guiard 1997; Khan and Franks 2000; Smits-Engelsman et al. 2002). Smits-

Engelsman et al. (2002) suggest two of the possible reasons for what they found to be a higher information-processing rate in cyclic than in discrete movements: alternative sources of force, and a more cost-effective use of the recruited force. They cite physiological studies showing that contractions are more effective when they occur in muscles which have just previously been stretched, and when they are eccentric, rather than concentric. Smits-Engelsman et al. (2002) offer an explanation for what may happen at the discrete/rhythmic interface: they argue that possibly, when performing cyclic movements, alternative sources of force recruitment are used, such as the elasticity of muscles and tendons. These may account for a check on the increase in impulse variability and may, in fact, contribute to the observed higher accuracy scores in the fast block.

Furthermore, in a rhythmic movement, the limb need not come to a full rest at the position extremes, such that acceleration does not equal zero at those points. Energy is saved in eliminating the need to coordinate agonist and antagonist muscle activity to reach a full stop before initiating the next movement portion (Guiard 1997). That maximally smooth movement is within 2% of that which minimizes energy expenditure has been demonstrated mathematically (Nelson 1983). Energy-saving considerations have been brought up in the context of gait patterns – e.g., running vs. walking (Alexander 1991) – and choice of gait type has been discussed in terms of both speed and step amplitude (Srinivasan and Ruina 2006), and these may well be paralleled in the upper limbs.

Discrete vs. rhythmic movements – can it explain our findings?

Our salient finding that at the highest examined movement speed (the fast block), as well as at the largest examined movement amplitude (the slow block), accuracy was higher than at an intermediate speed and amplitude (the medium block) seems at odds with the theories put forth by Schmidt et al. (1979): they posited that, for discrete rapid aiming movements, increased speed necessitates increased impulse size, which, in turn, leads to an increase in output variability; for reciprocal movements, they asserted that output variability is proportional to movement amplitude only. However, on the reciprocal task at hand, we found movements at larger amplitudes to be more accurate. What may account for this finding? It has been suggested that cyclic arm movements, if performed sufficiently slowly, exhibit kinematic features that suggest they may be executed as a sequence of discrete movements (Hogan and Sternad 2007; Wisleder and Dounskaia 2007). If, as we argue, the movements in the slow and the medium blocks in our experiment fall under this definition – that is, if they are executed as a string of discrete movements – as is suggested by the smoothness and harmonicity analyses, then Schmidt et al.'s (1979) theory regarding discrete movements holds for these two blocks: the faster speed in the intermediate condition compared to the slow condition resulted in increased error. That is, if we consider the slow and the medium, blocks in isolation from the fast block, then the model suggested by Schmidt et al. (1979) correctly predicts the decrease in accuracy with an increase in speed.

May it be that the movements in the slow and the medium blocks can be classified as more discrete in nature and ones in the fast block as more rhythmic in nature?

Indeed, a remarkable parallel can be observed between the fast (~2 Hz) movements in our experiment and maximally smooth movements on the one hand; and between the movements in the medium (~0.6 Hz) and slow (~0.2 Hz) ranges in our experiment and a concatenation of discrete movements on the other (Doeringer and Hogan 1998). The former are fast, yet relatively accurate and smooth, while the latter exhibit a decrease in accuracy and increase in smoothness with increasing speed. This is despite the fact that the task instructions were uniform throughout the experiment, calling for cyclic movements only (none of the tasks was discrete in nature).

Two regimes

These findings suggest a possible separation of the frequency/amplitude plane of repetitive movements into what may be called a "truly cyclic" regime, at frequency values in the vicinity of the inverse of the visual reaction time (>1 Hz), and small amplitudes, where movements approach maximal smoothness, and a "pseudo-cyclic" regime at lower frequencies and higher amplitudes, where movements are not maximally smooth, and higher speed results in decreased accuracy and increased smoothness. In our experiment, amplitude and frequency were co-varied, and therefore, we cannot comment on their individual

contributions to the choice of regime. Additionally, within what we term the "truly cyclic" regime, accuracy and smoothness may vary with speed, but we cannot comment on the form of the function, since we only measured behavior on a single frequency in that regime. Nagasaki's results (1991) suggest a third regime, above 3-4.3 Hz, where movements cease to be "rhythmic" and adopt a symmetric non-linear control mechanism. The boundaries that define these regimes may well depend on the executing limb and/or the limb segment.

Why two regimes?

Plamondon and Alimi (1997) suggested a model for rapid-aimed movements in which intermittency is not the result of feedback-based "corrections", but is part of a well-trained feedforward loop, which echoes suggestions made by Meyer et al. (1988) and Elliot et al. (1991). Intermittency, then, may be, at least in part, the result of limitations on the frequency/amplitude of the basic submovement. That is, there may be limits on the duration and amplitude of what may constitute a single, uninterrupted smooth motion. Movements that take longer to complete, or that stretch over larger amplitudes may necessitate the concatenation of several such movement subunits. As such, these movements would be characterized by high intermittency, as the jerk of a reciprocal maximally smooth movement is 1/6th of that of the smoothest back-to-back sequence of discrete movements (Hogan and Sternad 2007).

At the high-frequency end of the "pseudo-cyclic" regime, movements are inherently less smooth than maximally smooth movements, unable to benefit from the biomechanically induced increased accuracy privileges of the "truly cyclic" regime and, at the same time, have more limited time than lower-frequency movements to make use of feedback during the movement. Such a mechanism is congruent with our findings that show smoothness to decrease monotonically with decreasing speed, and that reveal movements in the "medium" block to have the lowest accuracy scores of all three examined frequencies.

It is important to keep in mind that the two "regimes" that we describe are not the result of different experimental procedures. Rather, the results are all the more illuminating because the type of task required of the subjects was identical: they were asked to perform a rhythmic motion in all three conditions. That they produced a maximally smooth movement in one of the conditions (fast, small-amplitude movements), and more intermittent movements in the two other conditions (slower, larger-amplitude), and that the accuracy score was not a monotonic function of speed suggests that when crossing a frequency/amplitude threshold, subjects switch to a different, possibly more energy-efficient mode, characterized by maximal smoothness and relatively higher accuracy. A similar notion of a frequency-dependence of the control mechanisms underlying cyclic motions was advanced by Nagasaki (1991), though he investigated transitions at

higher frequencies. He also noted a decrease in energy expenditure when subjects moved at frequencies greater than 3.3 Hz.

Unlike a significant number of the studies cited in this work, our task demanded accuracy throughout the movement, not just at the endpoints. Also, when comparing the results we report here to those of other experiments, it is important to note that most, if not all, previously reported experiments tested subjects on a rapid aiming task, whereas here we ask subjects to move at a range of pre-specified speeds. Furthermore, we prescribe a range of spatio-temporal profiles for subjects to stay within *throughout* the movement, rather then define only a temporal or only an endpoint spatial constraint, as has previously been done. Our findings thus complement previous work on the relation between speed and accuracy.

CONCLUSIONS

In summary, we tested subjects on a task involving rhythmic elbow movements at three speeds. We found that movement smoothness decreased with decreasing speed. However, accuracy of speed and position measured throughout the trajectory was not a monotonic function of speed. Movements at the intermediate condition were significantly less accurate than movements performed at either a higher or a lower speed. We suggest a model of rhythmic movements where the plane of the movements' frequency/amplitude

combinations is separated into two regimes. In the high-frequency, small-amplitude regime, movements approach maximal smoothness, possibly due to an exploitation of the elastic properties of the limb for achievement of movement accuracy. In the low-frequency, large-amplitude regime, movements are not maximally smooth, possibly due to the increased required duration and distance, and are more intermittent and more accurate with decreasing frequency, probably due to the dependence on sensory feedback for achievement of movement accuracy. The results of this study warrant further investigation into the individual contributions of movement duration and movement amplitude to movement smoothness.

REFERENCES

Alexander RM. Energy-saving mechanisms in walking and running. *J Exp Biol* 160: 55-69, 1991.

Beamish D, Bhatti SA, MacKenzie IS, Wu J. Fifty years later: A neurodynamic explanation of Fitts' law. *J R Soc Interface* 3: 649-54, 2006.

Buchanan JJ, Park JH, Ryu YU, Shea CH. Discrete and cyclical units of action in a mixed target pair aiming task. *Exp Brain Res* 150: 473-89, 2003.

Buchanan JJ, Park JH, Shea CH. Systematic scaling of target width: dynamics, planning, and feedback.
Neurosci Lett 367:317-22, 2004.

Buchanan JJ, Park JH, Shea CH. Target width scaling in a repetitive aiming task: switching between cyclical and discrete units of action. *Exp Brain Res* 175:710-25, 2006.

Crossman ERFW, Goodeve PJ Feedback control of hand-movement and Fitts' Law. Paper presented at the meeting of the Experimental Psychology Society, Oxford, July 1963. Published in *Q. J. Exp. Psychol.* 1983, 35A: 251-278, 1963/1983.

Doeringer JA, Hogan N. Intermittency in preplanned elbow movements persists in the absence of visual feedback. *J Neurophysiol* 80: 1787-99, 1998.

Elliott D, Helsen WF, Chua R. A century later: Woodworth's (1899) two-component model of goal-directed aiming. *Psychol Bull* 127: 342-57, 2001.

Fitts PM. The information capacity of the human motor system in controlling the amplitude of movement. *J Exp Psychol* 47: 381-391, 1954

Fitts PM and Peterson JR. Information capacity of discrete motor responses. *J Exp Psychol* 67:103--112, 1964.

Guiard Y. On Fitts's and Hooke's laws: simple harmonic movement in upper-limb cyclical aiming. *Acta Psychol (Amst)* 82:139-59, 1993.

Guiard Y. Fitts'law in the discrete vs. cyclical paradigm. *Human Movement Science* 16: 97-131, 1997.

Harris-Warrick RM. Voltage-sensitive ion channels in rhythmic motor systems. *Curr Opin Neurobiol* 12: 646-51, 2002.

Hogan N, Sternad D. On rhythmic and discrete movements: reflections, definitions and implications for motor control. *Exp Brain Res* 181: 13-30, 2007.

Kelso JA, Holt KG, Rubin P, Kugler PN. Patterns of human interlimb coordination emerge from the properties of non-linear, limit cycle oscillatory processes: theory and data. *J Mot Behav.* 13: 226-61, 1981.

Kelso JA, Southard DL, Goodman D. On the nature of human interlimb coordination. *Science* 203: 1029-31, 1979.

Kelso JA, Tuller B. Converging evidence in support of common dynamical principles for speech and movement coordination. *Am J Physiol* 246: R928-35, 1984.

Khan MA, Franks IM. The effect of practice on component submovements is dependent on the availability of visual feedback. *J Mot Behav* 32:227-40, 2000.

Krebs HI, Brashers-Krug T, Rauch SL, Savage CR, Hogan N, Rubin RH, Fischman AJ, Alpert NM. Robot-aided functional imaging: application to a motor learning study. *Hum Brain Mapp* 6:59-72, 1998.

Krebs HI, Hogan N, Hening W, Adamovich SV, Poizner H. Procedural motor learning in Parkinson's disease. *Exp Brain Res* 141: 425-37, 2001.

Krebs HI, Dipietro L, Levy-Tzedek S, Fasoli SE, Rykman-Berland A, Zipse J, Fawcett JA, Stein J, Poizner H, Lo AC, Volpe BT, Hogan N. A Paradigm Shift: Therapeutic Robotics (in press)

Lehéricy S, Bardinet E, Tremblay L, Van de Moortele PF, Pochon JB, Dormont D,
Kim DS, Yelnik J, Ugurbil K. Motor control in basal ganglia circuits using fMRI and brain atlas approaches. *Cereb Cortex* 16: 149-61, 2006.

Levy-Tzedek S, Krebs HI, Shils JL, Apetauerova D, Arle JE. Parkinson's disease: a motor control study using a wrist robot. *Advanced Robotics* 13: 1201-1213, 2007.

Messier J, Adamovich S, Jack D, Hening W, Sage J, Poizner H. Visuomotor learning in immersive 3D virtual reality in Parkinson's disease and in aging. *Exp Brain Res*;179: 457-74, 2007.

Meyer DE, Abrams RA, Kornblum S, Wright CE, Smith JE. Optimality in human motor performance: ideal control of rapid aimed movements. *Psychol Rev* 95: 340-70, 1988.

Nagasaki H. Asymmetrical trajectory formation in cyclic forearm movements in man. *Exp Brain Res* 87: 653-61, 1991.

Nelson WL. Physical principles for economies of skilled movements. *Biol Cybern*; 46: 135-47, 1983.

Plamondon R, Alimi AM. Speed/accuracy trade-offs in target-directed movements. *Behav Brain Sci* 20: 279-303, 1997.

Plenz D, Kital ST. A basal ganglia pacemaker formed by the subthalamic nucleus and external globus pallidus. *Nature* 400: 677-82, 1999.

Schaal S, Sternad D, Osu R, Kawato M. Rhythmic arm movement is not discrete. *Nat Neurosci* 7:1136-43, 2004.

Schmidt RA, Zelaznik H, Hawkins B, Frank JS, Quinn JT Jr. Motor-output variability: a theory for the accuracy of rapid motor acts. *Psychol Rev* 47: 415-51, 1979.

Smits-Engelsman BC, Van Galen GP, Duysens J. The breakdown of Fitts' law in rapid, reciprocal aiming movements. *Exp Brain Res* 145: 222-30, 2002.

Srinivasan M, Ruina A. Computer optimization of a minimal biped model discovers walking and running. *Nature* 439: 72-5, 2006.

Surmeier DJ, Mercer JN, Chan CS. Autonomous pacemakers in the basal ganglia: who needs excitatory synapses anyway? *Curr Opin Neurobiol* 15: 312-8, 2005.

Takakusaki K, Saitoh K, Harada H, Kashiwayanagi M. Role of basal ganglia-brainstem pathways in the control of motor behaviors. *Neurosci Res* 50:137-51, 2004.

Tunik E, Feldman AG, Poizner H. Dopamine replacement therapy does not restore the ability of Parkinsonian patients to make rapid adjustments in motor strategies according to changing
sensorimotor contexts. *Parkinsonism Relat Disord* 13: 425-33, 2007.

van Galen, GP and de Jong WP. Fitts' law as the outcome of a dynamic noise filtering model of motor control. *Human Movement Science* 14: 539-571, 1995.

van Mourik AM, Beek PJ. Discrete and cyclical movements: unified dynamics or separate control?
Acta Psychol (Amst) 117:121-38, 2004.

Wallace SA, Newell KM. Visual control of discrete aiming movements. *Q J Exp Psychol A* 35: 311-21, 1983.

Wisleder D, Dounskaia N. The role of different submovement types during pointing to a target. *Exp Brain Res* 176:132-49, 2007.

Woodworth RS. (1899). *The accuracy of voluntary movement* (Doctoral dissertation). Columbia University, 1899.

Wright CE, Meyer DE. Conditions for a linear speed-accuracy trade-off in aimed movements. *Q J Exp Psychol A* 35: 279-96, 1983.

CHAPTER 4

FURTHER SUPPORT FOR THE EXISTENCE OF TWO REGIMES

Introduction

In the previous chapter, we presented supporting evidence for the existence of two types of movement within rhythmic movement, where the choice of which type is employed depends on the frequency and on the amplitude of the executed movement. In this chapter, we provide further support for this model using three additional kinematic analysis tools: the (1) number and (2) type of movement primitives that best fit movements from the three experimental blocks, as well as (3) the differential effects of vision on movement smoothness on movements in the fast block compared with movements in the slow and the medium blocks.

At the conclusion of this chapter, we summarize the six kinematic analysis methods we used and their results, and how those support the model whereby there exist two types of movements within rhythmic movement – one that is more rhythmic in nature, and one that shares characteristics with discrete movements.

A. Submovement analysis

INTRODUCTION

Several aspects of human motor output allude to the existence of movement subunits that may combine to compose larger movements. Evidence of such stereotyped movement fragments comes, for example, from analysis of slow

movements: slow finger movements were found not to be smooth, but characterized by steps or discontinuities (Vallbo and Wessberg 1993). Similar findings of discontinuities and multiple velocity peaks were observed in rapid rotational movements (Novak et al. 2002), saccadic eye movements (van Donkelaar and Lee 1994), rhythmic movements (Doeringer & Hogan 1998), and both rhythmic and discrete movements that require a high degree of accuracy (Wisleder and Dounskaia 2007).

Such subunits of movement were suggested to serve as corrective additions to a primary movement (e.g., Meyer et al. 1988), or be an inherent part of a well-trained feedforward loop (Plamondon and Alimi 1997).

While the existence of submovements has not been demonstrated unequivocally, the concept of submovements is theoretically attractive since it provides a compact language for concisely coding movement, and affords a way to describe human movement on a fundamental level, not previously available (Rohrer and Hogan 2003).

A decomposition of movement into its constituent discrete building blocks can be a useful tool in understanding the human motor control system, through studying the differences in number and type of submovements and how those change depending on task requirements.

A wide range of definitions of submovements led to a development of diverse methodology for extracting submovements (Milner 1992; Berthier 1996; Walker

et al. 1997; Burdet and Milner 1998; Dounskaia et al. 2005). While earlier work assumed submovements were realized at fixed, nonoverlapping intervals (Crossman and Goodeve 1963/1983), or immediately following one another (Meyer et al. 1982, 1988), later work allowed for the possibility that the submovements overlap (Rohrer and Hogan 2003, 2006), and so did we in our analysis.

Visual inspection of the velocity traces recorded for movements in the medium and the slow blocks hinted at the existence of repeated stereotyped subunits of movement in those traces (see figure 2 in Chapter 3). This motivated us to perform a submovement decomposition, so that we might explore the number of submovements that would be extracted for movements of each block, and compare those to our hypothesis that movements in the fast block are generated by an elastic mechanism that affords a single submovement per half cycle, whereas movements in the slow and the medium blocks are composed of multiple component submovements, some of which are the result of visual-feedback-based corrections. We also wanted to test whether the differences among the blocks were significant.

Furthermore, the sinusoidal nature of movements in the fast block, and less so in the medium and the slow blocks, suggested to us that different movement primitives – one that is rhythmic, and one that is discrete – may be engaged in the different experimental blocks.

Submovement decomposition is a nonlinear optimization problem: simultaneously minimizing the fitting error and the number of submovements used, given a submovement shape (e.g., minimum-jerk (Hogan 1984) or Gaussian (Crossman and Goodeve 1963/1983)), and a summing modality. As a nonlinear optimization problem, it may have multiple local minima. Some previously applied optimization methods are sensitive to getting caught in local minima and cannot guarantee a globally optimal solution, thereby producing spurious decomposition results (Rohrer and Hogan 2003). We used the "scattershot" algorithm, which performs local optimization starting from a number of random initial conditions. The scattershot algorithm finds the globally optimal submovement composition probabilistically, such that the probability of finding the globally best fit can be made arbitrarily close to unity by increasing the number of random starting points used in the optimization (Rohrer and Hogan 2006). Since the probability does not equal to unity, the actual submovement characteristics extracted for a given submovement cannot be guaranteed to be the best fit for that movement in a global sense. However, this algorithm was demonstrated to allow strong statistical statements to be made, and even if the results of any given extraction may be uncertain, the differences among conditions examined are robust (Rohrer and Hogan 2006).

METHODS

The data from the same subjects and the same experimental procedure described in Chapter 3 were used here, as well as the filtering method and the statistical analysis.

Submovement extraction

The algorithm used for submovement extraction is adapted from Rohrer and Hogan's "scattershot" algorithm (2006). Briefly, submovements were extracted from velocity data using the *fmincon* function in MATLAB, initialized at ten randomly selected points in the solution space. The extracted submovement functions were scaled minimum-jerk profiles (Berthier 1996; Lee et al. 1997; Burdet and Milner 1998). The minimum-jerk model (Hogan 1984) assumes that movements of given amplitude and duration are generated in a way that minimizes the rate of change in acceleration (jerk).

The submovement extraction was performed twice:

1. Once with a discrete minimum jerk profile (Hogan 1984), where movement was terminated at the end points; That is, both velocity and acceleration were equal to zero at the end points; The velocity profile for a terminated minimum-jerk movement (v_{mjt}) is described by:

$$v_{mjt}(t) = \frac{d}{T}\left(\frac{30t^4}{T^5} - \frac{60t^3}{T^4} + \frac{30t^2}{T^3}\right) \qquad \text{(eqn. 1)}$$

Where d is the distance traversed, and T is the duration of the movement (Krebs et al. 2001). And

2. Once with a rhythmic, or non-terminated minimum jerk profile, where velocity, but not acceleration, was equal to zero at the end points; The velocity profile for a non-terminated minimum-jerk movement (v_{mjnt}) is described by (Hogan and Sternad 2007):

$$v_{mjnt}(t) = d\left[\frac{5}{2}\left(\left(\frac{t}{T}\right)^2 - \left(\frac{t}{T}\right)^4\right) + \left(\frac{t}{T}\right)^5\right] \qquad \text{(eqn. 2)}$$

In this study, submovements were allowed to take on a duration between 50 ms and the duration of the examined velocity trace. Velocity traces from only the last cycle of movement within each 20-second trial were used. This was done because of the exponential increase in computational power needed with the duration of the examined velocity trace. Since the visual display, and hence the subjects' movements, persisted after movements were no longer recorded, "end effects" were not a concern. All the parameters of all the submovements (amplitude, center point, duration) were optimized simultaneously. An increasing number of submovements were fit to each movement until the "fit error," ε, fell

below a predetermined threshold, which in this case was 3%. The fit error is defined as follows:

$$\varepsilon = \frac{\int |F(t) - G(t)| dt}{\int |G(t)| dt} \qquad \text{(eqn. 3)}$$

where *G(t)* is the movement's speed profile, and *F(t)* is the extracted speed profile. Figure 1 demonstrates two examples of extracted submovements – one using a discrete primitive to fit a movement from the medium block, and one using a rhythmic primitive to fit a movement from the fast block.

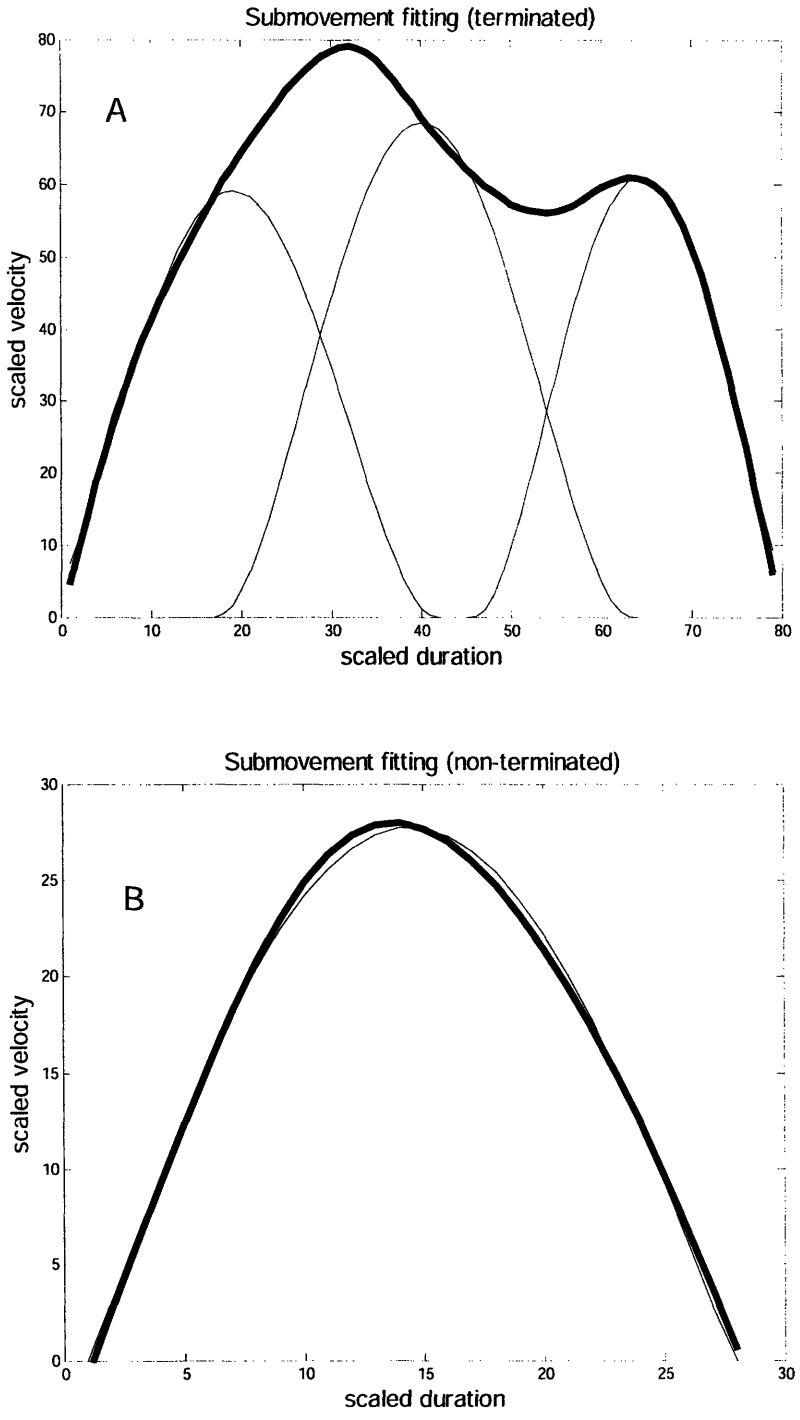

Figure 1. Examples of submovements (thin trace) fit to velocity traces of a subject (thick trace). **A:** Terminated minimum-jerk submovement primitives fit to a movement in the medium block. **B:** Non-terminated minimum-jerk submovement primitives fit to a movement in the fast block.

RESULTS

Using the terminated (discrete) basis function, movements were found to be composed, on average, of 5.0, 2.4 and 1.7 submovements per half cycle (either flexion or extension) in the slow, medium and the fast blocks, respectively (see figure 2). The number of submovements per half cycle differed significantly across the blocks ($p<0.0001$).

Using the non-terminated (rhythmic) basis function, movements were found to be composed, on average, of 9.1, 3.1 and 1.5 submovements per half cycle in the slow, medium and the fast blocks, respectively (see figure 3). The number of submovements per half cycle differed significantly across the blocks ($p<0.0001$). For each block, the difference between the terminated and the non-terminated fit was significant, where the non-terminated basis function gave a better fit (in terms of a lower number of submovements fit per half cycle) in the fast block, whereas the terminated basis function gave a better fit in the slow and medium blocks (see figure 4).

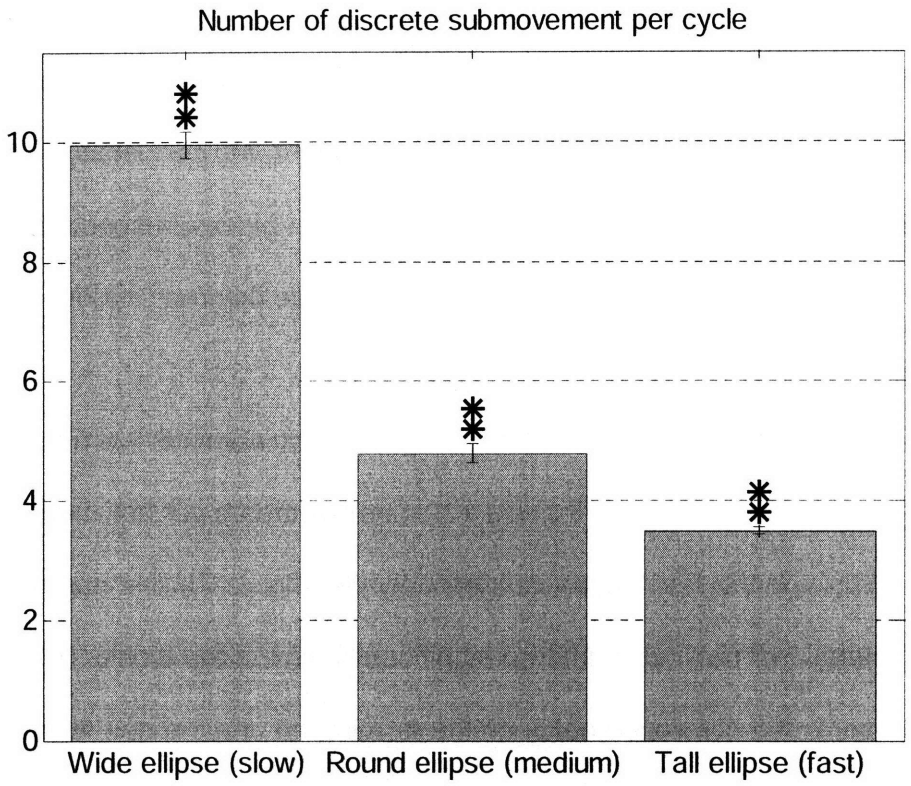

Figure 2. Number of terminated minimum-jerk submovements *per cycle* for the three vision blocks (slow, medium, fast). Two vertical asterisks denote this block is significantly different from both others ($p<0.0001$). Error bars represent standard error.

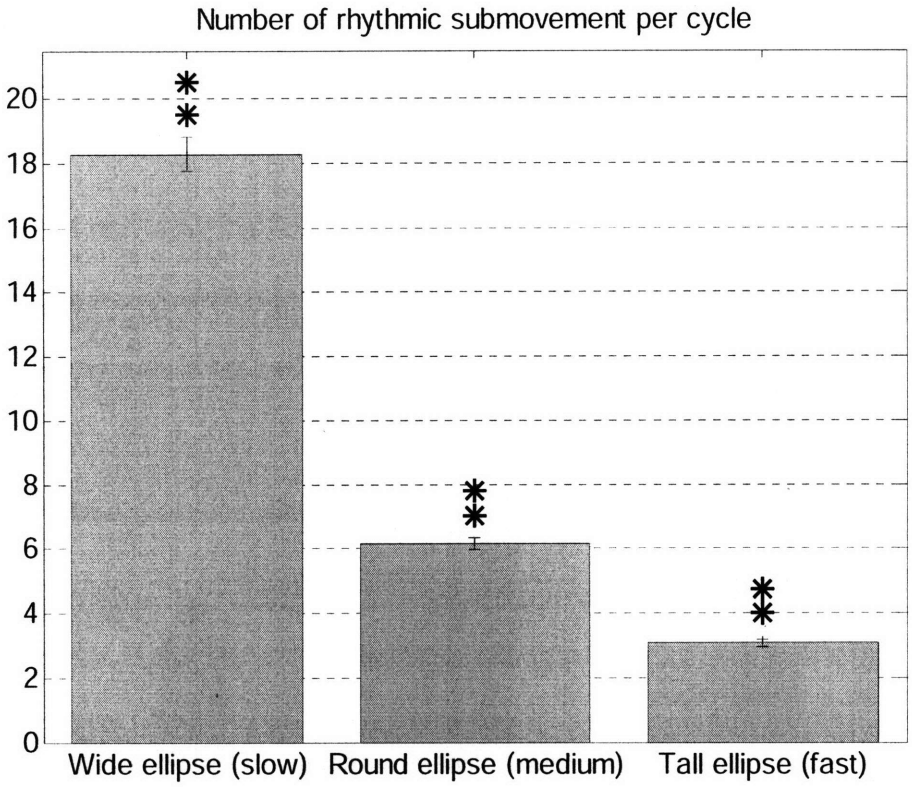

Figure 3. Number of non-terminated minimum-jerk submovements *per cycle* for the three vision blocks (slow, medium, fast). Two vertical asterisks denote this block is significantly different from both others ($p<0.0001$). Error bars represent standard error.

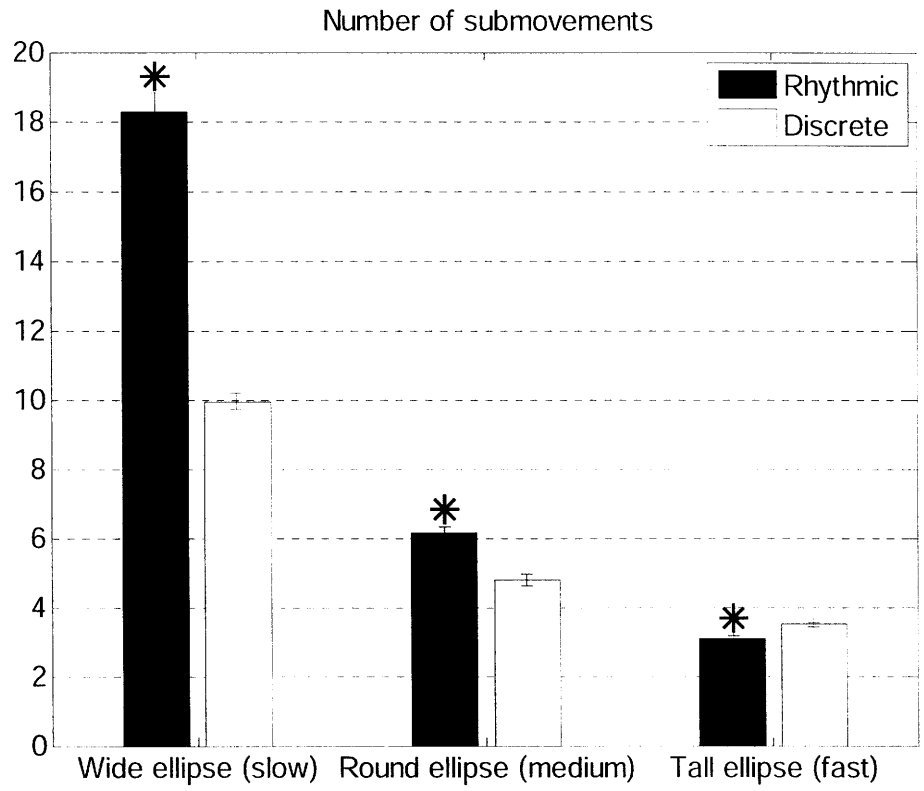

Figure 4. Number of terminated (white bars) and non-terminated (black bars) minimum-jerk-profile submovements in each of the three blocks (slow, medium, fast). An asterisk denotes a significant difference ($p<0.0001$) between the number of submovements fit using either movement primitive. Error bars represent standard error.

Discussion

We used submovement analysis to study the differences between the three experimental blocks (slow, medium and fast). Under the working hypothesis that movement primitives are used by the human motor control system, the submovement analysis reveals significant differences among the experimental blocks. One striking difference between the fast block on the one hand and the slow and the medium blocks on the other is the type of movement primitive that gave a better fit in each case. While the rhythmic movement primitive – that is, the non-terminated minimum-jerk speed profile – provided a significantly better fit to movements in the fast block, the discrete primitive – that is, the terminated minimum-jerk speed profile – gave a significantly better fit to movements in the slow and the medium blocks.

This finding suggests that movements in what we previously termed the "truly cyclic regime" (small-amplitude, high-frequency movements; the fast block in our experiment) are controlled using different movement primitives than those in what we previously called the "pseudo cyclic regime" (large-amplitude, low-frequency movements; the slow and the medium blocks in our experiment). Another important difference that came through from the submovement analysis was the number of submovements fit per half cycle. Using either movement primitive, movements in the fast block were fit using close to a single submovement per half cycle (1.5 ± 0.05 submovements per half cycle, on average, using the rhythmic primitive, mean ± SE). Using either movement

primitive, movements in the slow and the medium blocks were not fit with less than 2.4 submovements per half cycle (5.0 ± 0.11 and 2.4 ± 0.08 submovements per half cycle, on average, respectively, using the discrete primitive).

This finding suggests that, as we previously hypothesized, movements in the truly cyclic regime are often executed using a single, smooth movement in each half cycle; this, in turn, lends support to the idea that movements are governed by the elastic properties of the spring-like elements of the limb, which would not allow a concatenation of movements, such as that observed in the pseudo-cyclic regime.

In the following section we show that movements in the fast block are more intermittent when visual feedback is available. This difference is manifest in the number of submovements per cycle as well; Indeed, only 1.3 ± 0.07 submovements were fit, on average, per half cycle in the non-vision trials compared with 1.5 ± 0.05 in the vision trials, using the non-terminated basis function ($p<0.05$).

B. Differential effects of vision on movement smoothness

In Chapter 3 we described the monotonic relationship between movement intermittency and frequency of movement, which could be captured using a power-law model ($R^2=0.92$). We used the mean squared jerk ratio (MSJR), which is the ratio of the mean squared jerk of the movement to that of the corresponding maximally smooth movement. We showed that the MSJR value of

movements in the fast block approached unity, indicating a movement that is nearly maximally smooth. This finding was in contrast to the MSJR values of ~6 and ~600 for the medium and the slow blocks, respectively. We argued that a movement that is nearly maximally smooth (as in the fast block) is different from movements that are as smooth as the smoothest concatenation of discrete movements (as in the medium block), or less (as in the slow block). We further argued that this difference indicates different control mechanisms for movements in the "truly cyclic regime" vs. the "pseudo-cyclic regime" – that is, for small-amplitude, high-frequency movements vs. for large-amplitude, low-frequency movements.

In this chapter, we would like to examine yet another aspect of movement smoothness and how it can further illuminate the difference between the two regimes. We will examine the differential effects of visual feedback on movement smoothness in these two hypothesized regimes.

Employing the same methods to the same data as used in the previous chapter, we now focus on the vision vs. the non-vision trials.

Figure 5 depicts the MSJR values for both vision and blind (non-vision) trials for the three experimental blocks. While movements were significantly less intermittent when vision was available in the slow and the medium trials,

movements in the fast block were significantly more intermittent when vision was available.

The significant increase in intermittency when vision was withdrawn in the slow and medium blocks is congruent with a mechanism whereby vision is used, most likely together with other sensory feedback modalities, to achieve accuracy and smoothness of movement. When visual feedback is not available, subjects have to rely on less accurate (Meyer et al. 1988) sources of feedback, which result in a decrease in both accuracy (see figure 6) and smoothness.

In contrast, the significant decrease in intermittency when vision was withdrawn in the fast block suggests that, for this task, vision was not a source of movement smoothness. How, then is movement controlled differently in this case?

In the fast block, a half cycle lasts ~250 ms (for the ellipse at the very center of the doughnut shape), which is in the vicinity of the visual reaction time, or less than that, for the older population (~300 ms, Sparrow et al. 2006). Accordingly, it is likely that subjects do not make use of visual feedback to correct movement *within* a half cycle, but rather across cycles. Research on the interjection of discrete movement into an otherwise rhythmic movement, found that the discrete movement was done in phase with the rhythmic movement (de Rugy and Sternad 2003). That is, the discrete movement would normally not be initiated in mid-cycle, but rather at the point where a new rhythmic cycle would have started. The discrete vision-based correction to the otherwise rhythmic movement is then likely to occur between, and not within, cycles – or – in phase with the rhythmic

movement. These occasional, sparse vision-based corrections to the movement result in higher smoothness (and less submovements) in the fast block compared to the two other blocks, where vision-based corrections are more likely to occur within a cycle. In the absence of such corrections – that is, when visual feedback is not available in the fast block – movements are yet smoother (see figure 5). If vision, then, is not harnessed to achieve smoothness and accuracy within a cycle, what is? We argue that the elastic properties of the limb play a part in both. It has been argued that, when performing a rhythmic movement, it is only the limb's stiffness and neutral point that need to be set, and these, in turn, determine the amplitude and the frequency of the movement (Nelson 1983). In this task, we require particular combinations of amplitude and frequency; The implication of Nelson's (1983) argument for the task at hand is that, in the fast block, subjects could employ a "launch and go" strategy, so to speak: set the stiffness and neutral point, and further intervene only in the form of escapement – a mechanism whereby energy is released at exactly the amount needed to compensate for dissipative losses (Kelso et al. 1981) – and, when vision is available, by adjusting these two parameters to fit inside the target ellipse.

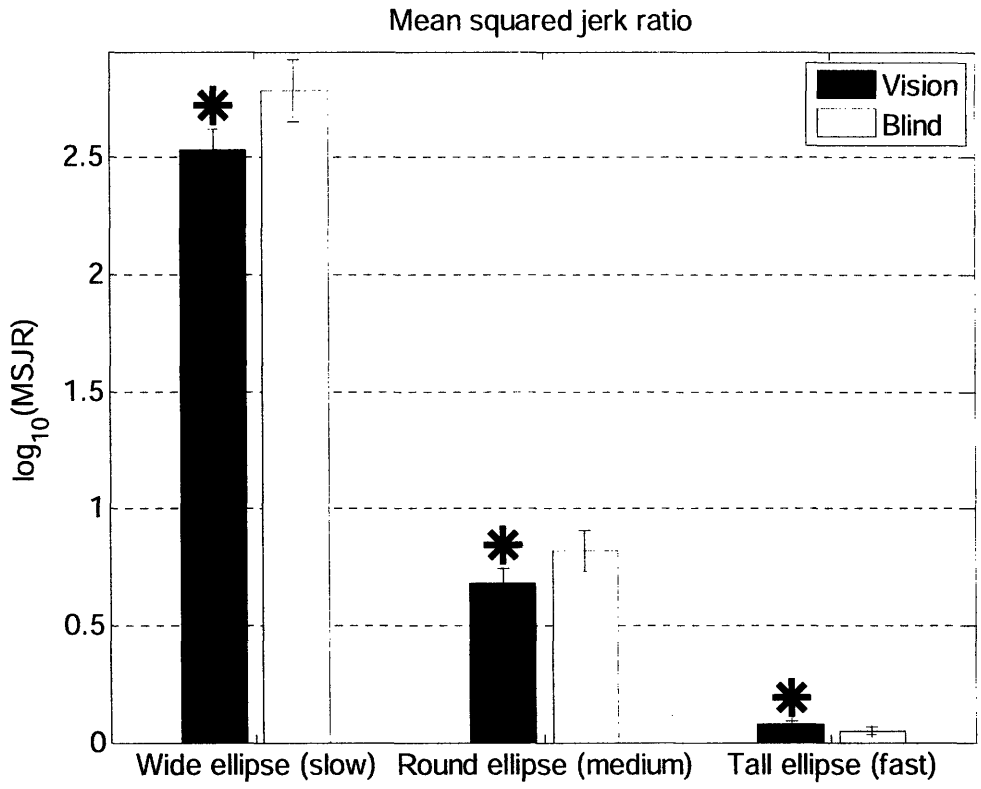

Figure 5. MSJR (relative smoothness) values for the three blocks (slow, medium, fast) showing both vision (black bars) and non-vision (white bars). The logarithm of the values is displayed, to facilitate comparison among the blocks. An asterisk denotes a significant difference between the vision and blind trials ($p<0.05$). Error bars represent standard error.

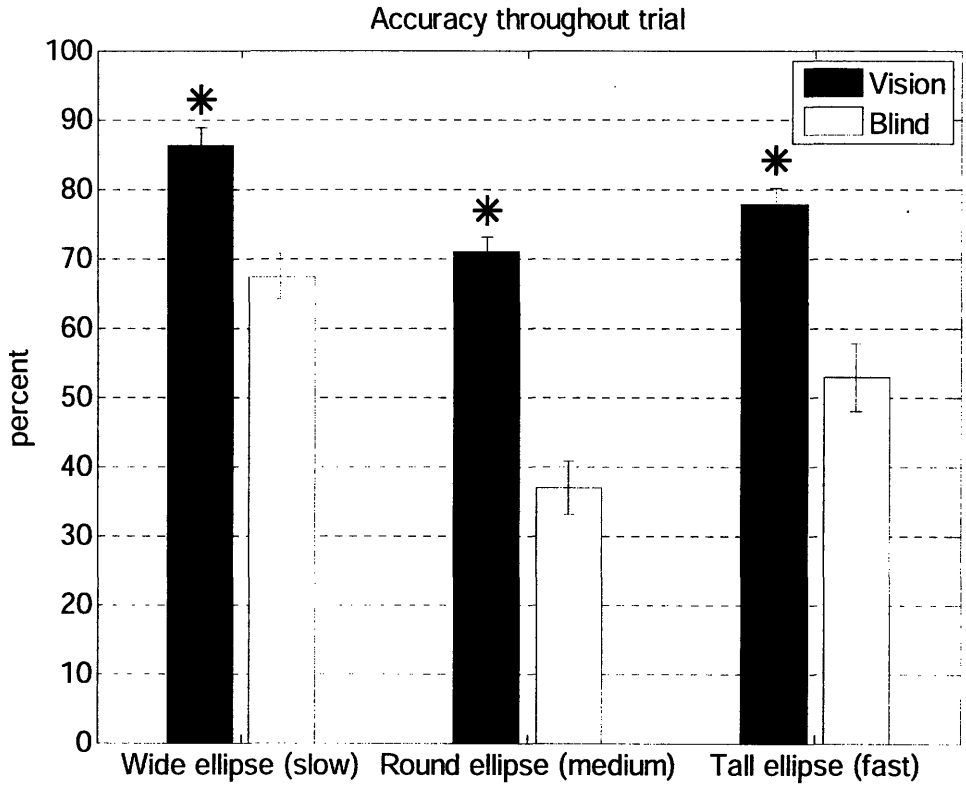

Figure 6. Accuracy scores for the three blocks (slow, medium, fast) showing both vision (black bars) and non-vision (white bars). An asterisk denotes a significant difference between the vision and blind trials ($p<0.005$). Error bars represent standard error.

To summarize, we have demonstrated that vision differentially affects movements in the fast block vs. those in the slow and the medium blocks. While in the former, withdrawal of vision led to significantly smoother movements, in the latter two, it led to a significant increase in movement intermittency. This finding supports an interpretation that there exist two regimes in the frequency/amplitude plane: one that is "truly cyclic", corresponding to movements that call for small

amplitude and high frequency, and one that is "pseudo-cyclic", where movements are of large amplitude and low frequency. Furthermore, the findings support an interpretation of two different control mechanisms applied at each regime: a sensory-feedback-based control scheme for the pseudo-cyclic regime, which suffers "losses" in smoothness when the most acute modality – that is, vision – is not available, and an elasticity-based control scheme for the truly cyclic regime, where vision-based corrections are "penalized" by an increase in movement intermittency.

C. Summary and conclusions

In the previous and the current chapter, we examined data collected from twenty three healthy subjects who performed a rhythmic elbow task at three different frequency/amplitude combinations, with and without visual feedback.
The analysis revealed six different facets in which movements in the fast block were different from movements in the slow and the medium blocks. These are:

1. Non-monotonicity of accuracy with speed

The increase in speed between the slow and the medium blocks was accompanied by a significant decrease in movement accuracy, in accordance with what is to be expected from the speed-accuracy tradeoff principle. However, with further increase in speed from the medium to the fast block, there was a

significant *increase* in accuracy. This break away from the otherwise observed trend, and from the expected result, suggests that perhaps the fast block does not lie on the same curve as do the other two blocks, and that perhaps different control mechanisms are responsible for separate speed-accuracy trade-off functions.

2. Movement smoothness

Using the mean squared jerk ratio (MSJR) as a way to rank the relative smoothness of a movement, we found movements in the fast block to have an MSJR value approaching unity, suggesting those movements are nearly maximally smooth. In contrast, movements in the slow and the medium blocks were found to be only as smooth as the smoothest concatenation of discrete movements, or less. This finding suggested that whereas movements in the fast block were performed in a smooth sinusoidal fashion, movements in the slow and the medium blocks were performed as a concatenated sequence of discrete movements.

3. Movement harmonicity

Harmonicity has been extensively used as a tool to judge how harmonic, or how discrete in nature a movement is. We used it to analyze data from the three experimental blocks, and found that while movements in the fast block were

scored as having harmonicity values close to 1, on average, indicating a strongly harmonic nature, movements in the medium and the slow blocks were scored as having harmonicity values close to 0.3 and to 0 on average, respectively, supporting an interpretation of them being composed of a string of discrete movements.

4. Number of submovements per half cycle

We found that movements in the fast block were fit with close to a single submovement per half cycle on average, whereas movements in the medium and the slow blocks were fit with no less than 2 submovements per half cycle on average. These results give a strong support to the notion that the movements in the medium and the slow blocks are composed of multiple concatenated submovements, as opposed to the fast block, where most of the time a single submovement is employed per half cycle.

5. Velocity profile of best-fit submovement

We used minimum-jerk speed profiles to fit movements from the three experimental blocks. Using two alternative minimum-jerk speed profiles – one for a terminated (discrete) movement, and one for a non-terminated movement (rhythmic) – we found that either one profile or the other provided a better fit for each block, with significant differences between the number of submovements fit

on average to movement in that block with each profile. We found that movements in the fast block were best fit using the rhythmic basis function, whereas the movements in the medium and in the slow blocks were best fit using the discrete basis function. These distinct speed profiles may represent differentially controlled movements, a concept which resonates with a finding that brain activation patterns are not identical when human subjects perform discrete vs. rhythmic movements (Schaal et al. 2004), and when both humans and primates make saccadic vs. pursuit eye movements (for a review, see Krauzlis 2005).

6. Effects of visual feedback on movement smoothness

We found that whereas movement in the slow and the medium blocks is significantly smoother when visual feedback is available, movement in the fast block is significantly more intermittent when visual feedback is available. This clear difference in the effect of vision on movement smoothness is in accord with a model whereby movements in the fast block are governed by the elastic properties of the limbs, with vision playing a *secondary* role in tuning of the movement for accuracy, at the cost of smoothness, whereas movements in the medium and the slow blocks make use of vision as a *primary* source for both accuracy and smoothness, such that when vision is not available, both are compromised.

These six methods of kinematic analysis support the hypothesis that movements in the fast block are controlled differently than movements in the slow and the medium blocks. We suggest that the difference between the two control modes stems from a limit on how large (amplitude) or how long (duration) a movement can be, and still be executed smoothly and accurately. In other words, we suggest that there exist two regimes in the frequency/amplitude plane, and the choice whether to operate in one vs. another regime depends on the frequency and the amplitude of the required movement. We suggest that small-amplitude, high-frequency (short duration per half cycle) movements form the "truly cyclic" regime – so named for the high smoothness and harmonicity values of the movements – whereas large-amplitude, low-frequency movements form the "pseudo-cyclic" regime – so named for the fact that movements are performed with a rhythmic "intention", but share many characteristics with discrete movements.

REFERENCES

Berthier NE. Learning to Reach: A Mathematical Model. *Developmental Psychology* 32: 811-823, 1996.

Burdet E, and Milner TE. Quantization of human motions and learning of accurate movements. *Biol Cybern* 78: 307-318, 1998.

Crossman ER, and Goodeve PJ. Feedback control of hand-movement and Fitts' Law. *Q J Exp Psychol A* 35: 251-278, (1963) 1983.

de Rugy A, and Sternad D. Interaction between discrete and rhythmic movements: reaction time and phase of discrete movement initiation during oscillatory movements. *Brain Res* 994: 160-174, 2003.

Doeringer JA, and Hogan N. Serial processing in human movement production. *Neural Netw* 11: 1345-1356, 1998.

Dounskaia N, Wisleder D, and Johnson T. Influence of biomechanical factors on substructure of pointing movements. *Exp Brain Res* 164: 505-516, 2005.

Hogan N. An organizing principle for a class of voluntary movements. *J Neurosci* 4: 2745-2754, 1984.

Hogan N, and Sternad D. On rhythmic and discrete movements: reflections, definitions and implications for motor control. *Exp Brain Res* 181: 13-30, 2007.

Kelso JA, Holt KG, Rubin P, and Kugler PN. Patterns of human interlimb coordination emerge from the properties of non-linear, limit cycle oscillatory processes: theory and data. *J Mot Behav* 13: 226-261, 1981.

Krauzlis RJ. The control of voluntary eye movements: new perspectives. *Neuroscientist* 11: 124-137, 2005.

Krebs HI, Hogan N, Hening W, Adamovich SV, and Poizner H. Procedural motor learning in Parkinson's disease. *Exp Brain Res* 141: 425-437, 2001.

Lee D, Port NL, and Georgopoulos AP. Manual interception of moving targets. II. On-line control of overlapping submovements. *Exp Brain Res* 116: 421-433, 1997.

Meyer DE, Abrams RA, Kornblum S, Wright CE, and Smith JE. Optimality in human motor performance: ideal control of rapid aimed movements. *Psychol Rev* 95: 340-370, 1988.

Meyer DE, Smith JE, and Wright CE. Models for the speed and accuracy of aimed movements. *Psychol Rev* 89: 449-482, 1982.

Milner TE. A model for the generation of movements requiring endpoint precision. *Neuroscience* 49: 487-496, 1992.

Nelson WL. Physical principles for economies of skilled movements. *Biol Cybern* 46: 135-147, 1983.

Novak KE, Miller LE, and Houk JC. The use of overlapping submovements in the control of rapid hand movements. *Exp Brain Res* 144: 351-364, 2002.

Plamondon R, and Alimi AM. Speed/accuracy trade-offs in target-directed movements. *Behav Brain Sci* 20: 279-303; discussion 303-249, 1997.

Rohrer B, and Hogan N. Avoiding spurious submovement decompositions: a globally optimal algorithm. *Biol Cybern* 89: 190-199, 2003.

Rohrer B, and Hogan N. Avoiding spurious submovement decompositions II: a scattershot algorithm. *Biol Cybern* 94: 409-414, 2006.

Schaal S, Sternad D, Osu R, and Kawato M. Rhythmic arm movement is not discrete. *Nat Neurosci* 7: 1136-1143, 2004.

Sparrow WA, Begg RK, and Parker S. Aging effects on visual reaction time in a single task condition and when treadmill walking. *Motor Control* 10: 201-211, 2006.

Vallbo AB, and Wessberg J. Organization of motor output in slow finger movements in man. *J Physiol* 469: 673-691, 1993.

van Donkelaar P, and Lee RG. Interactions between the eye and hand motor systems: disruptions due to cerebellar dysfunction. *J Neurophysiol* 72: 1674-1685, 1994.

Walker N, Philbin DA, and Fisk AD. Age-related differences in movement control: adjusting submovement structure to optimize performance. *J Gerontol B Psychol Sci Soc Sci* 52: P40-52, 1997.

Wisleder D, and Dounskaia N. The role of different submovement types during pointing to a target. *Exp Brain Res* 176: 132-149, 2007.

CHAPTER 5

MITIGATION OF BRADYKINESIA IN A RHYTHMIC MOVEMENT UPON WITHDRAWAL OF VISUAL FEEDBACK

ABSTRACT

Bradykinesia, or slowness of movement, is one of the principal symptoms in Parkinson's disease (PD); nonetheless, its causes are not yet clear. While some experimental evidence points towards deficits in the feed-forward control of movement, other evidence suggests that impairments in the feedback mechanisms are at fault. To address the question of whether the cause for bradykinesia lies, at least in part, within the feedback loop of the motor control system, we studied rhythmic elbow movements performed by PD patients when off dopaminergic medication, with and without visual feedback, and compared those to movements of healthy age-matched controls. We found that when visual feedback was not available: (1) both groups, PD and healthy control, performed higher-speed movements; (2) bradykinetic symptoms in the PD group were mitigated and even altogether eliminated when visual feedback was not available (3) unlike when visual feedback was available, the peak speed did not significantly differ. We suggest that training PD patients in performing rhythmic tasks in the absence of visual feedback as part of their physical therapy regimen may be beneficial.

INTRODUCTION

Bradykinesia

Bradykinesia, or slowness of movement, is one of the cardinal manifestations of Parkinson's disease (PD). While medication and deep-brain stimulation can act to ameliorate the condition, they do not normalize the patients' movement speed (Vaillancourt et al. 2004). A wide variety of contributing factors to bradykinesia has been suggested – from muscle weakness to bradyphrenia (slowness of thought; for a review, see Berardelli et al. 2001). Largely, the proposed causes may be divided into two main categories: those that are inherent in the motor control system, and therefore cannot be bypassed (located in the "feedforward" part of the motor control loop), and those that depend on various feedback modalities, and their integration for the generation of subsequent motor actions (located in the "feedback" part of the motor control loop).

Bradykinesia in the feedforward loop

In the first category are factors such as the abnormal muscle activation pattern recorded in PD patients. Unlike the stereotypical triphasic EMG pattern found in physiological studies of healthy subjects, patients with PD exhibit smaller-amplitude multiple agonist bursts (Hallett and Khoshbin 1980). When performing large-amplitude movements, these bursts do not increase in duration as do those of healthy subjects (Pfann et al. 2001). This abnormal activation pattern has been suggested to underlie the slower movement speeds observed in PD (Hallett and

Khoshbin 1980). It was further suggested that the multi-burst pattern may be a form of action tremor, postulated to play a fundamental role in bradykinesia (Carboncini et al. 2001). The reason for the reduction in the size of the agonist bursts is not known, and one hypothesis is that it is due to a saturation in the mechanism that produces the burst (Berardelli et al. 1986).

If a change in the ability to generate a normal muscle activation pattern, independently from the incoming sensory information, is indeed the cause for bradykinesia, then the expression of bradikinetic symptoms should be independent of the availability of sensory feedback. The same is true for any other "feedforward factor". The possibility that bradykinesia is independent of visual feedback is supported by findings that the peak speed of discrete movements does not change when visual feedback is withdrawn (Flash et al. 1992; Schettino et al. 2006).

Bradykinesia in the feedback loop

In the second category, the hypothesized cause for slowness of movement lies in the "feedback loop". Interestingly, while some researchers agree that the basal ganglia (BG) play a role in sensorimotor integration, there does not exist a uniform agreement as to how this role plays out in terms of the relation between visual feedback and bradykinesia.

On one end of the spectrum is the view that visual cues assist in relieving bradykinetic features (Marchese et al. 2000; Morris et al. 1996). On the other end is the view that vision may worsen bradykinesia. Several researchers interpreted

the typically observed PD behavior as indicating a deficit in the patients' sense of proprioception, or awareness of where the body is in space (Abbruzzese and Berardelli 2003; Jacobs and Horak 2006; Jobst et al. 1997; Klockgether et al. 1995; Klockgether and Dichgans 1994; Schneider et al. 1986). A decline in the sense of proprioception has been observed in healthy aging as well (Adamo et al. 2007). Others suggest that while proprioception may be intact in PD, it is the patients' ability to integrate this information successfully that is damaged (Almeida et al. 2005; Inzelberg and Korczyn 1996; Tatton et al. 1984). It has been further proposed that the deficits in PD – either in proprioception or in sensorimotor integration – lead to increased reliance on vision (Adamovich et al. 2001; Gale et al. 2008; Schettino et al. 2006), which, in turn, accentuates slowness of movement (Flash et al. 1992).

If an increased reliance on (or a difficulty in integrating) visual feedback is indeed the cause for bradykinesia, then the expression of bradikinetic symptoms should diminish upon withdrawal of visual feedback. Such an inverse dependence on visual feedback has not been observed in the context of discrete movements (Flash et al. 1992; Schettino et al. 2006).

Which is it?

The question, then, stands as to whether bradykinesia is the result of PD-induced changes to the motor system of PD patients, which cannot be bypassed (such as an inability to generate a normal muscle activation pattern), or whether it is the results of a deficit within the feedback loop.

To address the question of whether the cause for bradykinesia lies (at least in part) within the feedback loop of the motor control system, we studied rhythmic movements performed by PD patients, off dopaminergic medication, with and without visual feedback, and compared them to movements of healthy age-matched controls. A rhythmic task was chosen as the platform for the study since it has been suggested that PD performance may be more impaired when performing repetitive movements, compared with discrete (Agostino et al. 1994), as there may be greater dependence on sensorimotor integration during movement execution; according to this argument, the greater dependence stems from sensorimotor integration possibly occurring during the movement execution, in preparation for the initiation of consecutive movements (Almeida et al. 2005), which is not a concern when performing discrete movements.

METHODS

Subjects

A total of 23 subjects participated in this experiment. Ten PD patients after an overnight withdrawal from dopaminergic treatment (age: 72.1±9.9 years, mean±SD; 8 males and 2 females) and 13 healthy age-matched control subjects without any known neurological disorders or tremor were tested using their

dominant hand (71.3±5.9 years; 7 females, 6 males). All subjects gave their informed consent to participate.

Equipment

The equipment used for this experiment consisted of a modified version of the elbow-angle measurement device described in Doeringer & Hogan (1998). A forearm support, consisting of a commercially available wrist splint (Futuro splint wrist brace) strapped to a flat aluminum plate atop a lightweight aluminum tube, was hinged via precision ball bearings to a stationary support, mounted on a table in front of the seated subject, whose elbow joint coincided with the axis of rotation. The forearm support was deliberately designed to be as light as possible, to minimize its effect on the natural behavior of the limb. Its moment of inertia was ~0.0056 $kg \cdot m^2$, an order of magnitude less than the mean value of the subjects' forearm moment of inertia, ~0.075 $kg \cdot m^2$.

The forearm support was connected to the shaft of a rotary incremental encoder (Gurley Precision Instruments Model # R119). This provided a position resolution of 0.0003 radians per count. The encoder was in turn connected to a counter card inside a computer running a real-time Linux operating system. Using this angle sensor, we were able to display both the position and the velocity of the elbow directly to the subject in real time. The computer controlled the recording of the data, as well as the display, which was a 17-inch monitor, positioned ~80 cm from a subject's eyes. Data were recorded at 200Hz. A large, opaque plastic

cover was placed parallel to the table, and above the apparatus, such that during the experiment, the subjects' forearm was occluded from view (see Figure 1).

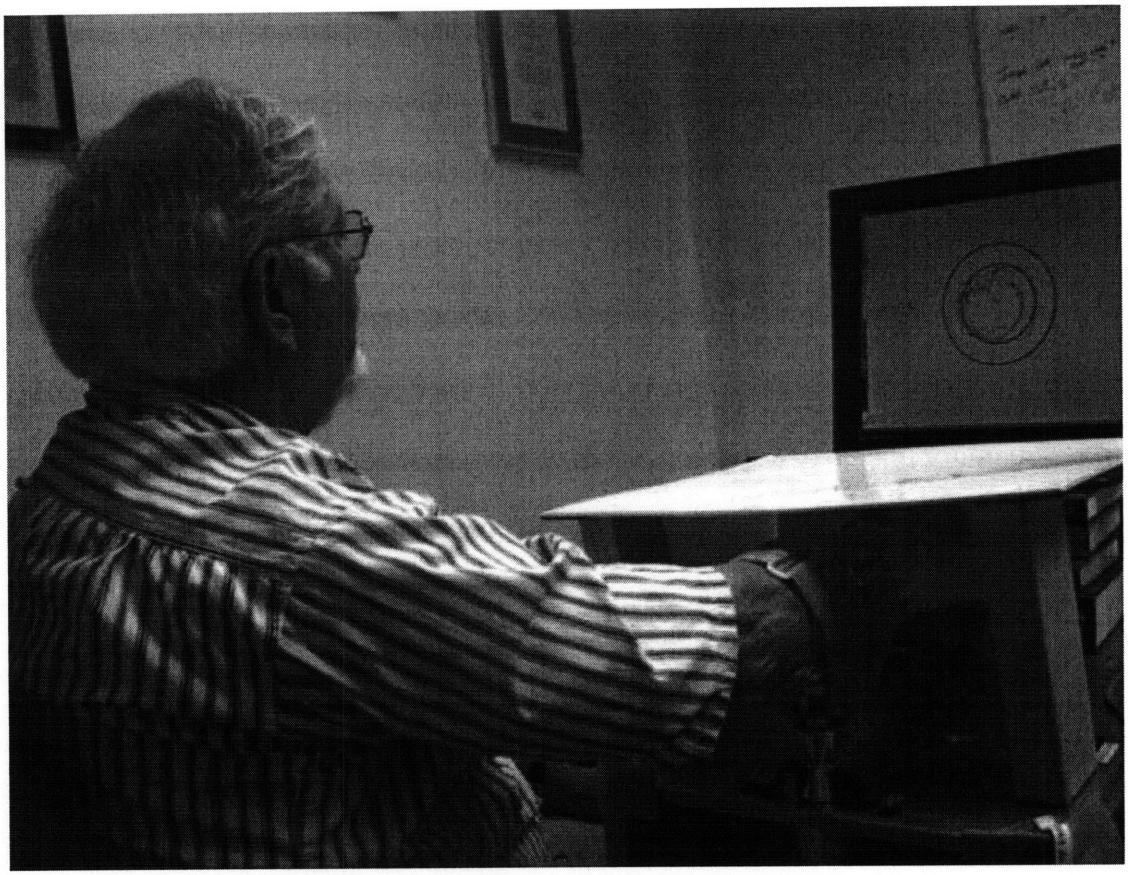

Figure 1. The experimental setup. The forearm is strapped to the angle-measuring device, and is occluded from the subject's view by an opaque cover. The subject coordinates simultaneous modulation of both speed and position to control a cursor displayed on a phase plane.

Protocol

Subjects were presented with a display of the phase plane of their elbow motion; the horizontal axis displayed angular position and the vertical axis displayed angular velocity. The target elbow behavior was indicated by a region of the phase plane; this region was a doughnut shape formed from two ellipses displayed on the screen. Each ellipse corresponds to a sinusoidal elbow motion, with the nonzero width of the doughnut shape allowing for a range of amplitudes and frequencies. Before testing commenced, subjects were allowed to practice the movement until they felt comfortable with the task, which usually took about four 40-second practice trials. Each test trial lasted for 20 seconds, and subjects performed 20 such trials. Of the 20 trials, 5 of them (the 2^{nd}, 5^{th}, 9^{th}, 15^{th} and 20^{th}) were non-vision trials; during these trials, subjects could see the doughnut-shaped target region, but not the trace corresponding to their own elbow motion. The instructions to the subjects were as follows:

> On the screen in front of you, you will see a cursor whose vertical position will depend on your elbow velocity, and whose horizontal position will depend on your elbow position. We ask that you move your elbow back and forth in cyclic movements (demonstrate) so that the cursor stays within the doughnut shape displayed on the screen. On some trials, the cursor will not be visible; you won't be able to see the trace of your

movement on the screen. In those trials, continue to try and move within the guidelines even though you cannot see the trace (demonstrate).

Subjects performed two more 20-trial blocks of cyclic movements to match two other doughnut shapes on the phase plane, which required slower and larger movements, but discussion of these data is beyond the scope of this article. The protocol was approved by the Institutional Review Boards of the Massachusetts Institute of Technology and of the University of California, San Diego.

Data analysis

Data were analyzed using MATLAB® (7.5, The MathWorks, Natick, MA). Trend was removed from the position data, so as to reduce the effects of drift. This was achieved by removing the best straight-line fit from the position data. Position and velocity were filtered using a zero-phase (bidirectional) digital filtering with a first order Butterworth filter (bidirectional filtering doubles the filter order) with a cutoff frequency of 20Hz. Velocity was calculated as the difference between every two consecutive points in the filtered position record, multiplied by the sampling frequency and then filtered as described above.

Statistical analysis A non-parametric test, the two-sided Wilcoxon rank sum test, was used to test the significance of differences between the PD group and the

healthy control group. A non-parametric paired test, the sign test, was used to test the significance of differences within a group between the vision and the non-vision trials. The nonparametric tests were chosen to eliminate the need for assumptions regarding population distributions required in parametric tests.

RESULTS

Velocity traces from one PD patient and one healthy control subject are depicted in Figure 2, from one vision trial and one non-vision trial, together with the target doughnut shape. As can be seen in Figure 2, parts A and C (vision trials), while the PD patient never reached the minimum required peak speed to stay within the target ellipse, the healthy control was able to, on average, reach peak speeds above the minimum required.

Bradykinesia

Bradykinesia was defined as the inability of a subject to reach the minimum required peak speed, when averaged across all trials within a category (vision or non-vision).

Vision trials

As a group, the healthy control subjects performed the task within task requirements (as denoted by the shaded area in Figure 3) when visual feedback

was available, whereas the PD group did not, on average, reach the minimum required peak speed. The difference between the groups was significant ($p = 0.02$).

Four out of the 13 healthy controls, or 30%, did not reach the minimum required peak speed on average when performing the task with visual feedback. Eight out of the 10 PD patients, or 80%, did not reach the minimum required peak speed on average when performing the task with visual feedback.

Both groups performed within task requirements, in terms of movement amplitude (see Figure 4), and did not differ significantly from each other. It is likely that hypokinesia (diminished movement) was not manifest in these trials because of the small amplitude of movement required by the task. We found the PD group to make significantly smaller-amplitude movements than the healthy control subjects when the required amplitude was larger (Levy-Tzedek et al. 2007).

Non-vision trials

Both groups performed higher-velocity movements when visual feedback was not available. On average, the peak speed of the healthy control group was 21% higher, and the peak speed of the PD patients' group was 25% higher when visual feedback was withdrawn (see figure 3). Within each group, the difference between vision and non-vision trials was significant (PD patients: $p = 0.02$, healthy controls: $p = 0.003$).

The peak speed of both the healthy controls and the PD patients was within task requirements when visual feedback was withdrawn (see Figure 3), and the two groups did not differ significantly from each other.

All four healthy controls who on average were below task requirements in terms of peak speed increased their movement speed, and two of them were able to reach the minimum required peak speed on average when performing the task without visual feedback.

Seven of the 8 PD patients, who on average were below task requirements in terms of peak speed increased their movement speed, and three of them were able to reach the minimum required peak speed on average when performing the task without visual feedback.

Both groups performed larger-amplitude movements when visual feedback was not available. On average, the movement amplitude of the healthy control group was 28% higher, and the movement amplitude of the PD patients' group was 21% higher when visual feedback was withdrawn (see Figure 4). Within the healthy group only, the difference between vision and non-vision trials was significant ($p = 0.003$).

As a group, the movement amplitude of the PD patients was within task requirements, but that of the healthy subjects was higher than the allowed range when visual feedback was withdrawn (see Figure 4). The two groups did not differ significantly from each other in terms of movement amplitude.

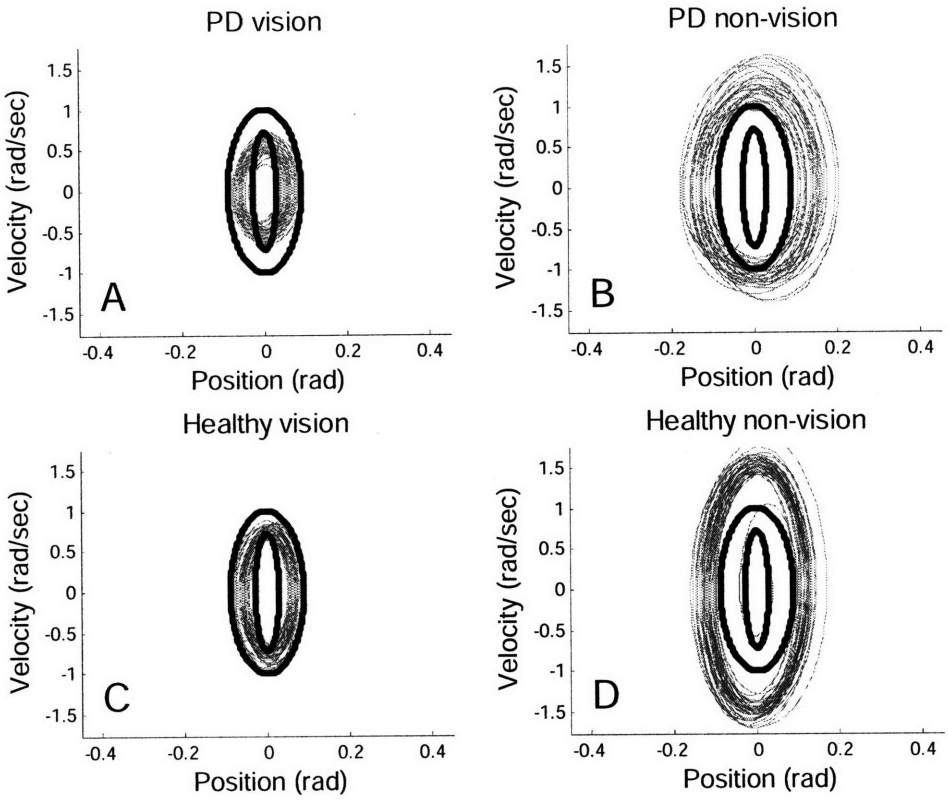

Figure 2. Phase-plane traces (in gray) of a PD patient and of a healthy control subject from one vision trial and one non-vision trial. Thick black outlines mark the target behavior; subjects were asked to move such that their movement traces remain between the two black ellipses.

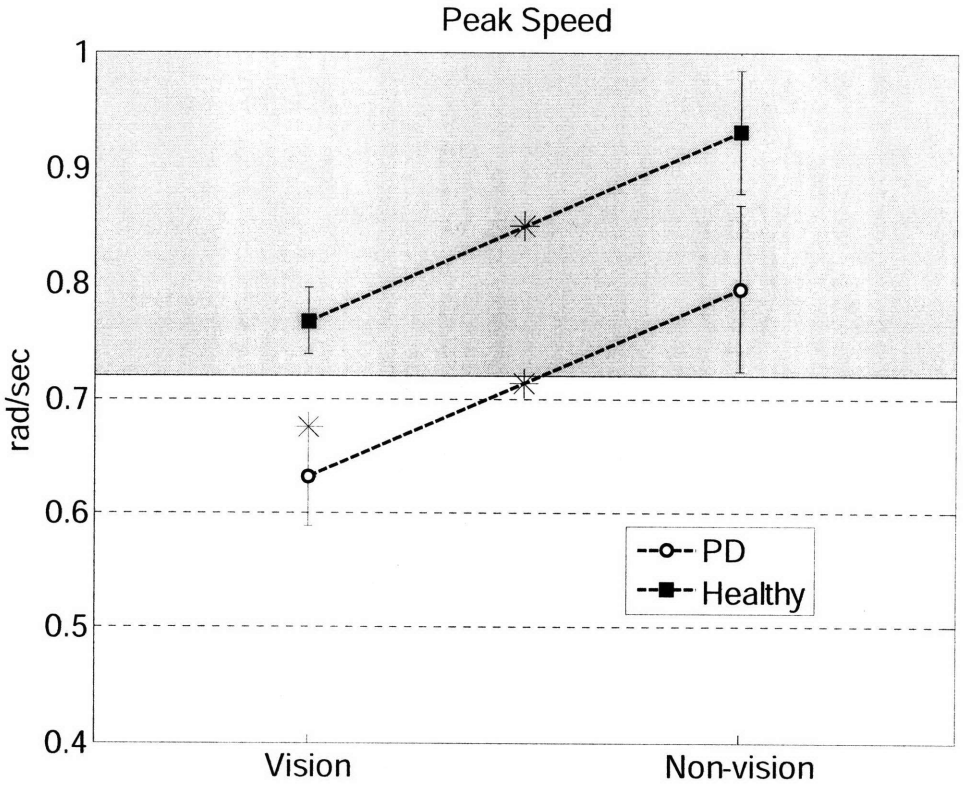

Figure 3. Peak speed (mean ± SE) of the PD patients (empty circles) and healthy controls (black squares). An asterisk above the empty circle denotes a significant difference between the two groups. An asterisk on the dashed line denotes a significant difference between the vision and non-vision conditions in the same group. The shaded area denotes the range of allowed peak speeds, according to task requirements.

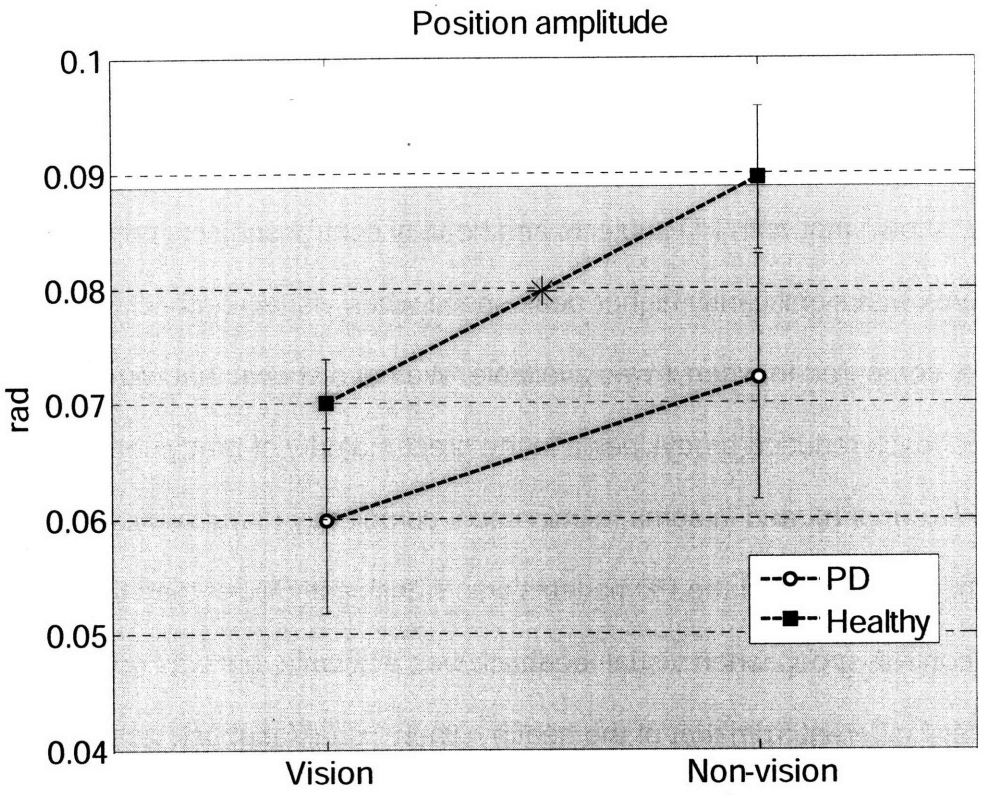

Figure 4. Position amplitude (mean ± SE) of the PD patients (empty circles) and healthy controls (black squares). No significant difference was found between the two groups in either condition (vision/non-vision). An asterisk on the dashed line denotes a significant difference between the vision and non-vision conditions in the same group. The shaded area denotes the range of allowed position amplitudes, according to task requirements.

DISCUSSION

Summary of results

We have shown that both PD subjects and healthy control subjects performed movements with significantly higher peak speed when visual feedback was not available, compared to when it was available. We have shown that withdrawal of visual feedback reduced bradykinesia in the great majority of bradykinetic patients (7 out of 8), and in some, eliminated it completely (3 out of 7). As a group, the peak speed of the PD patients was significantly lower than that of the healthy controls group when visual feedback was available, but was no longer significantly different from that of the healthy when visual feedback was withheld.

In what way may visual feedback interfere with normal execution of movement?

It has been suggested that, with bradykinesia, the problem lies with inappropriate *scaling* of the dynamic muscle force to the required movement's parameters (Berardelli et al. 1986; Fellows et al. 1998), perhaps as a result of incorrect perception of the necessary motor effort in order to achieve a desired motor outcome (Demirci et al. 1997). Indeed, PD patients were found to underscale their movements more when they had to compare movement extent with visual information, than when comparing it with proprioceptive feedback (Demirci et al. 1997).

That is, it may be that it is the ability to respond *appropriately* to visual input that is impaired, rather than the ability to generate the necessary motor commands. Various other PD behaviors, beyond bradykinesia, including abnormal grip force generation (Fellows et al. 1998) and reduced movement accuracy (Adamovich et al. 2001) have been attributed to a deficit in sensorimotor integration.

Bradykinesia is not the result of system saturation – more evidence

Apart from the results described herein, further indication that bradykinesia may be "bypassed" under certain conditions comes from studies that documented the ability of bradykinetic PD patients to make faster movements when required to make larger-amplitude movements(Berardelli et al. 1986), when they are verbally encouraged to make faster movements (Hallett and Khoshbin 1980) and when they are offered a reward for performing faster movements (Schwab 1972). Perhaps the most striking example of all for the PD patients' retained ability to perform movements at normal speeds is the phenomenon termed "paradoxic kinesia".

Paradoxic Kinesia

The temporary ability of PD patients to perform movements free of bradykinetic characteristics has previously been described as "paradoxic kinesia", and was

observed in the context of urgent or externally driven situations (Siegert et al. 2002). Experiments in lab settings, as well as anecdotal accounts of such episodes, included a visual cue (e.g., a runaway horse, an oncoming car, a fire, a flood, or a ball thrown at one) (e.g., Schwab and Zieper 1965), in response to which otherwise immobile patients were able to flee, or catch the ball; In contrast, auditory cues, such as a loud siren in time of war, warning of an impending missile attack, were not shown to induce paradoxic kinesia[1] (Schlesinger et al. 2007). Such an increase in movement speed in response to stress has been observed both in healthy subjects as well as in PD patients (Ballanger et al. 2006; Siegert et al. 2002), and was therefore suggested not to be a hallmark of the disease or a byproduct of BG dysfunction, but rather a general property of the motor system (Ballanger et al. 2006).

Did patients exhibit paradoxic kinesia in this study?

On the one hand, the phenomenon we describe seems to have characteristics similar to those of paradoxic kinesia: (1) it is observed in both healthy subjects and PD patients, and so is likely not the result of damage to the BG, and (2) it allows patients to move without bradykinetic symptoms.

However, there are six important differences between the two phenomena:

[1] Rhythmic auditory cues may, however, bring about an increase in the speed of gait of PD patients (**Hausdorff JM, Lowenthal J, Herman T, Gruendlinger L, Peretz C, and Giladi N**. Rhythmic auditory stimulation modulates gait variability in Parkinson's disease. *Eur J Neurosci* 26: 2369-2375, 2007.), as may increased attention to one's step size (**Morris ME, Iansek R, Matyas TA, and Summers JJ**. Stride length regulation in Parkinson's disease. Normalization strategies and underlying mechanisms. *Brain* 119 (Pt 2): 551-568, 1996.)

(1) whereas paradoxic kinesia has been concluded to result exclusively from visual feedback (Glickstein and Stein 1991; Schlesinger et al. 2007), the phenomenon we describe here was presented upon *withdrawal* of visual feedback; (2) paradoxic kinesia is described as occurring in distinct episodes (e.g., preventing a mug of boiling drink from spilling in one's lap, Schlesinger et al. 2007), whereas we observed the behavior when subjects performed a continuos *rhythmic* task; (3) while paradoxic kinesia is described as occurring in situations of imminent danger or otherwise stressful, subjects who participated in our experiment were not put under dangerous or stressful situations; (4) whereas paradoxic kinesia, when measured in both healthy subjects and PD patients, affected both groups similarly, such that the differences between them were maintained under the effect of the phenomenon, in our experiment, withdrawal of vision eliminated the significant difference between the healthy and the PD groups; (5) it was suggested that paradoxic kinesia is manifested when movement is externally cued, as opposed to self-initiated (Siegert et al. 2002); In our experiment, subjects were asked if they were ready before given the verbal 'go-ahead' to initiate movement; (6) it appears that paradoxic kinesia is a transient behavior, disappearing as fast as it appears, whereas, in our experiment, most subjects exhibited the behavior in each of the repeated non-vision trials, and maintained it throughout each of the 20-sec trials.

Finally, it has been suggested that paradoxic kinesia may represent a switch from using neural circuits that include the supplementary motor area (SMA), thought to be a major projection area for the BG (Fellows et al. 1998) – a

connection believed to be disrupted in PD (Morris et al. 1996; Oliveira et al. 1997; van den Berg et al. 2000) – that is preferentially activated in proprioception-guided movements that are executed in the absence of external cues, to ones that include the premotor cortex (PMC), preferentially activated in the presence of sensory cues (Jacobs and Horak 2006; Oliveira et al. 1997). Once again, the absence of visual cues in our no-vision condition suggests that the increase in movement speed is not yet another instance of paradoxic kinesia.

Why is this pattern observed in rhythmic and not discrete movements?

It is interesting to note that the increase in movement speed upon withdrawal of vision happens when subjects perform rhythmic, but not discrete movements (Flash et al. 1992; Schettino et al. 2006). What may account for this difference? A plausible explanation may be that, unlike a discrete movement, a rhythmic movement allows subjects to operate at resonance, leading to a large oscillation amplitude, and therefore speed, for minimal forcing input from the neuromuscular system, thereby minimizing the subject's energy expenditure (Raftery et al. 2008) and allowing for stable and reproducible movements (Hatsopoulos and Warren 1996).

Why, then, do we not observe this behavior in the vision trials?

It is presumed that proprioceptive information influences potential neural oscillators such that the timing of preferred oscillatory movements is not simply dictated by the central nervous system, but is constrained by the dynamics of the musculoskeletal system (Hatsopoulos and Warren 1996). Since, in the vision

trials, visual feedback is also available, in addition to proprioception, it may act to constrain the movement to be within the task's requirements. A deficit in the ability to integrate the different modalities of sensory feedback may then result in rhythmic movements that at once are not performed at resonance, and that do not match task requirements in terms of speed and/or amplitude.

Is the source for bradykinesia exclusively in the feedback loop?

While the experimental results we present here offer no evidence for the existence of a source of bradykinesia in the feedforward loop, this possibility cannot be ruled out altogether. It is conceivable that there are multiple sources of movement slowness, and whereas some may be overcome – for example, by withdrawal of visual feedback – others cannot. After all, bradykinesia was not eliminated in all the bradykinetic patients in our study, but rather, it was reduced in the great majority of them, and eliminated in close to half of those. Furthermore, the fact that movement speed increased in both groups – PD patients and healthy controls, suggests that the increase in speed observed in the PD group is not a "return to normal" performance. Rather, it appears to be a parallel process, where movement speed increases regardless of whether bradykinesia is present, and if it is present, it acts to reduce its effects. In other words, the patients appear to exhibit a normal mechanism (increase in speed upon withdrawal of visual feedback) overlaid on top of an abnormal mechanism (slowness of movement). If that is the case, can any claims at all be made as to the location of the source of bradykinesia in the motor control loop? We argue

that it is possible to conclude that the source of bradykinesia lies, at least in part, in the feedback loop, since the "normal" mechanism responsible for increase in speed upon withdrawal of visual feedback is not affected in those patients, and allows them to reach speeds not distinguishable from healthy speeds, whereas production of required speed when visual feedback is available is damaged.

Interestingly, even factors that logically would be classified as "feedforward factors", such as an abnormal muscle-activity pattern, can be modified under certain circumstances. For example, it was found that bradykinetic subjects were able to move between two to four times as fast when asked to make movements of larger, compared to smaller, amplitude with their upper limb; a change in movement speed was accompanied by a change in the duration of the agonist burst (Berardelli et al. 1986).

Implications for physical therapy in PD

Our finding that bradykinesia can be mitigated and even eliminated when PD patients perform rhythmic elbow movements in the absence of visual feedback may have important implications for therapy. Physical therapy for PD patients is often used in conjunction with pharmacological treatment, especially in advanced stages of the disease (Marchese et al. 2000; Morris et al. 1996). There have been several reports indicating that visual cues added to the patients' normal environment (e.g., horizontal strips placed on the floor) assist patients in

overcoming difficulties in initiating movement and help them to maintain a more rhythmic gait pattern, associated with a lower risk of falling (Morris et al. 1996). However, visual feedback may, in some cases, elicit the "freezing" phenomenon, characteristic of PD (Almeida et al. 2003; Demirci et al. 1997). In addition, Morris et al. (1996) found that, while visual cues were helpful in normalizing gait, they were not necessary, as focusing the patients' attention on the task gave similar results. Finally, some results were confounded by training subjects with a range of sensory cues (visual, auditory and tactile), and, in addition, training them in the absence of visual feedback, yet classifying the resulting effects under "cued" training (Marchese et al. 2000).

What is becoming clear, then, is that PD patients do not lose their ability to perform faster movements, and proper training may assist them in achieving a mitigation of their bradykinetic symptoms, at least in the short term (Morris et al. 1996; Platz et al. 1998).

Considering the results of our study, it may be beneficial to include training paradigms where PD patients would perform rhythmic tasks in the absence of visual feedback, as part of their normal physical therapy regimen.

CONCLUSION

We have demonstrated that when PD patients perform a cyclic elbow movement in the absence of vision, bradykinetic symptoms are mitigated and, in some cases, even eliminated. We argue that this behavior is not an instance of paradoxic kinesia. The results we present here support a role for the basal ganglia in sensorimotor integration. We suggest that training PD patients in performing rhythmic tasks in the absence of visual feedback as part of their physical therapy regimen may be advantageous.

REFERENCES

Abbruzzese G, and Berardelli A. Sensorimotor integration in movement disorders. *Mov Disord* 18: 231-240, 2003.

Adamo DE, Martin BJ, and Brown SH. Age-related differences in upper limb proprioceptive acuity. *Percept Mot Skills* 104: 1297-1309, 2007.

Adamovich SV, Berkinblit MB, Hening W, Sage J, and Poizner H. The interaction of visual and proprioceptive inputs in pointing to actual and remembered targets in Parkinson's disease. *Neuroscience* 104: 1027-1041, 2001.

Agostino R, Berardelli A, Formica A, Stocchi F, Accornero N, and Manfredi M. Analysis of repetitive and nonrepetitive sequential arm movements in patients with Parkinson's disease. *Mov Disord* 9: 311-314, 1994.

Almeida QJ, Frank JS, Roy EA, Jenkins ME, Spaulding S, Patla AE, and Jog MS. An evaluation of sensorimotor integration during locomotion toward a target in Parkinson's disease. *Neuroscience* 134: 283-293, 2005.

Almeida QJ, Wishart LR, and Lee TD. Disruptive influences of a cued voluntary shift on coordinated movement in Parkinson's disease. *Neuropsychologia* 41: 442-452, 2003.

Ballanger B, Thobois S, Baraduc P, Turner RS, Broussolle E, and Desmurget M. "Paradoxical kinesis" is not a hallmark of Parkinson's disease but a general property of the motor system. *Mov Disord* 21: 1490-1495, 2006.

Berardelli A, Dick JP, Rothwell JC, Day BL, and Marsden CD. Scaling of the size of the first agonist EMG burst during rapid wrist movements in patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry* 49: 1273-1279, 1986.

Berardelli A, Rothwell JC, Thompson PD, and Hallett M. Pathophysiology of bradykinesia in Parkinson's disease. *Brain* 124: 2131-2146, 2001.

Carboncini MC, Manzoni D, Strambi S, Bonuccelli U, Pavese N, Andre P, and Rossi B. The relation between EMG activity and kinematic parameters strongly supports a role of the action tremor in parkinsonian bradykinesia. *Mov Disord* 16: 47-57, 2001.

Demirci M, Grill S, McShane L, and Hallett M. A mismatch between kinesthetic and visual perception in Parkinson's disease. *Ann Neurol* 41: 781-788, 1997.

Doeringer JA, and Hogan N. Intermittency in preplanned elbow movements persists in the absence of visual feedback. *J Neurophysiol* 80: 1787-1799, 1998.

Fellows SJ, Noth J, and Schwarz M. Precision grip and Parkinson's disease. *Brain* 121 (Pt 9): 1771-1784, 1998.

Flash T, Inzelberg R, Schechtman E, and Korczyn AD. Kinematic analysis of upper limb trajectories in Parkinson's disease. *Exp Neurol* 118: 215-226, 1992.

Gale JT, Amirnovin R, Williams ZM, Flaherty AW, and Eskandar EN. From symphony to cacophony: Pathophysiology of the human basal ganglia in Parkinson disease. *Neurosci Biobehav Rev* 32: 378-387, 2008.

Glickstein M, and Stein J. Paradoxical movement in Parkinson's disease. *Trends Neurosci* 14: 480-482, 1991.

Hallett M, and Khoshbin S. A physiological mechanism of bradykinesia. *Brain* 103: 301-314, 1980.

Hatsopoulos NG, and Warren WH. Resonance Tuning in Rhythmic Arm Movements. *J Mot Behav* 28: 3-14, 1996.

Hausdorff JM, Lowenthal J, Herman T, Gruendlinger L, Peretz C, and Giladi N. Rhythmic auditory stimulation modulates gait variability in Parkinson's disease. *Eur J Neurosci* 26: 2369-2375, 2007.

Inzelberg R, and Korczyn AD. Concerning" visual control of arm movement in Parkinson's disease". *Mov Disord* 11: 115, 1996.

Jacobs JV, and Horak FB. Abnormal proprioceptive-motor integration contributes to hypometric postural responses of subjects with parkinson's disease. *Neuroscience* 141: 999-1009, 2006.

Jobst EE, Melnick ME, Byl NN, Dowling GA, and Aminoff MJ. Sensory perception in Parkinson disease. *Archives of Neurology* 54: 450-454, 1997.

Klockgether T, Borutta M, Rapp H, Spieker S, and Dichgans J. A defect of kinesthesia in Parkinson's disease. *Movement Disorders* 10: 460-465, 1995.

Klockgether T, and Dichgans J. Visual control of arm movement in Parkinson's disease. *Movement Disorders* 9: 48-56, 1994.

Levy-Tzedek S, Poizner H, Song D, and Krebs HI. Dopamine-replacement therapy acts to alleviate hypokinesia in Parkinson's disease but fails to normalize coordinative aspects of movement when performing a rhythmic task. In: *Society for Neuroscience Abstracts* 2007, p. 818.819.

Marchese R, Diverio M, Zucchi F, Lentino C, and Abbruzzese G. The role of sensory cues in the rehabilitation of parkinsonian patients: a comparison of two physical therapy protocols. *Mov Disord* 15: 879-883, 2000.

Morris ME, Iansek R, Matyas TA, and Summers JJ. Stride length regulation in Parkinson's disease. Normalization strategies and underlying mechanisms. *Brain* 119 (Pt 2): 551-568, 1996.

Oliveira RM, Gurd JM, Nixon P, Marshall JC, and Passingham RE. Micrographia in Parkinson's disease: the effect of providing external cues. *British Medical Journal* 63: 429-433, 1997.

Pfann KD, Buchman AS, Comella CL, and Corcos DM. Control of movement distance in Parkinson's disease. *Movement Disorders* 16: 1048-1065, 2001.

Platz T, Brown RG, and Marsden CD. Training improves the speed of aimed movements in Parkinson's disease. *Brain* 121: 505-514, 1998.

Raftery A, Cusumano J, and Sternad D. Chaotic frequency scaling in a coupled oscillator model for free rhythmic actions. *Neural Comput* 20: 205-226, 2008.

Schettino LF, Adamovich SV, Hening W, Tunik E, Sage J, and Poizner H. Hand preshaping in Parkinson's disease: effects of visual feedback and medication state. *Exp Brain Res* 168: 186-202, 2006.

Schlesinger I, Erikh I, and Yarnitsky D. Paradoxical kinesia at war. *Mov Disord* 2007.

Schneider JS, Diamond SG, and Markham CH. Deficits in orofacial sensorimotor function in Parkinson's disease. *Annals of neurology* 19: 275-282, 1986.

Schwab RS. Akinesia paradoxica. *Electroencephalogr Clin Neurophysiol* 31: 87-92, 1972.

Schwab RS, and Zieper I. Effects of mood, motivation, stress and alertness on the performance in Parkinson's disease. *Psychiatr Neurol (Basel)* 150: 345-357, 1965.

Siegert RJ, Harper DN, Cameron FB, and Abernethy D. Self-Initiated Versus Externally Cued Reaction Times in Parkinson's Disease. *Journal of Clinical and Experimental Neuropsychology* 24: 146-153, 2002.

Tatton WG, Eastman MJ, Bedingham W, Verrier MC, and Bruce IC. Defective utilization of sensory input as the basis for bradykinesia, rigidity and decreased movement repertoire in Parkinson's disease: a hypothesis. *Can J Neurol Sci* 11: 136-143, 1984.

Vaillancourt DE, Prodoehl J, Verhagen Metman L, Bakay RA, and Corcos DM. Effects of deep brain stimulation and medication on bradykinesia and muscle activation in Parkinson's disease. *Brain* 127: 491-504, 2004.

van den Berg C, Beek PJ, Wagenaar RC, and van Wieringen PCW. Coordination disorders in patients with Parkinson's disease: a study of paced rhythmic forearm movements. *Experimental Brain Research* 134: 174-186, 2000.

CHAPTER 6

RANGES OF FREQUENCY IN THE SIX EXPERIMENTAL GROUPS

Introduction

In this chapter, we examine how the frequency at which the rhythmic task is generated varies with age and with PD treatment – medication and deep-brain stimulation. The motivation for this study was ultimately to test the effects of deep-brain stimulation – itself a "pacemaker" of sorts (Pahwa 2006, Plenz and Kital 1999, Surmeier et al. 2005) – on frequency of movement. Its target – the basal ganglia – have been implicated in the control of rhythmic movement (Freeman et al. 1993).

We hypothesized that the stimulation, which is suggested to override the aberrant neuronal firing pattern in PD (Meissner et al. 2005), would either impose a (nearly) uniform movement frequency, or have a consistent effect (such as an increase or a decrease) on it.

We begin with an affirmation of previous results regarding "preferred frequency ranges" obtained with young, healthy subjects (Doeringer and Hogan 1998), and extend those to a healthy aged population, and then to the two groups of PD patients – those tested on/off medication and those tested on/off stimulation. We then examine individual patients' change in frequency in response to treatment in the three different experimental blocks.

At the conclusion of the chapter we discuss the sources of variation in the data, which lead to a difficulty in identifying clear trends for the effects of the dopaminergic medication and the deep-brain stimulation.

Preferred frequency in healthy subjects

Free rhythmic actions, or rhythmic behaviors performed at self-selected amplitude-frequency combinations are ubiquitous in animal behavior. They are used in a variety of activities that underlie animal mobility, such as locomotion and flight. There is research supporting the hypothesis that these self-selected frequencies correspond to the linear resonance frequencies of the oscillating system, thereby minimizing the animal's energy expenditure (Hatsopoulos and Warren 1996; Raftery et al. 2008).

Apart from supporting evidence for the existence of a unique preferred frequency, which may vary with massive and viscoelastic loads (e.g., Hatsopoulos and Warren 1996), there appears to be evidence to support the existence of a "preferred frequency *range*", both upper- and lower-bound (Doeringer and Hogan 1998). We tested the existence and the variation of this range with age. We hypothesized that changes in size (Langenecker et al. 2007) and activation patterns (Riecker et al. 2006) of brain areas associated with control of rhythmic movement would be thus reflected.

Comparison with previous work on young healthy subjects

Doeringer and Hogan (1998) found that when healthy young (22 to 28 years of age) male subjects were asked to draw elliptical figures on a phase-plane display which required cyclic movements at different frequencies, the dominant frequency of the data did not generally correspond to the middle of the tracking

shape, which in effect, made the task more difficult because a subject had less room for error near the edges of the shape. They concluded that this indicated that subjects had preferences for a particular range of frequencies. Subjects generated frequencies that were biased in the direction of the intermediate ellipse (the medium condition). The possibility that the subjects were somehow reacting to the display and not the task was ruled out since it was observed that subjects continued to be biased toward the intermediate condition's frequencies even when the display was turned off (see Figure 1, from Doeringer and Hogan (1998)).

We repeated the experiment with a young, healthy population, this time extending it to include both male and female subjects.

Data from ten young adults (28.5±4.7 years, range: 22-39 years, 3 females, 7 males) who did not suffer from tremor or any other neurological disorder were analyzed in this section.

As in Doeringer & Hogan's original study (1998), the average frequency of movement did not generally correspond to the central frequency (see Figure 2-Figure 5). This suggests that the subjects had a preference for a particular range of frequencies that is both upper- and lower-bound, confirms the results of the study by Doeringer and Hogan (1998), and extends them to both male and

female subjects. Subjects generated frequencies that were biased in the direction of the circular shape (the medium condition) in both the vision and the blind trials.

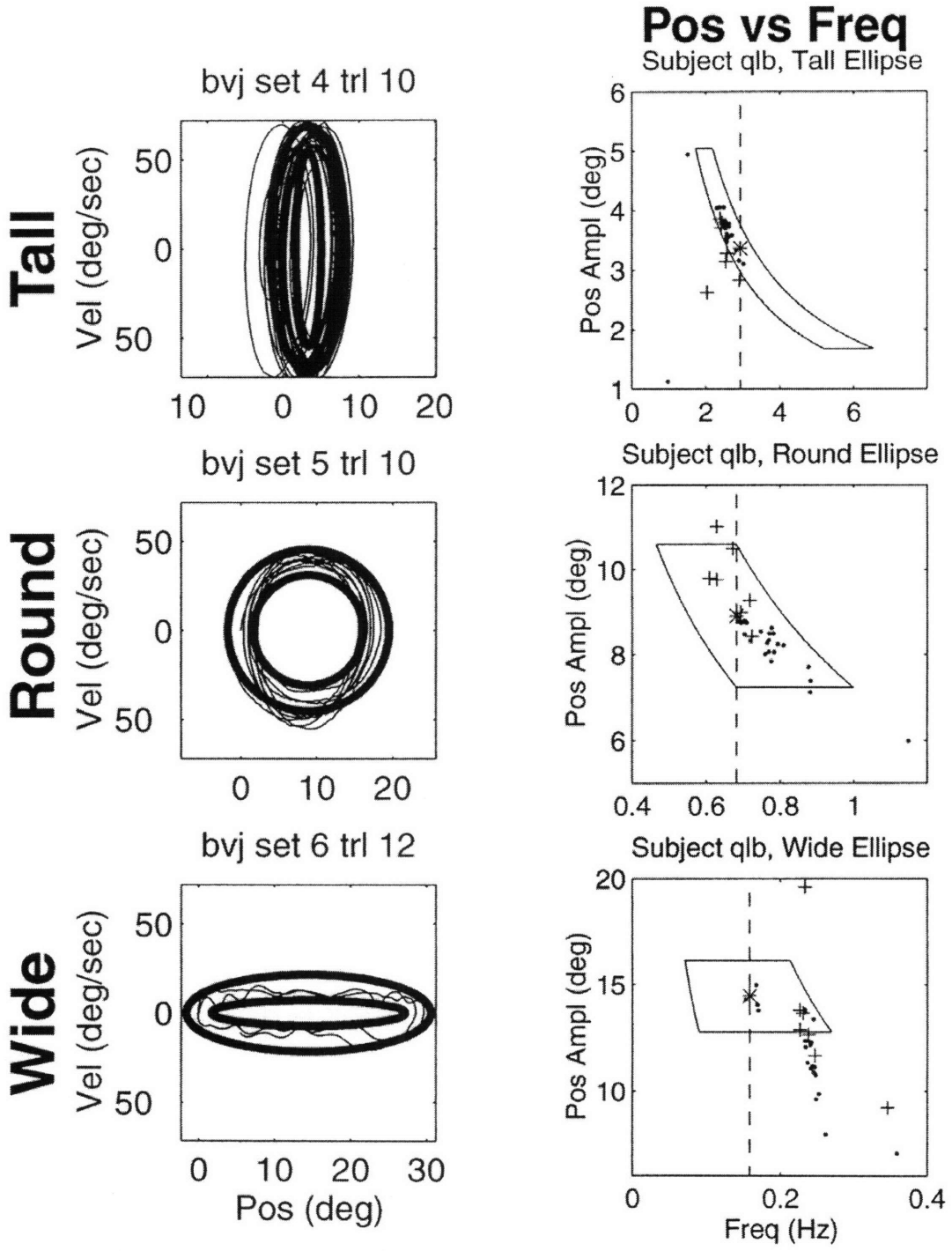

Figure 1. From Doeringer and Hogan (1998): Phase plane raw data and dominant frequencies from a single subject, suggesting that subjects had preferences for a particular range of frequencies. Originally, Figures 7 and 8 from Doeringer & Hogan (1998); used with permission.

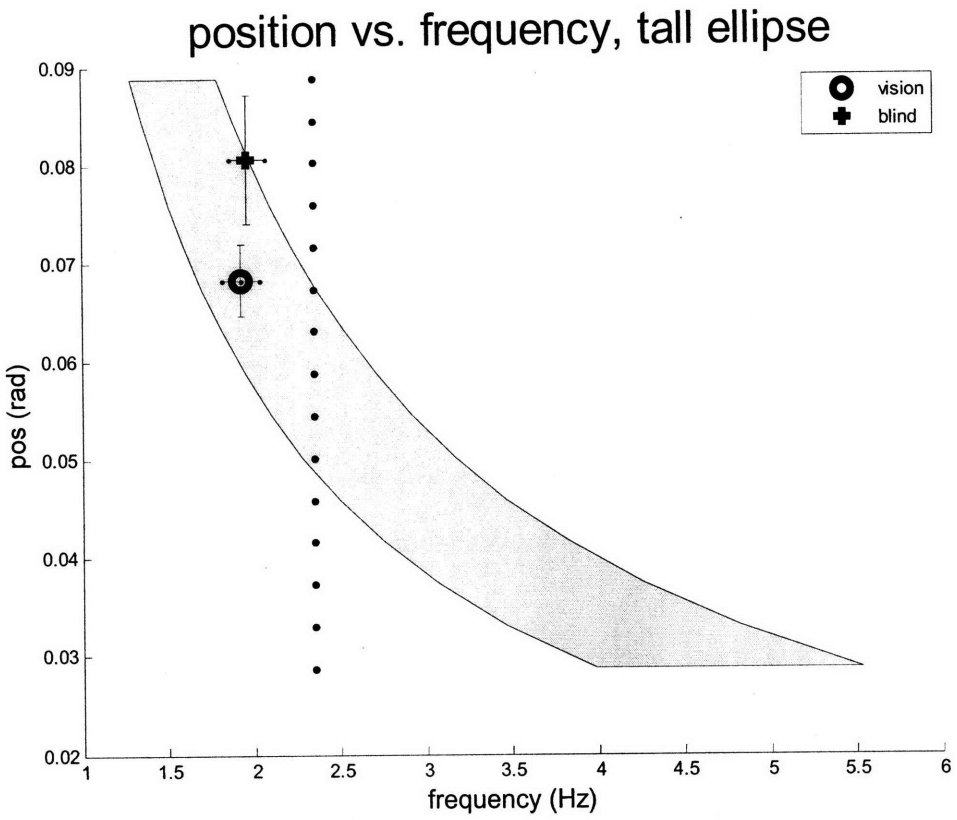

Figure 2. Amplitude vs. frequency. The closed shape defines the allowable ranges of amplitudes and frequencies for the fast task. The circle (vision trials) and plus sign (blind trials) indicate the average amplitudes and frequencies chosen by the subjects. The vertical dotted line corresponds to a sinusoid in the center of the doughnut shape. Error bars represent standard errors.

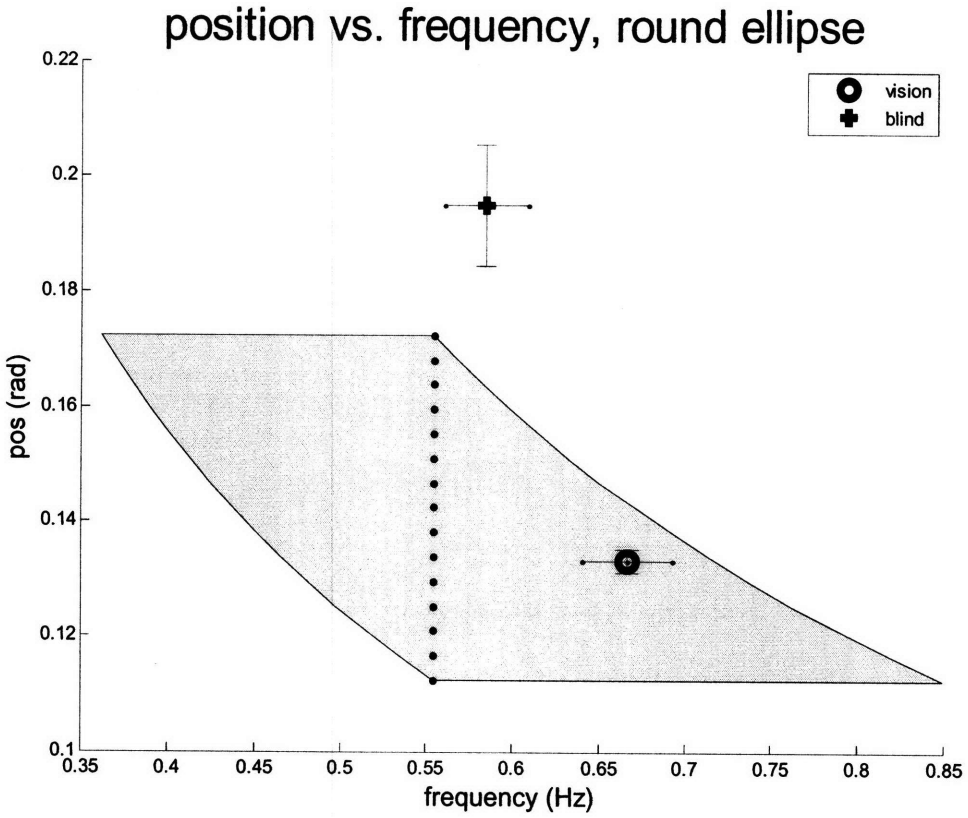

Figure 3. Amplitude vs. frequency. The closed shape defines the allowable ranges of amplitudes and frequencies for the intermediate task. The circle (vision trials) and plus sign (blind trials) indicate the average amplitudes and frequencies chosen by the subjects. The vertical dotted line corresponds to a sinusoid in the center of the doughnut shape. Error bars represent standard errors.

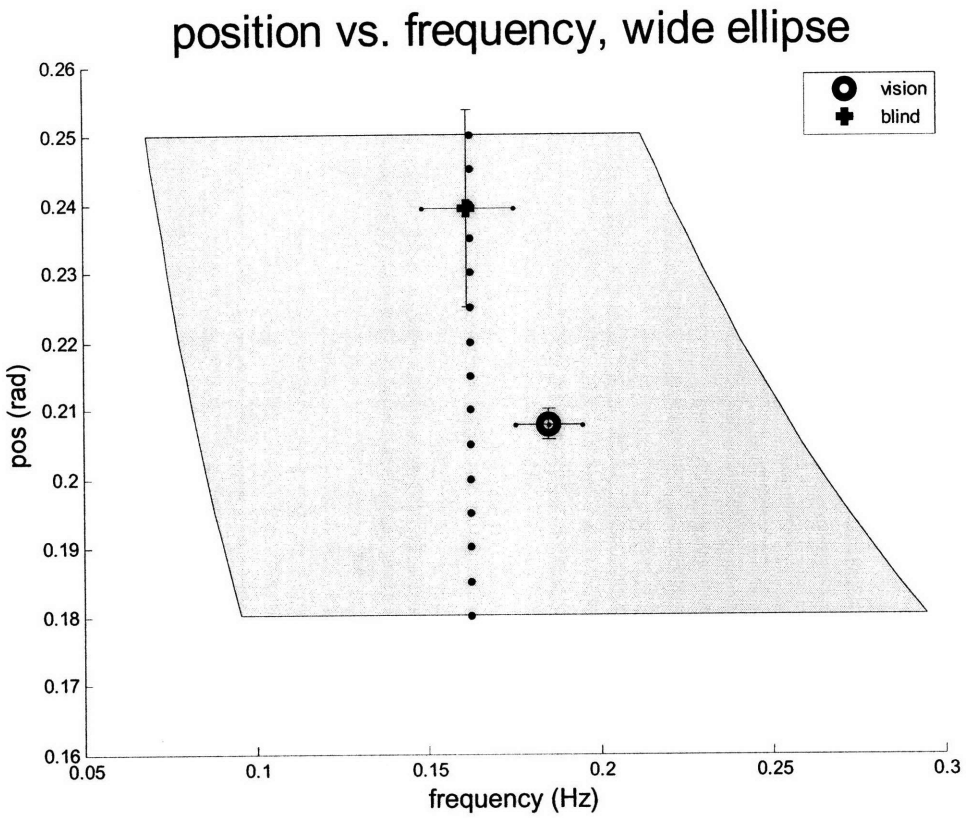

Figure 4. Amplitude vs. frequency. The closed shape defines the allowable ranges of amplitudes and frequencies for the slow task. The circle (vision trials) and plus sign (blind trials) indicate the average amplitudes and frequencies chosen by the subjects. The vertical dotted line corresponds to a sinusoid in the center of the doughnut shape. Error bars represent standard errors.

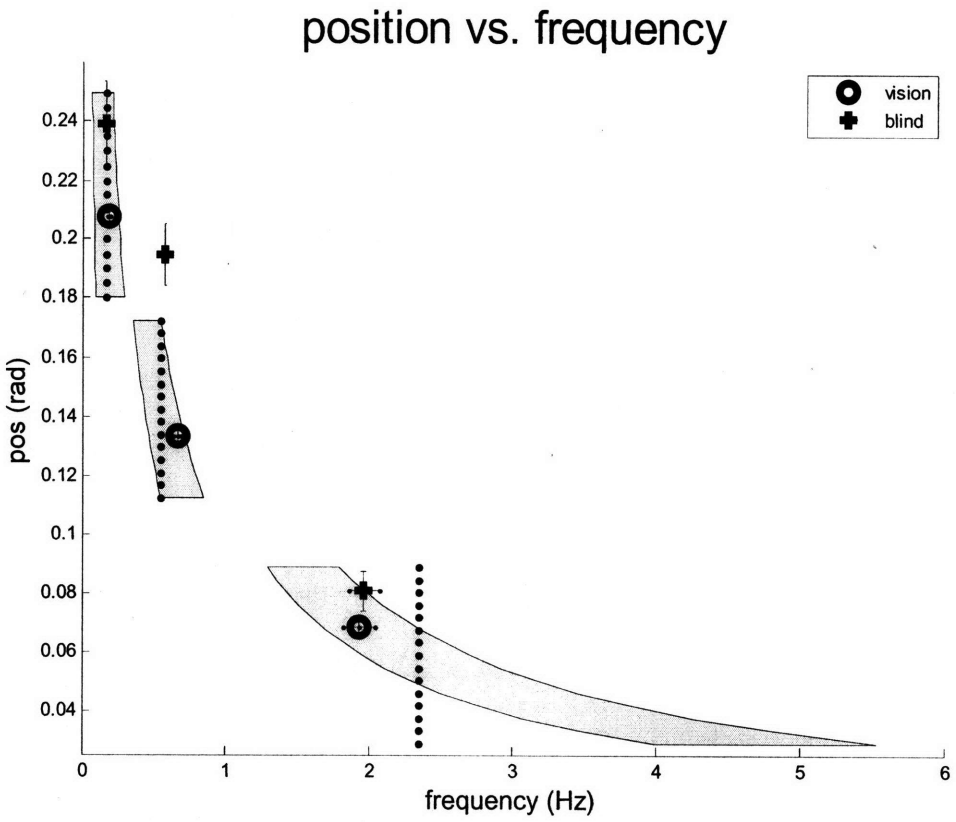

Figure 5. Amplitude vs. frequency. The closed shapes define the allowable ranges of amplitudes and frequencies for all three blocks. The circles (vision trials) and plus signs (blind trials) indicate the average amplitudes and frequencies chosen by the subjects. The vertical dotted lines correspond to the sinusoids in the centers of the doughnut shapes. Error bars represent standard errors.

Extension to older healthy population

Background and hypothesis

Motor function has been shown to decline with age (Smith et al. 1999), and variability, or reduced control of the motor output when performing discrete

movements was shown to increase with age (Galganski et al. 1993, Christou & Carlton 2002, Christou & Carlton 2001, Sosnoff and Newell 2006a-c). Age-related variability has been attributed to enhanced noise in the neural control system with advancing age (Kail, 1997). Increased noise with age can be the consequence of several factors, among them, a degeneration of motor units that involves the progressive death of α-motorneurons and the subsequent reinnervation of some of the denervated muscle fibers by surviving motor units, impairing the ability to finely grade muscle force (Galganski et al. 1993). Some of the age-related differences may be accounted for by deficits in visual-motor integration in the elderly (Sosnoff and Newell 2006a). In addition, aging brains were found to decrease in size (Scahill et al. 2003), and have a different activation pattern than younger brains (Riecker et al. 2006). At least two brain regions that are implicated in control of movement, i.e., the basal ganglia (BG; Takakusaki et al. 2004; Kaji et al. 2005) and the sensorimotor cortex (SMC) are affected by aging. Specifically, the BG were shown to reduce in size with age (Langenecker et al. 2007), and the SMC was found to be overactivated in the elderly, when performing a finger-tapping task (Riecker et al. 2006). Pacemaking cells were found in the BG (Plenz and Kital 1999, Surmeier et al. 2005), which could potentially drive rhythmic muscle activity (Harris-Warrick 2002; Goulding and Pfaff 2005). In addition, activation of specific components of the BG was correlated with particular aspects of movement control, such as the frequency of finger tapping (Lehéricy et al. 2006), and failure of PD patients to reproduce rhythms successfully was associated with a role of the BG in the internal cueing

of repetitive voluntary movements (Freeman et al. 1993). Similarly, activation of the SMC has been shown to correlate with movement frequency (Lehéricy et al. 2006). Progressive damage to these brain areas implicated in control of rhythmic movement may result in altered rhythmic behavior with age.

We tested the hypothesis that movement frequency when performing a rhythmic task would be affected by age, as manifested by a shift, an expansion or a narrowing-down of the range of "preferred frequencies".

The data from twenty-three subjects – thirteen old adults (71.3±5.9 years, range: 60-81 years; 7 females, 6 males) and ten young adults (28.5±4.7 years, range: 22-39 years, 3 females, 7 males) who did not suffer from tremor or any other neurological disorder – were analyzed in this section.

Results

When examining the average frequency at each of the three blocks (slow, medium and fast), we found no significant differences between the old and the young groups, in either the vision or the non-vision conditions (see Figure 6-Figure 7). A Lilliefors test for normality of the data did not warrant the use of statistical tests that assume normality of the data. Therefore, a non-parametric test – the Wilcoxon rank sum test – was used to test for differences between the groups.

We found the overall tendency to move at frequencies that are lower than the middle-of-the-ellipse frequency in the fast block, and higher than the middle-of-the-ellipse frequency in the slow block, were maintained in the movements of older group, whether they were performed with or without vision (see Figure 8 through Figure 11).

When the ranges of average frequencies were tested – that is, the frequency in the slow condition subtracted from the frequency in the fast condition – we found no significant difference between the groups in the vision trials ($p = 0.6$), but the differences reached significance when subjects performed the task in the absence of vision: the older subjects tended to move in a more limited range of frequencies ($p = 0.032$; see Figure 12).

If the blind trials are a better indication of the "preferred frequencies", we find a clear trend for the older subjects to move within a narrower range of frequencies than the young subjects. That trend, visible in the vision trials, is intensified in the blind trials and reaches significance. Lower-frequency movements are performed at a faster pace, and higher-frequency movements are performed at a slower pace, compared with the young subjects. This pattern is reminiscent of similar behaviors – termed hastening and faltering, respectively – which have been observed when PD patients were asked to regenerate a rhythmic pattern

(Freeman et al. 1993), and raises the question of whether PD is similar to an accelerated aging process (Hawkes 2008).

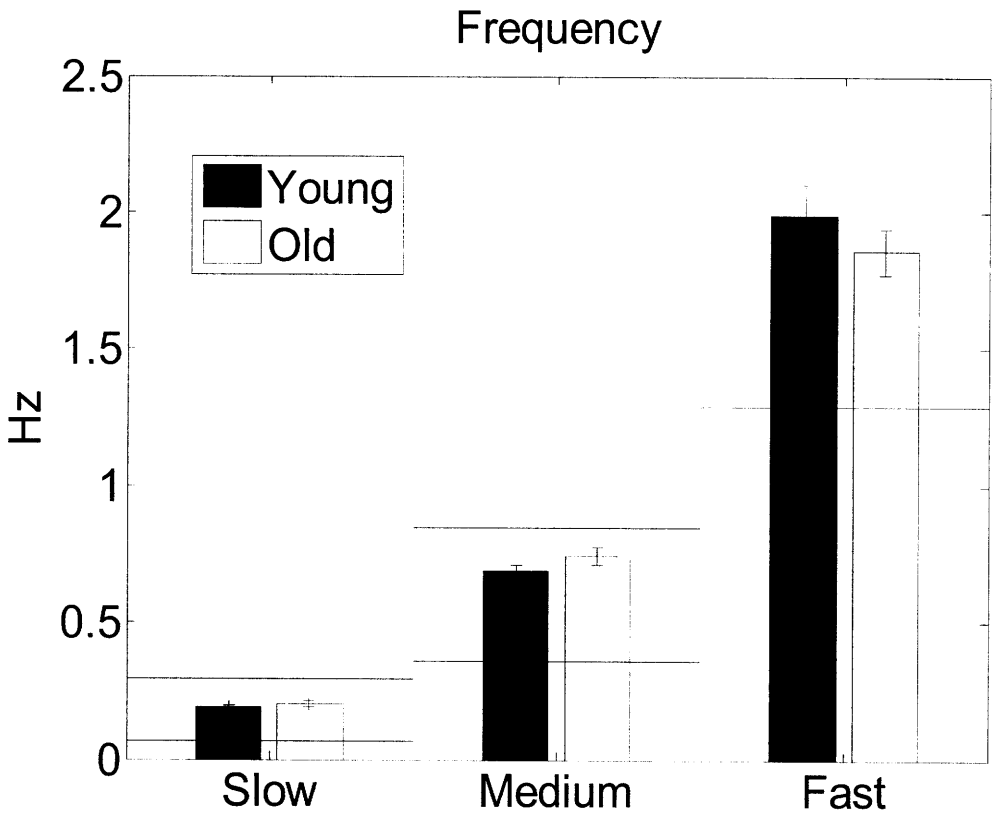

Figure 6. Average movement frequencies on the vision trials. Horizontal bars denote range of allowed frequencies (upper bound not shown for the fast block). Error bars denote standard error.

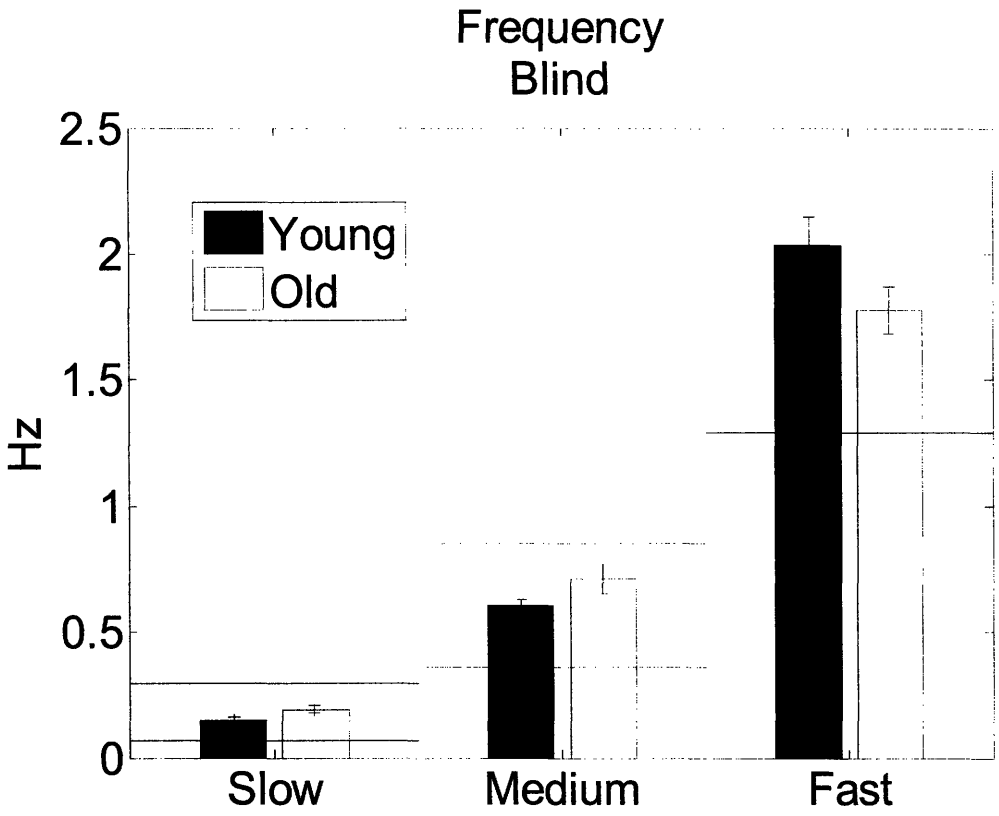

Figure 7. Average movement frequencies on the blind trials. Horizontal bars denote range of allowed frequencies (upper bound not shown for the fast block). Error bars represent standard error.

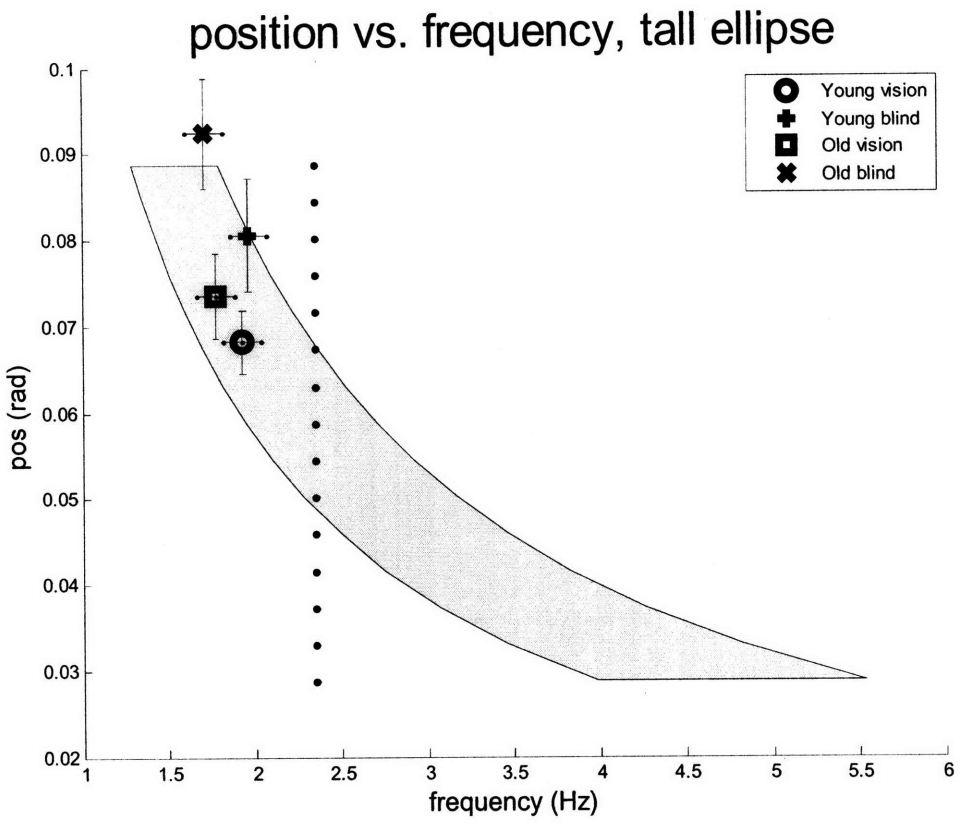

Figure 8. Amplitude vs. frequency. The closed shape defines the allowable ranges of amplitudes and frequencies for the fast task. The circle and the square (vision trials) and the plus sign and the X (blind trials) indicate the average amplitudes and frequencies chosen by the subjects of the young and the old groups, respectively. The vertical dotted line corresponds to a sinusoid in the center of the doughnut shape. Error bars represent standard errors.

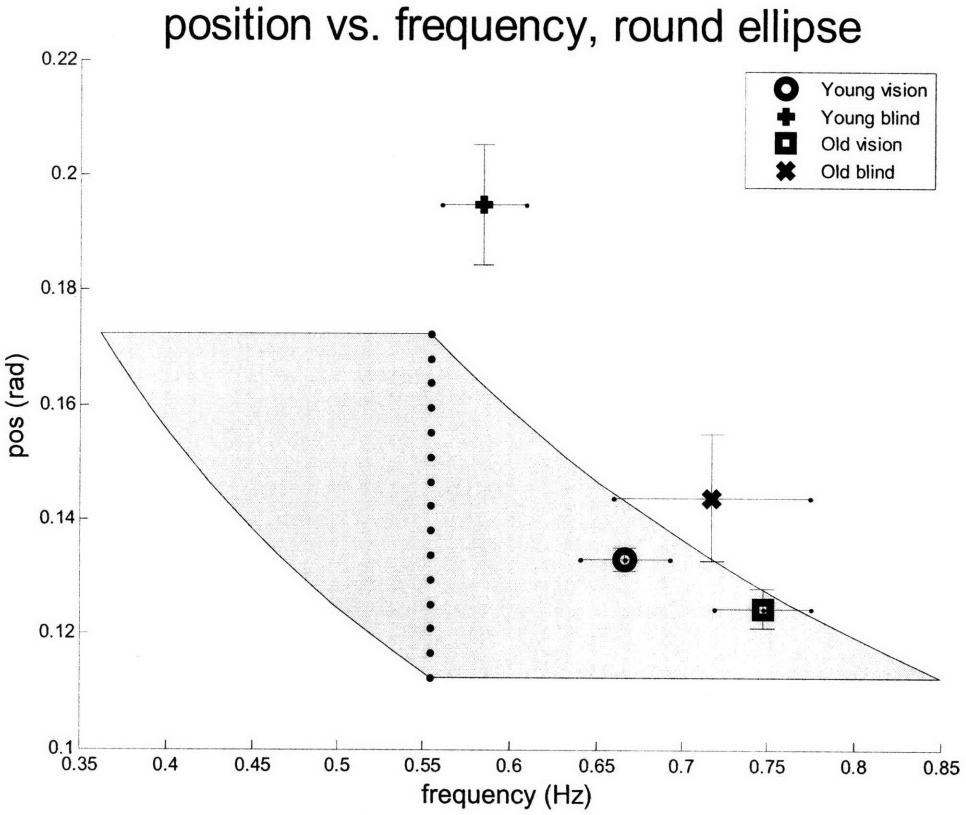

Figure 9. Amplitude vs. frequency. The closed shape defines the allowable ranges of amplitudes and frequencies for the intermediate task. The circle and the square (vision trials) and the plus sign and the X (blind trials) indicate the average amplitudes and frequencies chosen by the subjects of the young and the old groups, respectively. The vertical dotted line corresponds to a sinusoid in the center of the doughnut shape. Error bars represent standard errors.

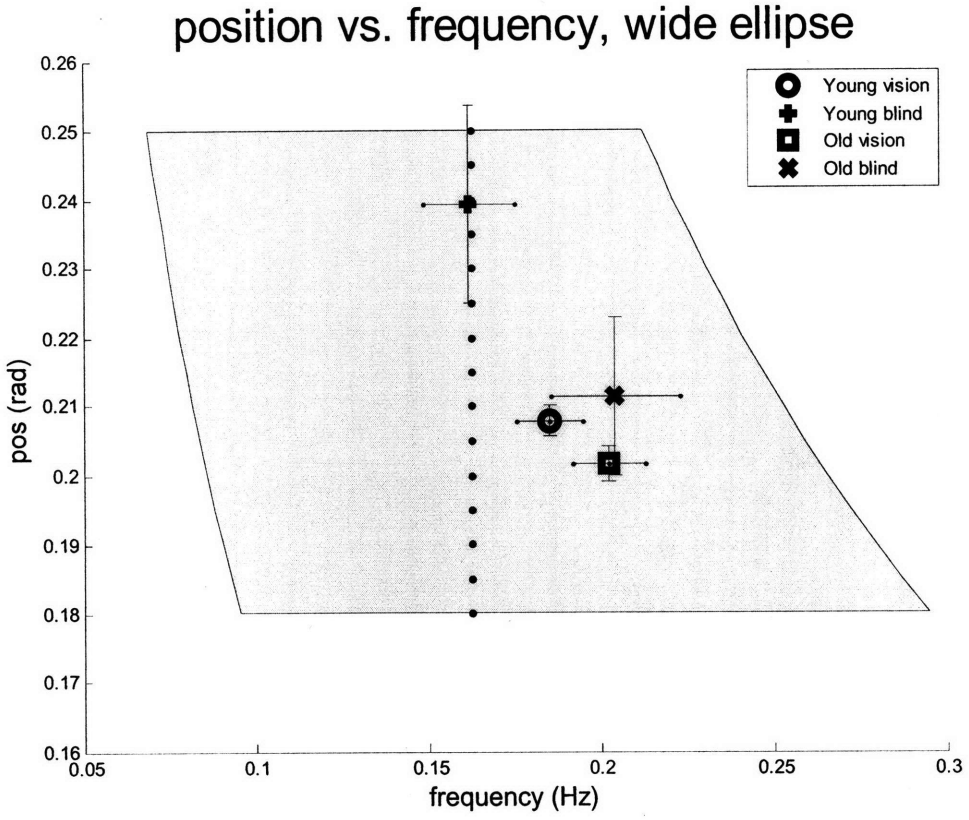

Figure 10. Amplitude vs. frequency. The closed shape defines the allowable ranges of amplitudes and frequencies for the slow task. The circle and the square (vision trials) and the plus sign and the X (blind trials) indicate the average amplitudes and frequencies chosen by the subjects of the young and the old groups, respectively. The vertical dotted line corresponds to a sinusoid in the center of the doughnut shape. Error bars represent standard errors.

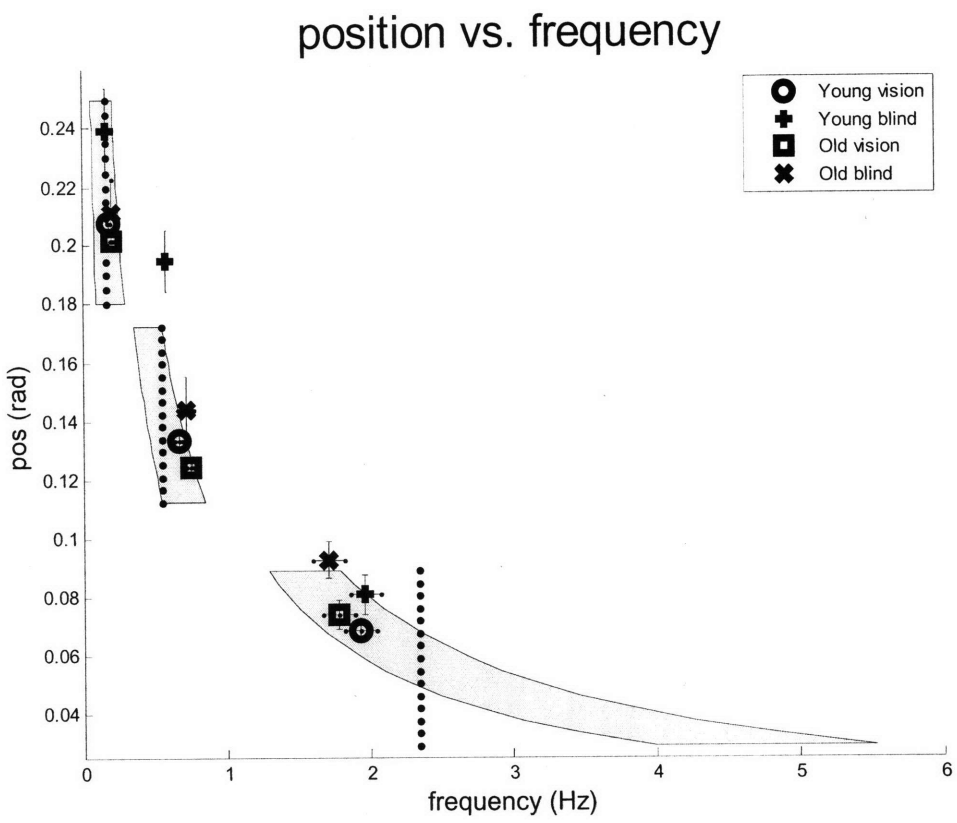

Figure 11. Amplitude vs. frequency. The closed shapes define the allowable ranges of amplitudes and frequencies for all three blocks. The circles and the squares (vision trials) and the plus signs and the Xs (blind trials) indicate the average amplitudes and frequencies chosen by the subjects of the young and the old groups, respectively. The vertical dotted lines correspond to the sinusoids in the center of the doughnut shapes. Error bars represent standard errors.

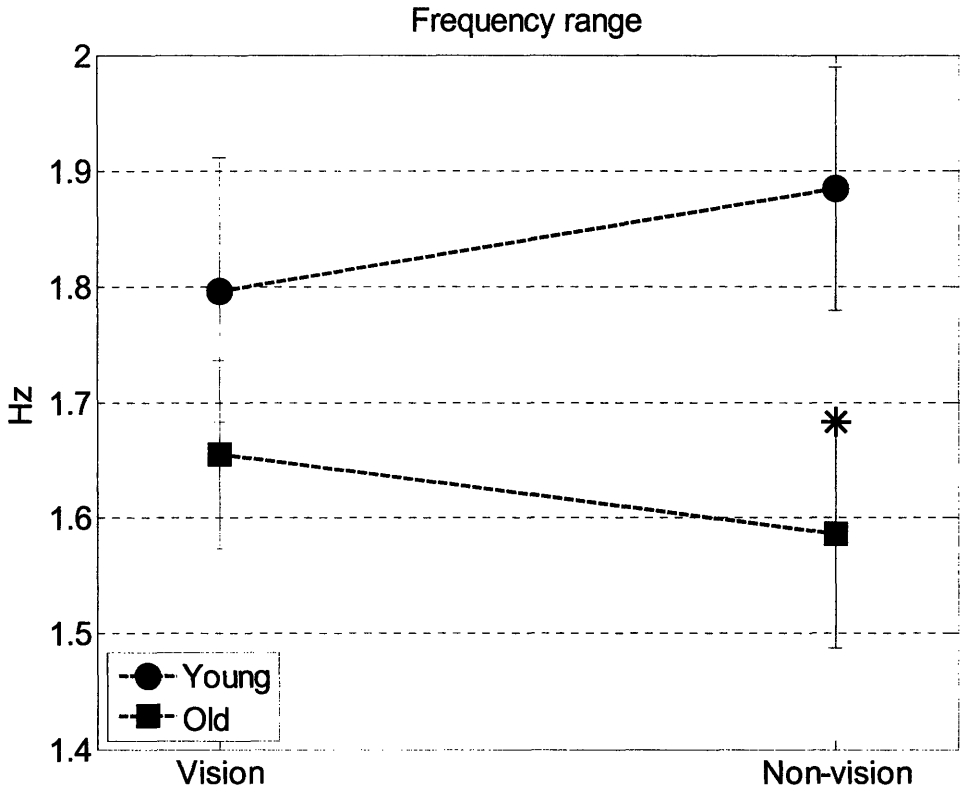

Figure 12. Average frequency ranges in the vision (left) and the non-vision (right) trials of the young (circles) and old (squares) groups. An asterisk represents a significant difference between the groups ($p<0.05$). Error bars represent standard error.

The effects of dopaminergic medication and deep-brain stimulation on movement frequency

As outlined in the previous section, the basal ganglia have been implicated in control of rhythmic movements. Further support for this role of the BG comes from studies with PD patients, who suffer severe damage to the BG (for a

detailed account, please see the Background section of the Introduction – Chapter 1). Patients with PD were found to have significantly larger fluctuations in gait timing than age-matched controls (Bartsch et al. 2007), to have abnormalities in time processing (Koch et al. 2008), and to exhibit hastening and faltering, or abnormalities in internal rhythm generation both in the presence and absence of external timing signals (Freeman et al. 1993; Nakamura et al. 1978; Nagasaki et al. 1978).

With deep-brain stimulation suggested to override the aberrant firing pattern of the subthalamic nucleus in PD (Meissner et al. 2005), and its – as well as dopaminergic medication's – positive impact on gait (Lubik et al. 2006) – a rhythmic activity – we anticipated they would have a significant effect on the frequency at which subjects perform the task.

We tested the hypothesis that movement frequency when performing a rhythmic task would be affected by the PD treatments, both of which target the BG in their therapeutic activity, and shown to affect rhythmic activity, as manifested by a shift, an expansion or a narrowing-down of the range of "preferred frequencies".

Data from a total of seventeen subjects was analyzed in this section. Movements recorded from ten PD patients (age: 72.1±9.9 years, mean±SD; 8 males and 2 females) – tested on and off (after an overnight withdrawal) their dopaminergic medication (the "Meds" group) – and seven PD patients (age: 72.9±6.5 years; 6 males and 1 female) – tested on and off (for at least 1.5 hours) deep-brain

stimulation of the subthalamic nucleus (the "DBS" group), were examined. Subjects in the DBS group continued to follow their normal medication regimen throughout the experiment. All but two subjects (dbs3 and dbs6) had bilaterally implanted stimulators. All but dbs3 were tested using their dominant hand (dbs3's implant was ipsilateral to his dominant hand). The scores of the patients – both on and off treatment – on the Unified Parkinson's Disease Rating Scale (UPDRS) are shown in Figure 13.

From Figure 14 through Figure 17, it is evident that the overall tendency to perform tasks within a more limited range than that prescribed by the task is maintained for all experimental groups: young healthy, old healthy, PD patients on/off medication and PD patients on/off stimulation.

In performing the task at the three specified frequency-amplitude combinations, patients in the Meds group were not found to perform the task at movement frequencies, or at a frequency range different than that of the healthy either in the vision or in the blind conditions (see Figure 18 through Figure 21).
In contrast, the patients in the DBS group, whether on or off stimulation, performed lower-frequency movements than the healthy subjects in the fast vision condition. This difference reached significance in the "stimulation on" condition ($p = 0.0055$; The difference between the "stimulation off" group and the healthy did not quite reach significance when accounting for the Bonferroni

correction: p = 0.04; This is probably due to the increased inter-subject variability in this condition).

As a result, this group performed the task at an overall shorter range of frequencies in the vision condition than the healthy age-matched control subjects.

There was no significant difference in the fast blind frequency, or in the range of performed frequencies, between the DBS group and the healthy group in the blind trials (see Figure 19 and Figure 21).

A non-parametric paired statistical test (the Sign Test) within each treatment group – Meds or DBS – did not reveal any differences in the *range* between either treatment's on/off conditions.

So far, we established that, as was observed in the healthy population, the overall tendency to move at frequencies that are lower than the middle-of-the-ellipse frequency in the fast block, and higher than the middle-of-the-ellipse frequency in the slow block was maintained in the PD population as a group, whether 'on' or 'off' either treatment, and whether with or without the presence of visual feedback. We then evaluated the change in the range of frequencies at which the task is performed, by group, compared to the healthy controls. Finally, in the section that follows, we examine the specific effects of the treatments on individual subjects.

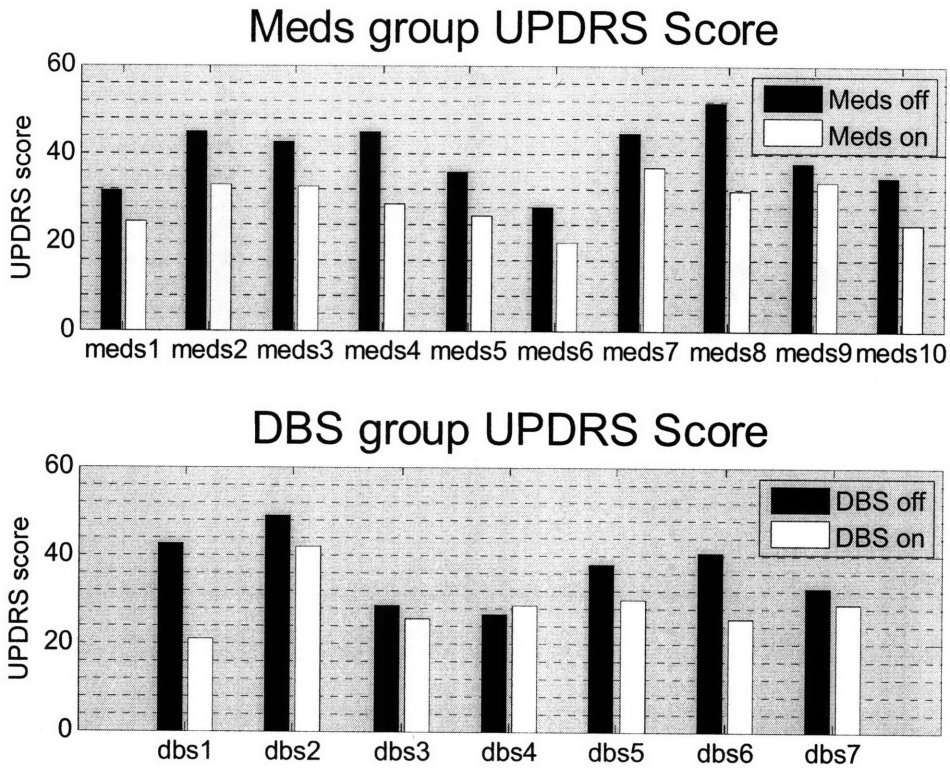

Figure 13. Clinical scores for the PD patients who participated in this experiment. The top panel shows the scores for PD patients that were tested on (white bars) and off (black bars) medication (the Meds group). The bottom panel shows the scores for PD patients that were tested with stimulation turned on (white bars) or off (black bars; the DBS group).

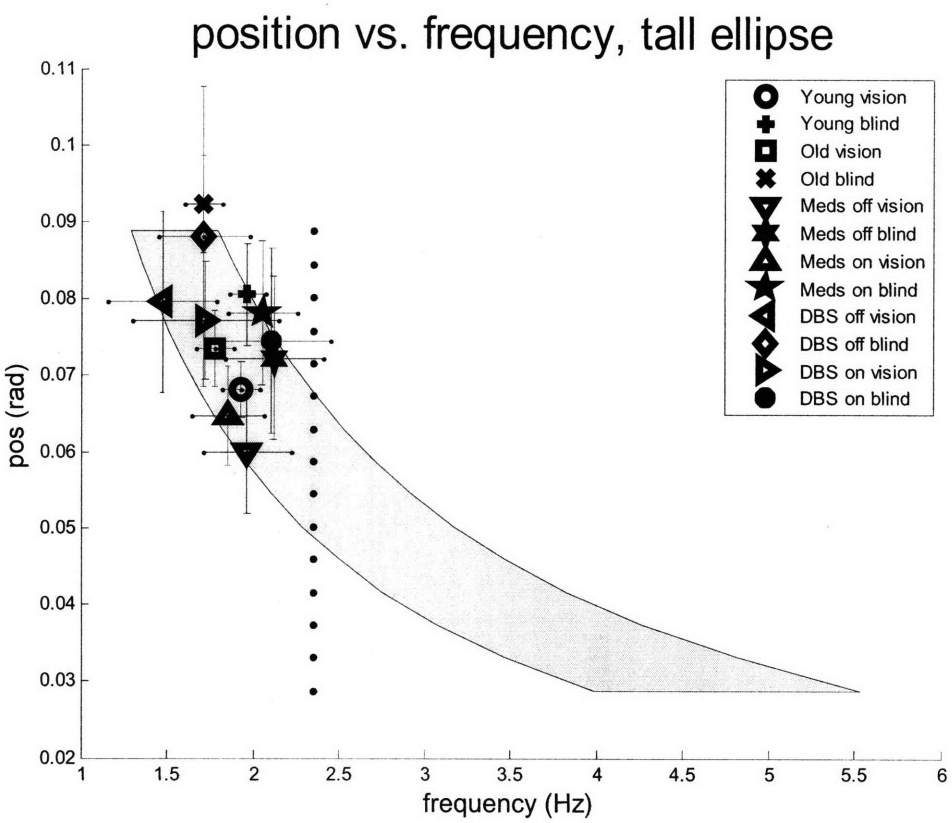

Figure 14. Amplitude vs. frequency. The closed shape defines the allowable ranges of amplitudes and frequencies for the fast task. The vertical dotted line corresponds to a sinusoid in the center of the doughnut shape. Error bars represent standard errors.

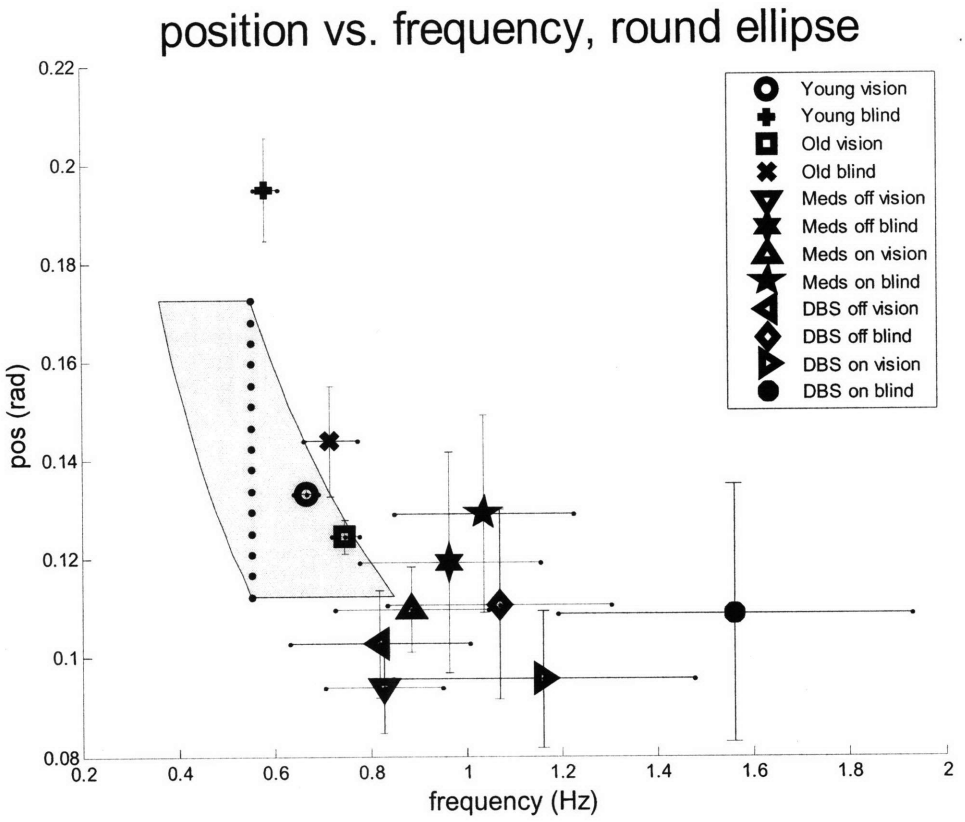

Figure 15. Amplitude vs. frequency. The closed shape defines the allowable ranges of amplitudes and frequencies for the intermediate task. The vertical dotted line corresponds to a sinusoid in the center of the doughnut shape. Error bars represent standard errors.

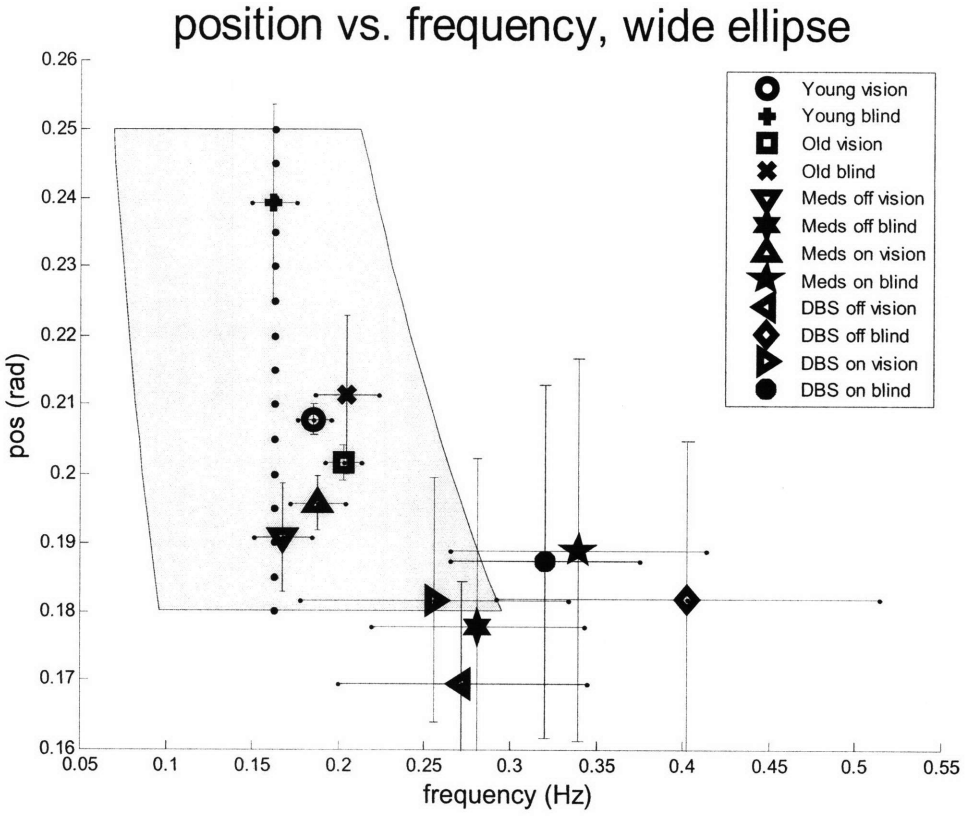

Figure 16. Amplitude vs. frequency. The closed shape defines the allowable ranges of amplitudes and frequencies for the slow task. The vertical dotted line corresponds to a sinusoid in the center of the doughnut shape. Error bars represent standard errors.

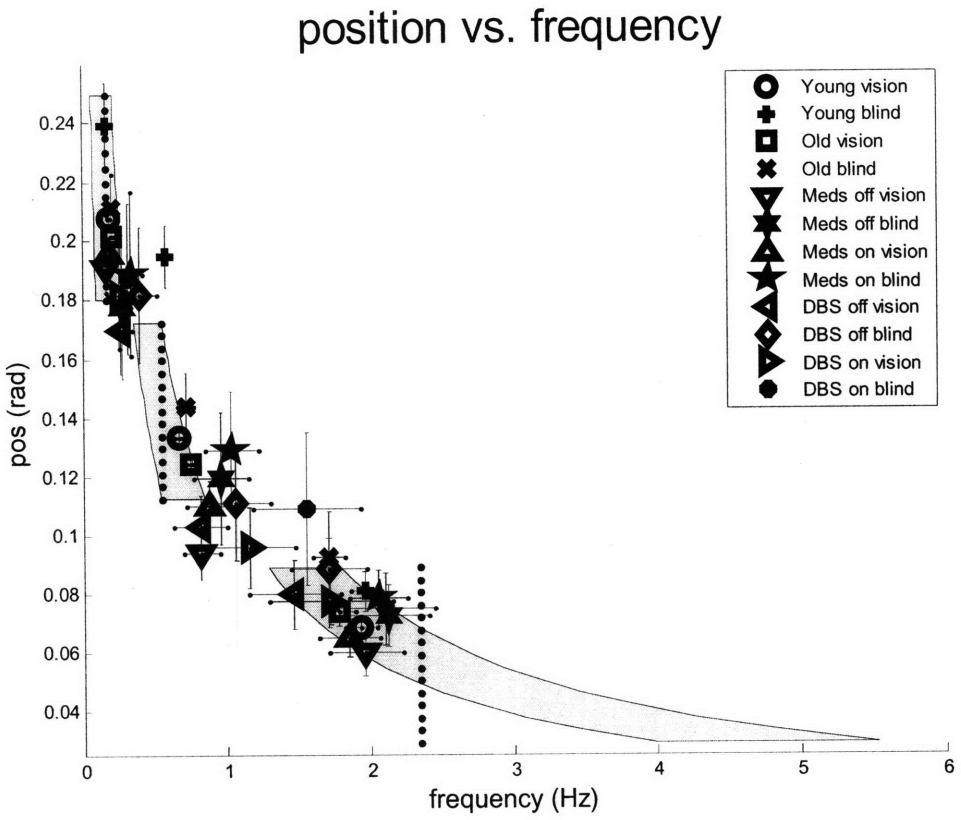

Figure 17. Amplitude vs. frequency. The closed shapes define the allowable ranges of amplitudes and frequencies for all three blocks. The vertical dotted line corresponds to a sinusoid in the center of the doughnut shape. Error bars represent standard errors.

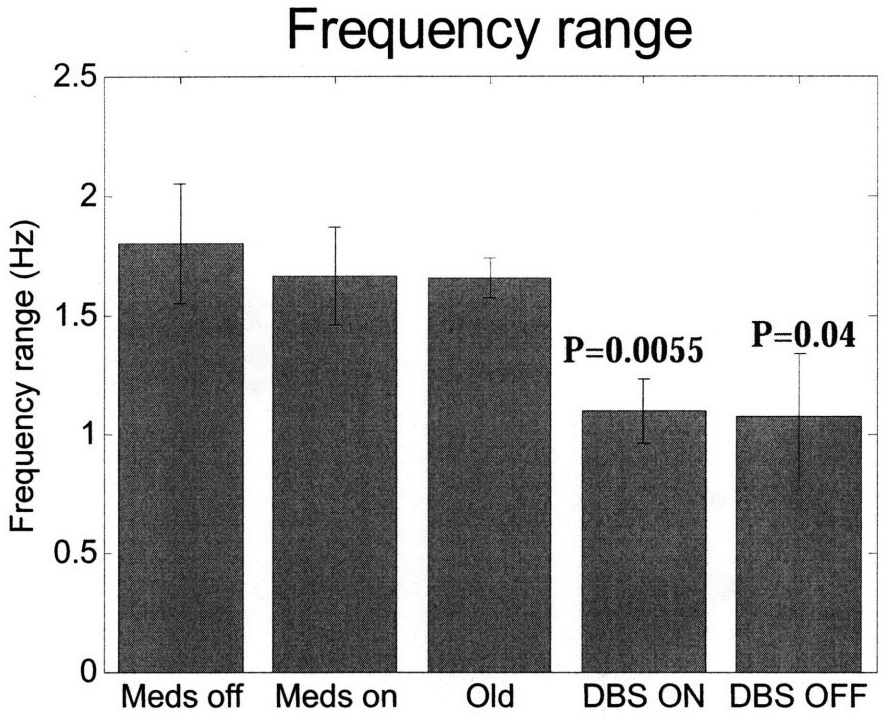

Figure 18. Average frequency ranges in the vision trials of the four PD groups and the healthy control group. The differences reach significance in the "stimulation on" condition. P-values denote differences from the healthy control subjects. Error bars represent standard error.

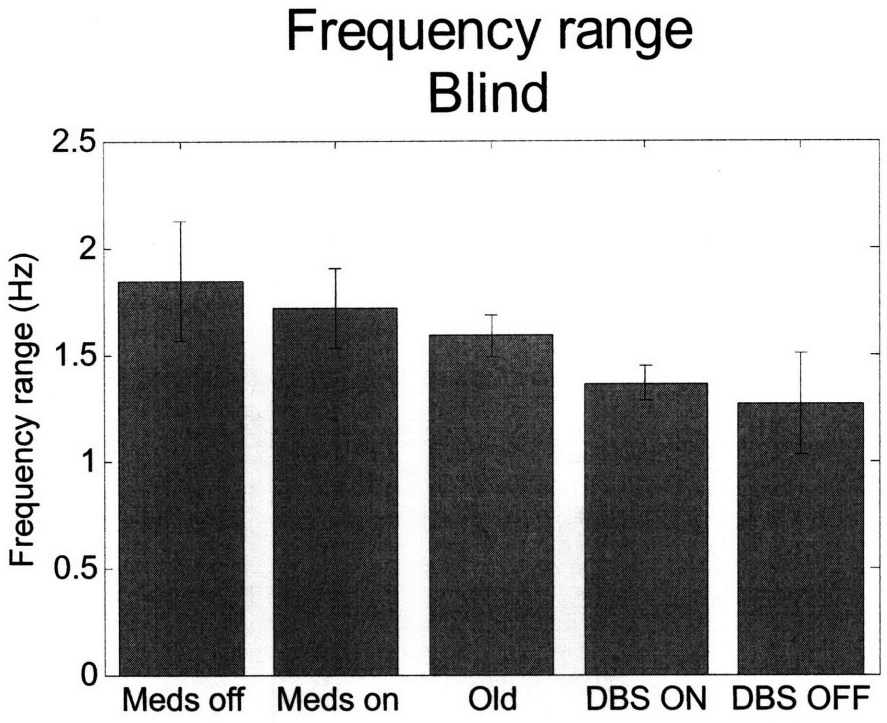

Figure 19. Average frequency ranges in the blind trials of the four PD groups and the healthy control group. Error bars represent standard error.

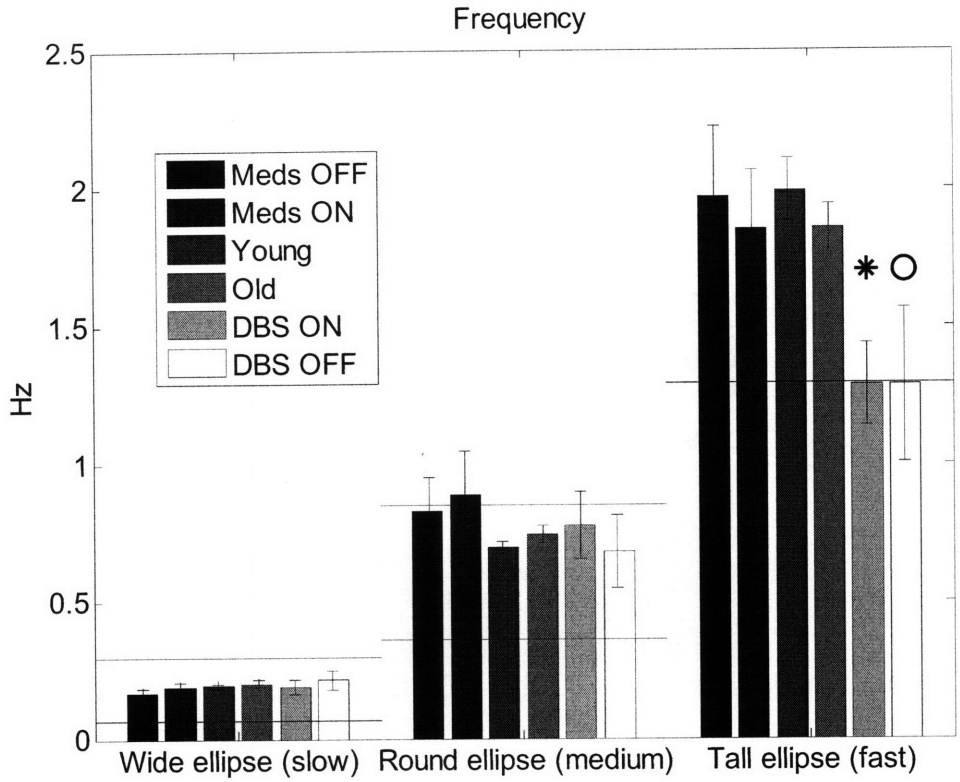

Figure 20. Average frequency per group, per block, on vision trials. Horizontal bars denote range of allowed frequencies (upper bound not shown for the fast block). An asterisk denotes a significant difference between the DBS ON group and the healthy control group. An empty circle denotes a nearly significant difference between the DBS OFF group and the healthy control group. Error bars represent standard error.

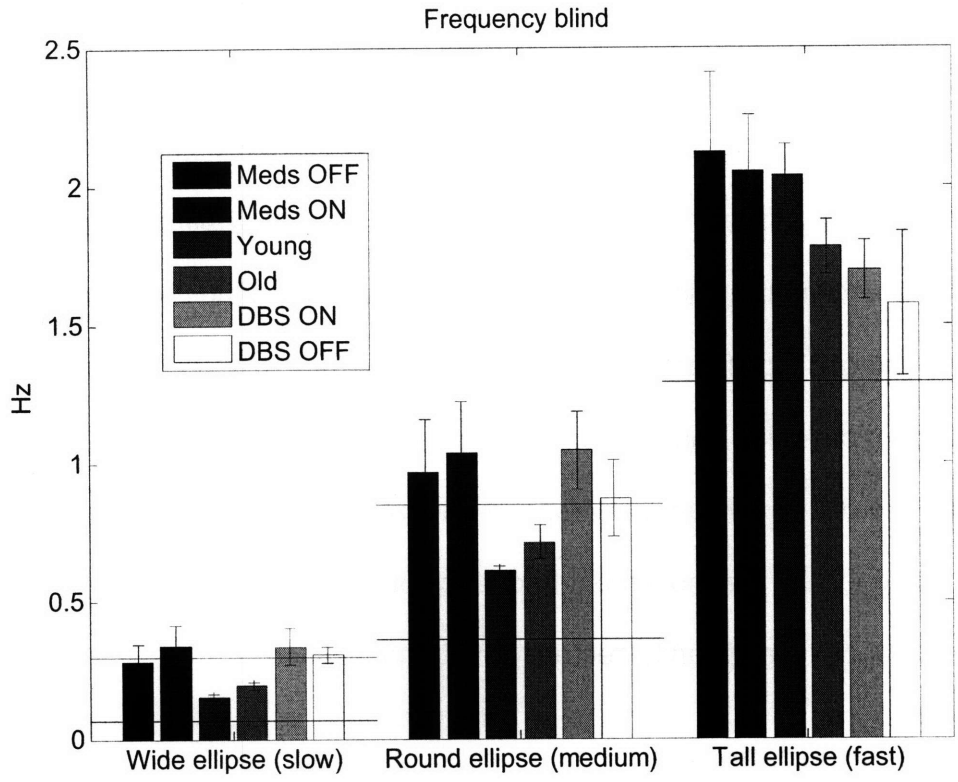

Figure 21. Average frequency per group, per block, on blind trials. Horizontal bars denote range of allowed frequencies (upper bound not shown for the fast block). Error bars represent standard error.

Dopaminergic medication

For each of the 10 PD patients in the Meds group, at each of the three experimental blocks, we used a non-parametric paired test – the Sign Test – to study the effects of dopaminergic medication (see Figure 22). In Figure 23 are

plotted the frequencies at which the patients performed the task in relation to the allowed frequency ranges (shaded areas).

Of the 30 subject/block combinations, 10 experienced a significant increase, and 7 experienced a significant decrease in movement frequency with medication.

Of the 10 patients in the fast condition, the movement frequency of 3 significantly increased and of 3 significantly decreased with medication.

In the medium condition, the movement frequency of 3 patients significantly increased and of 2 significantly decreased with medication.

In the slow condition, the movement frequency of 4 patients significantly increased and of 2 significantly decreased with medication.

Deep-brain stimulation

For each of the 7 PD patients in the DBS group, at each of the three experimental blocks, we used the Sign Test to study the effects of deep-brain stimulation (see Figure 24). In Figure 25 are plotted the frequencies at which the patients performed the task in relation to the allowed frequency ranges.

Of the 21 subject/block combinations, 10 experienced a significant increase, and 7 experienced a significant decrease in movement frequency with stimulation.

Of the 7 patients in the fast condition, the movement frequency of 4 significantly increased and of 1 significantly decreased with stimulation.

In the medium condition, the movement frequency of 4 patients significantly increased and of 3 significantly decreased with stimulation.

In the slow condition, the movement frequency of 2 patients significantly increased and of 3 significantly decreased with stimulation.

Discussion

We found that, as a group, the PD patients that were tested on/off medication did not perform the task at frequencies, or at a frequency range, that were significantly different from the healthy old population. In contrast, the PD patients that were tested on/off stimulation performed the fast block at lower frequencies than the healthy old (significant for the 'on stimulation' condition; $p = 0.007$); consequently, the range of frequencies at which they performed all three experimental blocks was shorter than that of the healthy old subjects (significant for the 'on stimulation' condition; $p = 0.006$).

What may account for this pattern in the DBS, but not in the Meds group?

One possibility is the advanced stage of the disease. While the UPDRS clinical scores for the Meds and for the DBS groups were comparable (29.1 ± 5.3 and 39.6 ± 7.3 for on/off medication and 28.8 ± 6.6 and 36.8 ± 8.1 on/off stimulation, mean ± SD; see Figure 13), it should be noted that the DBS group was *on medication* throughout the experiment, and hence when their disease symptoms were evaluated. These patients, as a group, were therefore, in effect, more affected by the disease than the patients in the Meds group. Additionally, surgery is usually a treatment employed at later stages of the disease, often once the

effects of the medication are diminished, and/or side effects from the medication become debilitating (Pahwa 2006).

An alternative interpretation would be that DBS may hinder generation of high-frequency voluntary movements and that this effect may last at least for a couple of hours after turning stimulation off. This may be the result of an alteration of the neural networks the basal ganglia take part in (Vaillancourt et al. 2004), or of the microlesion formed during surgery (Russmann et al. 2004).

Yet another possible explanation is that the result reflects the effect of low-doses of dopaminergic medication either it itself or in combination with the long-term effects of stimulation (Vaillancourt et al. 2004), though such an effect has not been clearly documented in the literature, and, in fact, there have been arguments made for a lower toxicity level with low-dose levodopa (Fahn 1996). As mentioned earlier, PD patients with implanted stimulators were in their "on medication" state throughout the testing, whether they were on- or off-stimulation, and post-surgery doses are often lower than pre-surgery doses (Zibetti et al. 2007).

When examining the individual changes in frequency with treatment, the results make clear that neither medication nor deep-brain stimulation impose a preferred movement frequency on all patients (see Figure 23 and Figure 25 – the 'on treatment' frequency is not in the same general vicinity across patients), nor do

they work to change the movement frequency such that subjects are moving within task requirements (see Figure 23 and Figure 25 – the 'on treatment' frequency does not always place patients within the task requirements, and, on occasion, causes them to move away from the required frequencies), nor do they uniformly increase or decrease movement frequency in all patients (see Figure 22 and Figure 24 – the 'on treatment' frequency is not always higher/lower than the 'off treatment' frequency), nor do they condense or expand the range of preferred frequencies uniformly in all patients (see Figure 22 and Figure 24 – while some subjects move across a wider range of frequencies, others move within a narrower one with treatment), nor is their effect uniform within a subject (while some subjects experience a significant and uniform increase (e.g., dbs1 and meds3) or decrease (e.g., dbs3 and meds5), for others, the changes are not uniform (e.g., dbs4 and meds1; see Figure 24 and Figure 22)).

Subjects in both treatment groups varied on many levels, including age, time since disease onset, time since surgery (in the DBS group), UPDRS clinical scores – and their change with treatment, and the specific manifestations of the disease symptoms. No correlation between these factors and the change in frequency was found. Parkinson's disease is, in fact, one of a collection of similar diseases, together termed parkinsonian syndromes. Precise diagnosis is challenging, and as recently as in the 1990s, accuracy of the clinical diagnosis of PD was estimated at only 76% (Tuite and Krawczewski 2007). A more careful choice of subjects, more uniform in regard to the parameters mentioned above

would likely reduce the inter-subject variability and facilitate a clearer distinction of the effects of the treatments.

Summary

As a group, PD patients, either on or off either medication or deep-brain stimulation, exhibit similar tendencies as the healthy subjects, in terms of a lower- and upper-bound frequency range that generally falls between the "middle track" of the wide (slow) ellipse and that of the tall (fast) ellipse.

The DBS group was found to have a shorter overall range, due to lower movement frequencies when performing the fast task. This trend reached significance when patients' stimulators were turned on.

We find that qualitatively, there is no trend that distinguishes the effects of medication from those of stimulation on movement frequency in the context of a rhythmic elbow movement.

While both treatments were found to significantly affect the movement frequencies of individual subjects within a given movement speed, it was not possible to tease out an overall consistent trend for their effect. That is to say, they were not found to impose a uniform preferred frequency, or preferred frequency range, to increase or decrease the movement frequencies of the patients as a group or per individual, nor to uniformly expand or narrow down –

as was observed as a tendency with age (see previous section) – the range of preferred frequencies. This may well be due to the well-documented heterogeneity in the causes for, the effects of, and the progression of the disease in the various patients (Poewe 2006).

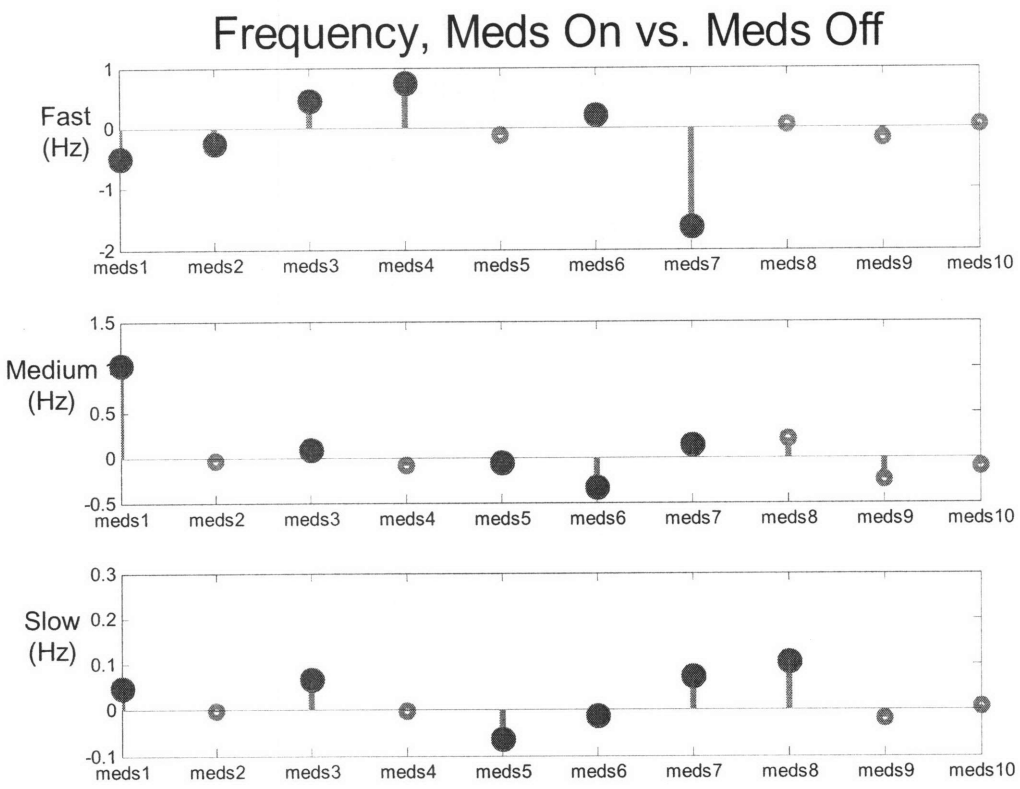

Figure 22. Differences between average frequency values in the on- and off medication states. Large filled circles indicate a significant difference exists between the two. The vertical location of the large filled circles denotes the absolute value of the difference. The actual value of the difference is shown by empty small circles.

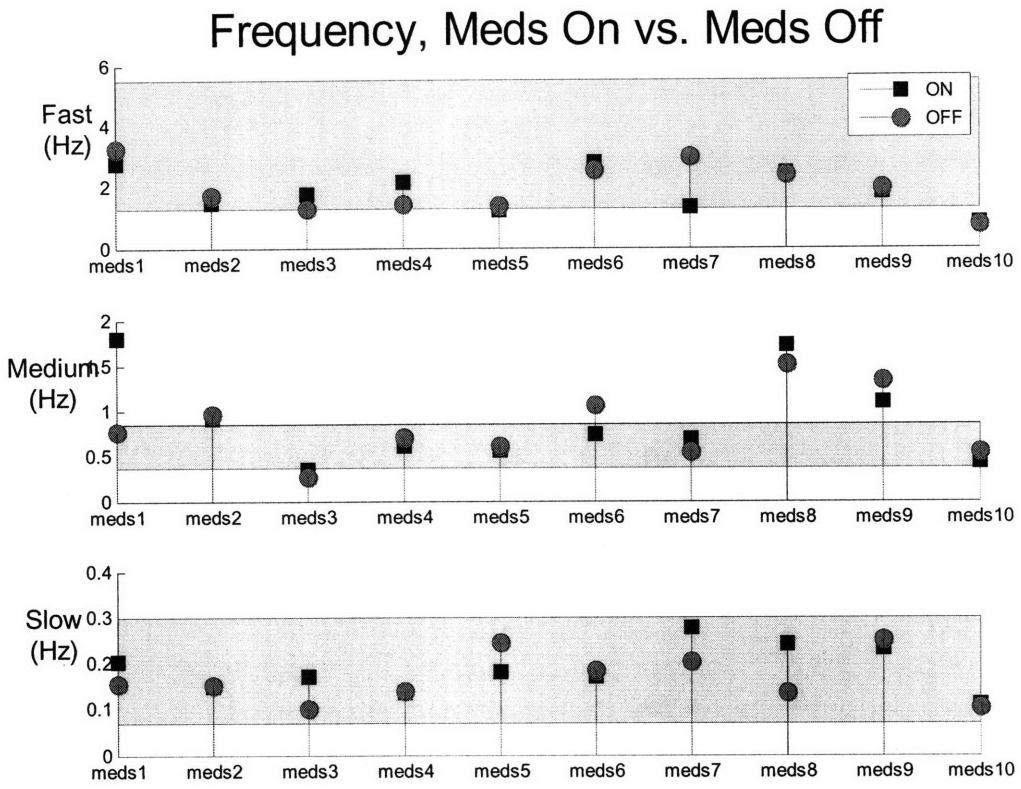

Figure 23. Frequency values for patients on (squares) and off (circles) medication. Shaded areas mark the ranges of frequencies allowed by the task.

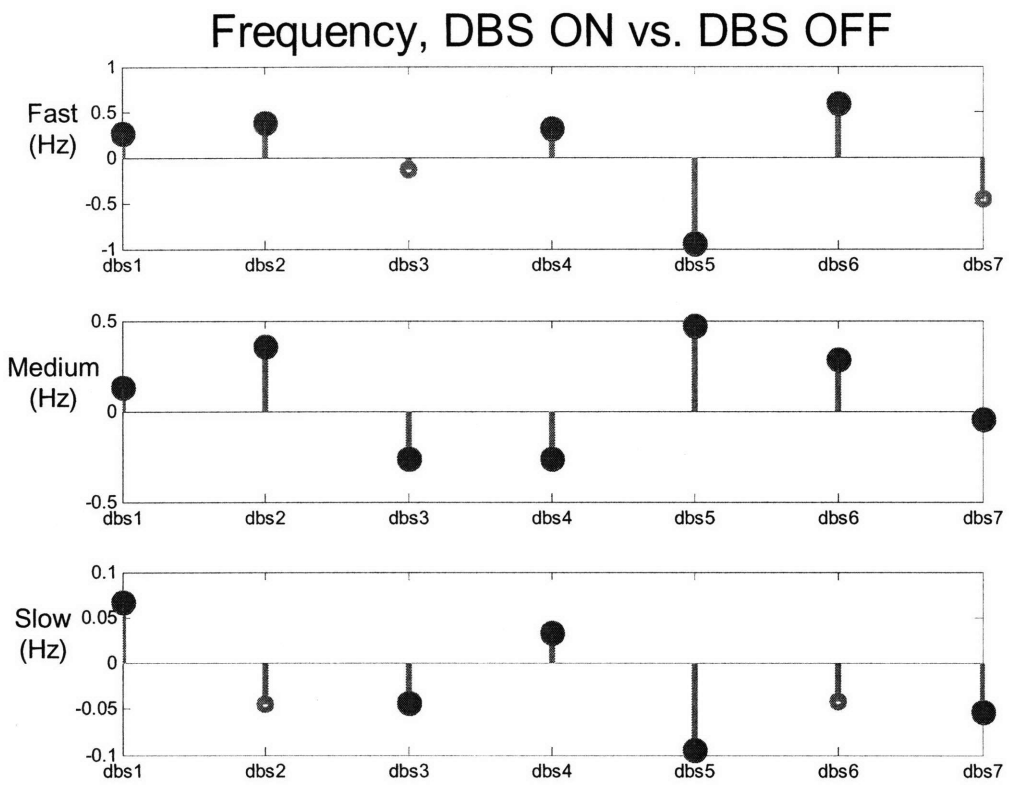

Figure 24. Differences between average frequency values in the on- and off stimulation states. Large filled circles indicate a significant difference exists between the two. The vertical location of the large filled circles denotes the absolute value of the difference. The actual value of the difference is shown by empty small circles.

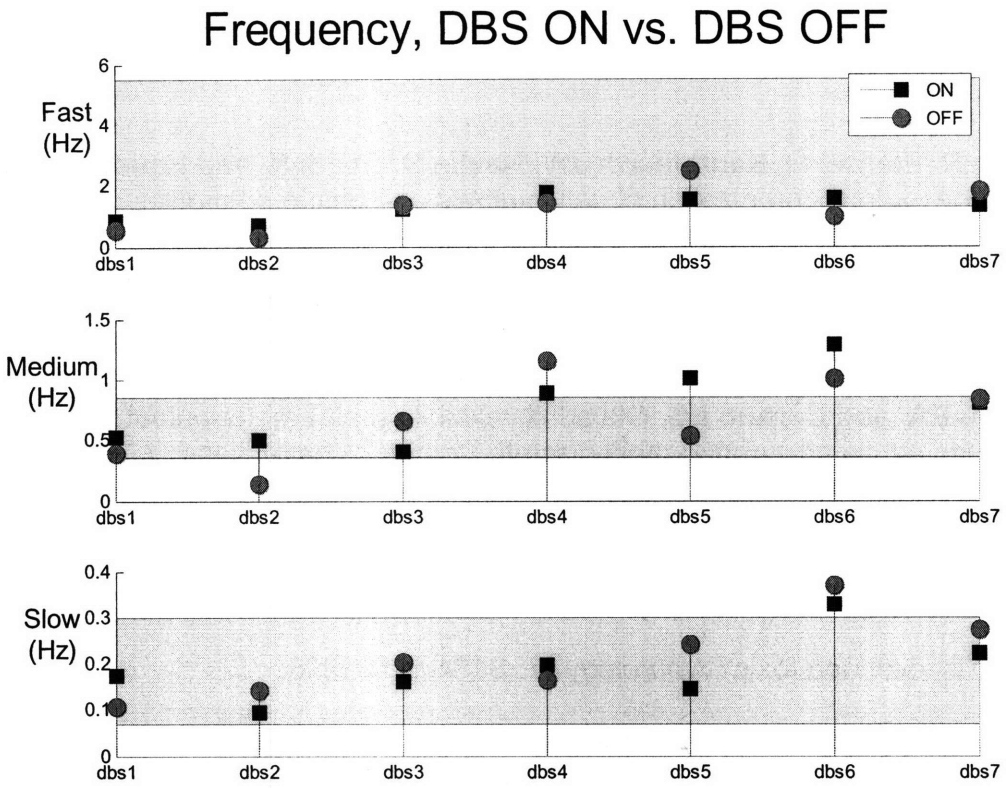

Figure 25. Frequency values for patients on (squares) and off (circles) stimulation. Shaded areas mark the ranges of frequencies allowed by the task.

REFERENCES

Bartsch R, Plotnik M, Kantelhardt JW, Havlin S, Giladi N, and Hausdorff JM. Fluctuation and synchronization of gait intervals and gait force profiles distinguish stages of Parkinson's disease. *Physica A* 383: 455-465, 2007.

Christou EA, and Carlton LG. Age and contraction type influence motor output variability in rapid discrete tasks. *J Appl Physiol* 93: 489-498, 2002.

Christou EA, and Carlton LG. Old adults exhibit greater motor output variability than young adults only during rapid discrete isometric contractions. *J Gerontol A Biol Sci Med Sci* 56: B524-532, 2001.

Doeringer JA, and Hogan N. Serial processing in human movement production. *Neural Netw* 11: 1345-1356, 1998.

Fahn S. Is levodopa toxic? *Neurology* 47: S184-195, 1996.

Freeman JS, Cody FW, and Schady W. The influence of external timing cues upon the rhythm of voluntary movements in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 56: 1078-1084, 1993.

Galganski ME, Fuglevand AJ, and Enoka RM. Reduced control of motor output in a human hand muscle of elderly subjects during submaximal contractions. *J Neurophysiol* 69: 2108-2115, 1993.

Goulding M, and Pfaff SL. Development of circuits that generate simple rhythmic behaviors in vertebrates. *Curr Opin Neurobiol* 15: 14-20, 2005.

Harris-Warrick RM. Voltage-sensitive ion channels in rhythmic motor systems. *Curr Opin Neurobiol* 12: 646-651, 2002.

Hatsopoulos NG, and Warren Jr WH. Resonance Tuning in Rhythmic Arm Movements. *J Mot Behav* 28: 3-14, 1996.

Hawkes CH. Parkinson's disease and aging: Same or different process? *Mov Disord* 23: 47-53, 2008.

Kail R. The neural noise hypothesis: Evidence from processing speed in adults with multiple sclerosis. *Aging, Neuropsychology, and Cognition* 4: 157-165, 1997.

Kaji R, Urushihara R, Murase N, Shimazu H, and Goto S. Abnormal sensory gating in basal ganglia disorders. *J Neurol* 252 Suppl 4: IV13-IV16, 2005.

Koch G, Costa A, Brusa L, Peppe A, Gatto I, Torriero S, Gerfo EL, Salerno S, Oliveri M, Carlesimo GA, and Caltagirone C. Impaired reproduction of second but not millisecond time intervals in Parkinson's disease. *Neuropsychologia* 2008.

Langenecker SA, Briceno EM, Hamid NM, and Nielson KA. An evaluation of distinct volumetric and functional MRI contributions toward understanding age and task performance: a study in the basal ganglia. *Brain Res* 1135: 58-68, 2007.

Lehericy S, Bardinet E, Tremblay L, Van de Moortele PF, Pochon JB, Dormont D, Kim DS, Yelnik J, and Ugurbil K. Motor control in basal ganglia circuits using fMRI and brain atlas approaches. *Cereb Cortex* 16: 149-161, 2006.

Lubik S, Fogel W, Tronnier V, Krause M, Konig J, and Jost WH. Gait analysis in patients with advanced Parkinson disease: different or additive effects on gait induced by levodopa and chronic STN stimulation. *J Neural Transm* 113: 163-173, 2006.

Meissner W, Leblois A, Hansel D, Bioulac B, Gross CE, Benazzouz A, and Boraud T. Subthalamic high frequency stimulation resets subthalamic firing and reduces abnormal oscillations. *Brain* 128: 2372-2382, 2005.

Nagasaki H, Nakamura R, and Taniguchi R. Disturbances of rhythm formation in patients with Parkinson's disease: part II. a forced oscillation model. *Percept Mot Skills* 46: 79-87, 1978.

Nakamura R, Nagasaki H, and Narabayashi H. Disturbances of rhythm formation in patients with Parkinson's disease: part I. Characteristics of tapping response to the periodic signals. *Percept Mot Skills* 46: 63-75, 1978.

Pahwa R. Understanding Parkinson's disease: an update on current diagnostic and treatment strategies. *J Am Med Dir Assoc* 7: 4-10, 2006.

Plenz D, and Kital ST. A basal ganglia pacemaker formed by the subthalamic nucleus and external globus pallidus. *Nature* 400: 677-682, 1999.

Poewe W. The natural history of Parkinson's disease. *J Neurol* 253 Suppl 7: VII2-6, 2006.

Raftery A, Cusumano J, and Sternad D. Chaotic frequency scaling in a coupled oscillator model for free rhythmic actions. *Neural Comput* 20: 205-226, 2008.

Riecker A, Groschel K, Ackermann H, Steinbrink C, Witte O, and Kastrup A. Functional significance of age-related differences in motor activation patterns. *Neuroimage* 32: 1345-1354, 2006.

Russmann H, Ghika J, Villemure JG, Robert B, Bogousslavsky J, Burkhard PR, and Vingerhoets FJG. Subthalamic nucleus deep brain stimulation in Parkinson disease patients over age 70 years. AAN Enterprises, 2004, p. 1952-1954.

Scahill RI, Frost C, Jenkins R, Whitwell JL, Rossor MN, and Fox NC. A longitudinal study of brain volume changes in normal aging using serial registered magnetic resonance imaging. *Arch Neurol* 60: 989-994, 2003.

Smith CD, Umberger GH, Manning EL, Slevin JT, Wekstein DR, Schmitt FA, Markesbery WR, Zhang Z, Gerhardt GA, Kryscio RJ, and Gash DM. Critical decline in fine motor hand movements in human aging. *Neurology* 53: 1458-1461, 1999.

Sosnoff JJ, and Newell KM. Aging, visual intermittency, and variability in isometric force output. *J Gerontol B Psychol Sci Soc Sci* 61: P117-124, 2006a.

Sosnoff JJ, and Newell KM. Are age-related increases in force variability due to decrements in strength? *Exp Brain Res* 174: 86-94, 2006b.

Sosnoff JJ, and Newell KM. The generalization of perceptual-motor intra-individual variability in young and old adults. *J Gerontol B Psychol Sci Soc Sci* 61: P304-310, 2006c.

Surmeier DJ, Mercer JN, and Chan CS. Autonomous pacemakers in the basal ganglia: who needs excitatory synapses anyway? *Curr Opin Neurobiol* 15: 312-318, 2005.

Takakusaki K, Saitoh K, Harada H, and Kashiwayanagi M. Role of basal ganglia-brainstem pathways in the control of motor behaviors. *Neurosci Res* 50: 137-151, 2004.

Tuite PJ, and Krawczewski K. Parkinsonism: a review-of-systems approach to diagnosis. *Semin Neurol* 27: 113-122, 2007.

Vaillancourt DE, Prodoehl J, Verhagen Metman L, Bakay RA, and Corcos DM. Effects of deep brain stimulation and medication on bradykinesia and muscle activation in Parkinson's disease. *Brain* 127: 491-504, 2004.

Zibetti M, Torre E, Cinquepalmi A, Rosso M, Ducati A, Bergamasco B, Lanotte M, and Lopiano L. Motor and nonmotor symptom follow-up in parkinsonian patients after deep brain stimulation of the subthalamic nucleus. *Eur Neurol* 58: 218-223, 2007.

CHAPTER 7

CONCLUSIONS AND FUTURE DIRECTIONS

In this chapter we will succinctly revisit the main accomplishments of the work, and discuss their implications and future directions.

The overarching goal of this work was to devise objective metrics of movement quality that can be used to quantitatively asses the level of motor impairment in Parkinson's disease patients and the level of motor improvement with deep-brain stimulation, so that these can be used as aides in the therapeutic process.

We introduced a novel platform for the study of DBS in PD and demonstrated its potential benefit alongside conventional clinical tools.

Through our experience we found that the metrics that we devised for the study of the disease were instrumental in identifying different subtypes of movement within rhythmic movement in the healthy population.

We sought to shed light on the role of the basal ganglia in sensorimotor integration, and found that in the absence of visual feedback PD patients experience a mitigation and even an elimination of bradykinetic symptoms, opening the door to new approaches for physical therapy which integrate exercises with visual cues with no-vision exercises to overcome bradykinesia.

Our finding suggest themselves as seeds from which a wealth of new research avenues may spring. We summarize our findings and their implications, and suggest some future experiments that may follow.

Discrete movements

We introduced the use of the "wrist robot" as a novel platform for studying motor control in Parkinson's disease patients with implanted deep-brain stimulators, with the goal of correlating kinematic aspects of movement with stimulation parameters, so that the former can be used to find an optimum in the latter. We demonstrated how the robotic apparatus can serve as a complement to existing clinical tools: we characterized typical PD movement, identified cases where the apparatus is not appropriate for testing (e.g., when PD is manifest mostly in the lower limbs), and cases where the robotic testing illuminated aspects of motor control that were not otherwise apparent in the conventional neurological testing (Levy-Tzedek et al. 2006a; Levy-Tzedek et al. 2006b; Levy-Tzedek et al. 2007). Finally, we presented preliminary indication that motor learning (adaptation to a force field) may be taking place in patients with DBS (Levy-Tzedek et al. 2006c; Levy-Tzedek et al. 2007).

Further testing, with a more carefully selected group of patients – i.e., with primarily upper-limb impairments, without much tremor and within a narrow range of UPDRS[1] scores – would be necessary in order to get data that provide a better resolution, and allow stronger inferences to be made.

[1] Unified Parkinson Disease Rating Scale

Rhythmic movements

Two movement subtypes, two movement regimes

We tested subjects from four experimental groups – PD patients with DBS, PD patients without DBS, healthy age-matched controls and healthy young controls – who performed rhythmic elbow movements, with the goal of studying the effects of deep-brain stimulation on movement frequency. In each of three experimental blocks subjects were presented with speed ranges within which they were asked to perform the task, either with or without visual feedback. Analysis of data from 23 healthy subjects revealed that movements in the three experimental blocks could be grouped into two subgroups, which can be distinguished using the following six kinematic analysis methods:

1. Non-monotonicity of accuracy with speed

The non-monotonic relation of accuracy with speed suggests that the faster movements may not lie on the same curve as do movements from the other two blocks, suggesting they may be differentially controlled, leading to separate speed-accuracy trade-off functions.

2. Movement smoothness

We found movements in the fast block to be nearly maximally smooth. In contrast, movements in the slow and the medium blocks were found to be only as smooth as the smoothest concatenation of discrete movements, or less, suggesting the former were performed in a smooth sinusoidal fashion, while the latter were performed as a concatenated sequence of discrete movements.

3. Movement harmonicity

We found movements in the fast block to be strongly harmonic nature, while movements in the medium and the slow blocks shared characteristics with a string of discrete movements.

4. Number of submovements per half cycle

We found that movements in the fast block were fit with close to a single submovement per half cycle on average, whereas movements in the medium and the slow blocks were fit with no less than 2 submovements per half cycle on average.

5. Velocity profile of best-fit submovement

We found that movements in the fast block were best fit using a rhythmic basis function, whereas the movements in the medium and in the slow blocks were best fit using a discrete basis function, potentially representing differentially controlled movements.

6. Effects of visual feedback on movement smoothness

Whereas movement in the slow and the medium blocks is significantly smoother when visual feedback is available, movement in the fast block is significantly more intermittent when visual feedback is available, suggesting the former use vision as a *primary* source for both accuracy and smoothness, while for the latter vision plays a *secondary* role, increasing accuracy at the cost of smoothness.

These six aspects of movement in which the two suggested subtypes of movements can be distinguished support the hypothesis that movements in the fast block are controlled differently than movements in the slow and the medium blocks. We suggested that the difference between the two control modes stems from a limit on how large or how long a movement can be, and still be executed smoothly and accurately. That is, we suggested that there exist two regimes in the frequency/amplitude plane, and the choice of whether to operate in one vs. another regime depends on the frequency and the amplitude of the required

movement. We suggest that small-amplitude, high-frequency movements harness the elastic properties of the limb to achieve accuracy and smoothness, whereas large-amplitude, low-frequency movements rely on sensory feedback to achieve accuracy and smoothness.

The ability to both deduce the subtype employed based on the movement's kinematic characteristics and to predict the subtype that would be employed based on the task's frequency/amplitude combinations is important for the understanding of human movement, its limitations, and how it is controlled. Furthermore, it is an important tool for future research; brain imaging studies, for example, are more likely to give clearer distinction between rhythmic and discrete movements (Schaal et al. 2004) if a discrete movement is compared to a *truly rhythmic* movement, as opposed to a *pseudo rhythmic* one, which shares many kinematic characteristics with discrete movements, and so potentially also shares associated brain activity patterns.

Bradykinesia and visual feedback

The role of the basal ganglia in sensorimotor integration has long been debated. We demonstrated that when PD patients perform a cyclic elbow movement in the absence of vision, bradykinetic symptoms are mitigated and, in some cases, even eliminated. These results support a role for the basal ganglia in sensorimotor integration. They suggest that the processing and harnessing of

visual feedback into an ensuing motor command may contribute to the accentuation of (Flash et al. 1992) – if not be the cause for – bradykinesia. These findings, unparalleled in the realm of discrete tasks (Flash et al. 1992; Schettino et al. 2006) may have important implication for physical therapy for PD patients: training the patients to perform rhythmic tasks in the absence of visual feedback may become an important part of their exercise and therapy regimen.

Clinical implications

Understanding healthy rhythmic behavior can be instrumental in early detection of movement disorders (e.g., Parkinson's disease), as well as design and evaluation of therapies. In fact, we had an opportunity to observe that in play while running this experiment. One of the participants, recruited as a young, healthy control – a male of 20 years old – declared prior to the testing session that, on occasion, he would experience some action tremor while eating. No tremor was apparent (to the untrained eye, at least) during the testing session, and his on-screen performance appeared normal for his age-group (compare the left columns of figures 1 and 2). When his data were analyzed, however, it showed characteristics similar to those of the PD patients (compare, for example, the right columns of figures 1 and 2 and those in figures 2 and 3). While his data were subsequently not included in the group analysis, it gave us an indication that the rhythmic task we employed, coupled with the suite of analytical methods

we have developed in this work may be further refined to be used to detect movement disorders – perhaps at their early stages.

FUTURE DIRECTIONS

Two regimes – or are there?

We have described two subtypes of rhythmic movement, and how they are differentially employed depending on the frequency and amplitude combinations of a rhythmic elbow movement. We termed the frequency/amplitude combinations that give rise to nearly maximally smooth, harmonious movements "truly rhythmic", and those leading to movements with more discrete characteristics were termed "pseudo-rhythmic". These represent two "regimes" within the frequency/amplitude plane.

In the experimental design we used, the required frequency/amplitude ranges were co-varied. A natural follow-up experiment would allow isolation of the effects of each factor – frequency vs. amplitude – through exploration of more frequency/amplitude combinations. That is, changing the movement amplitude while keeping the frequency constant, and vice versa.

In the context of the "two regimes", another intriguing exploration would be which regime subjects choose to operate in if given the choice. In that experiment, subjects would be asked to move at a self-selected frequency/amplitude combination ("preferred frequency") prior to being introduced to the given set of

task requirements, which may otherwise influence their choice. A consistent choice of one regime vs. another would indicate a relative advantage (e.g., in terms of energy considerations) of one regime over the other.

Together, these two experimental questions (self-selected movement parameters and a wider range of frequency/amplitude combinations) would allow:

1. A distinction to be made between the contributions of amplitude vs. frequency to determining in which regime movements are performed.
2. An in-depth examination of the behavior within the "truly rhythmic" regime, which, in the current experimental design is represented by a single frequency/amplitude combination.
3. Alternatively, refute the two-regimes theory by demonstrating a multi-peaked speed-accuracy function, indicating multiple sources of movement accuracy, in addition to the currently suggested visual feedback and limb elasticity.
4. Teach us about the possible factors that go into the selection of a "preferred frequency": for example, do factors apart from the dimensions of the limb play a role (as they would for the resonant frequency of a pendulum).

To then build on these results, it would be of interest to design a similar experiment, wherein the phase-plane display is continuously modified between

frequency/amplitude combinations that were classified as forming the "truly rhythmic" regime and ones in the "pseudo-rhythmic" regime.

This will allow exploration of "carry over" effects: that is, does the benefit gained from performing in the "truly rhythmic" regime – in the form of "primed" muscles, for example, as has been claimed to occur in muscles engaged in a rhythmic activity (Smits-Engelsman et al. 2002) – carry over into the "pseudo rhythmic" regime. Should those exist, they would illuminate the nature of the "bisector" of the frequency/ampitude plane: whether it stems from a physical limitation on the ability to generate perfectly smooth movements when they are large and slow, as opposed to a preference.

Direct comparison with a Fitts task

As we have emphasized in previous chapters, the phase-plane task was quite different in several respects from the traditional "Fitts task" (Fitts 1954). It would be of interest to design an experiment where the two experimental paradigms are directly compared and contrasted. That is, test subjects on a task where movement requirements are defined only at the endpoints (as in the Fitts task), and test whether the same frequency/amplitude combinations lead to the same movement subtypes as when subjects perform a task with the requirements are imposed throughout the movement, as they were in this body of work.

Brain imaging

In a seminal work by (Schaal et al. 2004), it was demonstrated that there is no complete overlap between brain-activation patterns when performing a rhythmic vs. a discrete task. Having identified two movement subtypes within rhythmic movements, it would be of interest to test whether the two also diverge in terms of the associated brain activity.

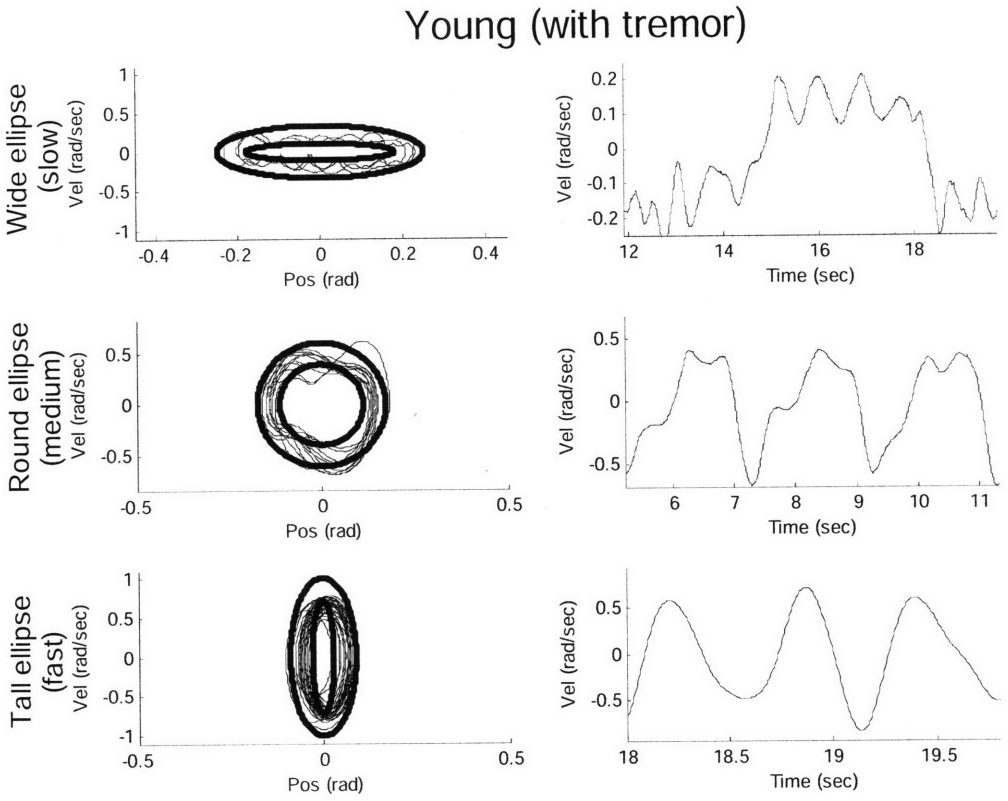

Figure 1. Left column: phase plane trajectories from the young subject that complained about tremor, in the slow, medium and fast blocks. Y axis: angular velocity (rad/sec), x axis: position (rad). Right column: velocity traces from the same subject in the slow, medium and fast blocks. Y axis: angular velocity (rad/sec), x axis: time (sec).

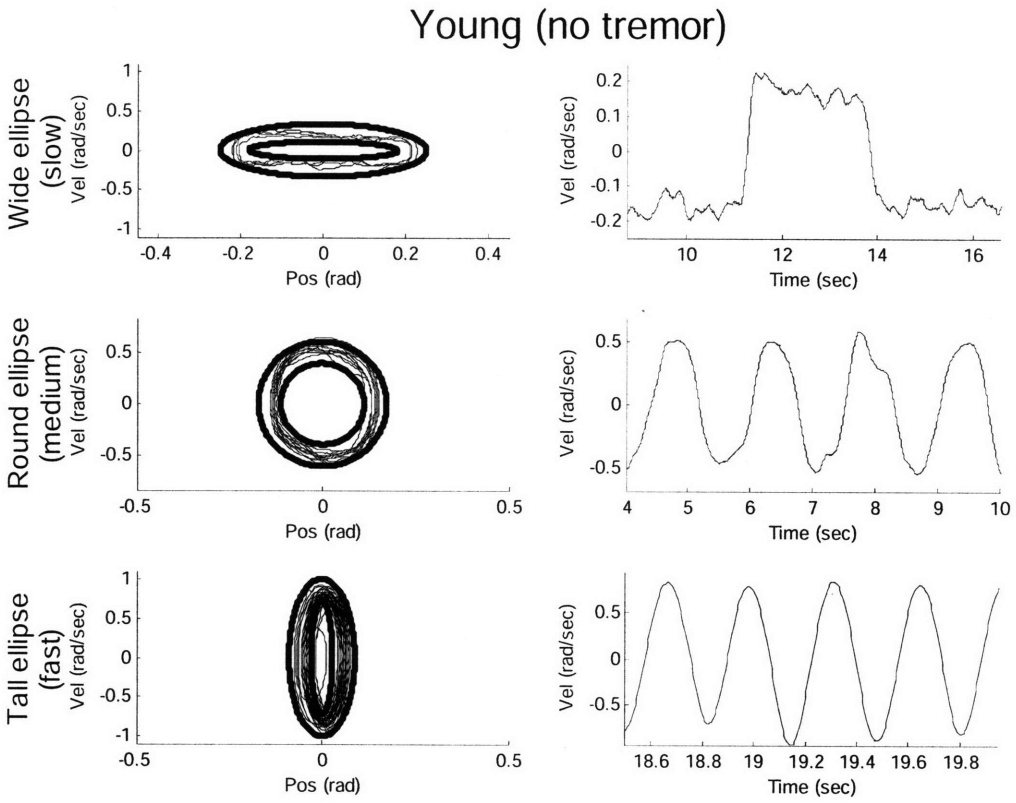

Figure 2. Left column: phase plane trajectories from a young subject in the slow, medium and fast blocks. Y axis: angular velocity (rad/sec), x axis: position (rad). Right column: velocity traces from the same subject in the slow, medium and fast blocks. Y axis: angular velocity (rad/sec), x axis: time (sec).

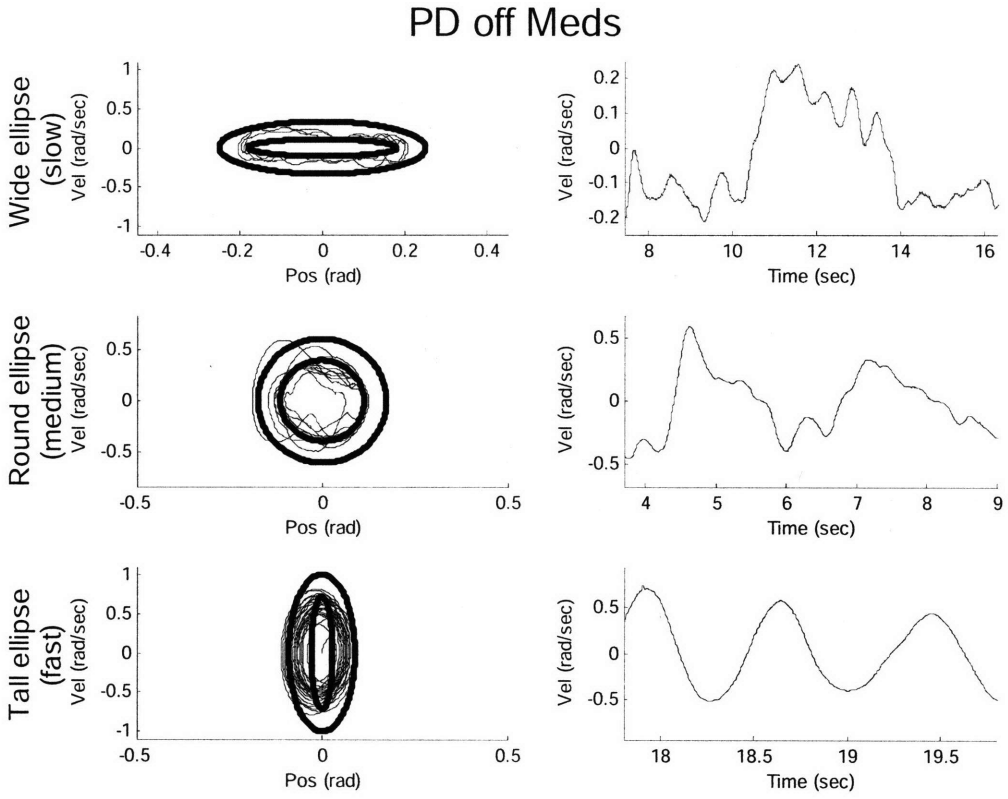

Figure 3. Left column: phase plane trajectories from a PD patient off medication, in the slow, medium and fast blocks. Y axis: angular velocity (rad/sec), x axis: position (rad). Right column: velocity traces from the same subject in the slow, medium and fast blocks. Y axis: angular velocity (rad/sec), x axis: time (sec).

REFERENCES

Fitts PM. The information capacity of the human motor system in controlling the amplitude of movement. *J Exp Psychol* 47: 381-391, 1954.

Flash T, Inzelberg R, Schechtman E, and Korczyn AD. Kinematic analysis of upper limb trajectories in Parkinson's disease. *Exp Neurol* 118: 215-226, 1992.

Levy-Tzedek S, Arle J, Apetauerova D, Shils JL, Gould C, and Krebs H. Clinical Score Improves While Motor Performance Deteriorates in a Parkinsonian Patient With Deep-Brain Stimulation: A Case Report. In: *Archives of Physical Medicine and Rehabilitation* 2006a, p. 25-26.

Levy-Tzedek S, Arle J, Shils JL, Gould C, Krebs H, and Penny D. Impaired Visual Perception in a Patient With Idiopathic Parkinson's Disease With Otherwise Intact Cognitive Function: A Case Report. In: *Archives of Physical Medicine and Rehabilitation* 2006b, p. 26-26.

Levy-Tzedek S, Arle JE, Shils JL, Apetaurova D, and Krebs HI. Effects of Brain Stimulation on Motor Performance & Learning: A Systematic Exploration. In: *Abstracts of the 2nd Computational Motor Control Workshop*. Ben Gurion University, Israel: 2006c.

Levy-Tzedek S, Krebs HI, Shils JL, Apetauerova D, and Arle JE. Parkinson's disease: a motor control study using a wrist robot. *Advanced Robotics* 21: 1201-1213, 2007.

Schaal S, Sternad D, Osu R, and Kawato M. Rhythmic arm movement is not discrete. *Nat Neurosci* 7: 1136-1143, 2004.

Schettino LF, Adamovich SV, Hening W, Tunik E, Sage J, and Poizner H. Hand preshaping in Parkinson's disease: effects of visual feedback and medication state. *Exp Brain Res* 168: 186-202, 2006.

Smits-Engelsman BC, Van Galen GP, and Duysens J. The breakdown of Fitts' law in rapid, reciprocal aiming movements. *Exp Brain Res* 145: 222-230, 2002.