Progressive Resistance Exercise and its Effects on Movement and Cognition in Parkinson’s Disease

BY

FABIAN JUDE DAVID
B.S., Sri Ramachandra Medical College and Research Institute, Chennai, India, 1998
Post-Graduate Diploma, Spastic Society of India, Chennai, India, 1999
M.S., University of North Carolina at Chapel Hill, North Carolina, USA, 2004

THESIS

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Defense Committee:

Daniel M. Corcos, Chair and Advisor
Julie A. Robichaud
David E. Vaillancourt
Cynthia L. Comella, Rush University Medical Center
Sue E. Leurgans, Rush University Medical Center
To my mom, dad, brother, son, wife, and ayah
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<td>1RM</td>
<td>One Repetition Maximum</td>
</tr>
<tr>
<td>au</td>
<td>Arbitrary Units</td>
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<tr>
<td>ANOVA</td>
<td>Analysis of Variance</td>
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<td>CONSORT</td>
<td>Consolidated Standards of Reporting Trials</td>
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<tr>
<td>DBS</td>
<td>Deep Brain Stimulation</td>
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<tr>
<td>DTI</td>
<td>Diffusion Tensor Imaging</td>
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<tr>
<td>EEG</td>
<td>Electroencephalography</td>
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<td>EMG</td>
<td>Electromyogram</td>
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<tr>
<td>EMG20</td>
<td>Mean EMG in the interval 20-40ms prior to EMG response</td>
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<td>FC</td>
<td>Fitness Counts</td>
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<td>fMRI</td>
<td>Functional Magnetic Resonance Imaging</td>
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<td>GPi</td>
<td>Internal Globus Pallidus</td>
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<tr>
<td>H-reflex</td>
<td>Hoffman's Reflex</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
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<tr>
<td>MPP⁺</td>
<td>1-methyl-4-phenylpyridinium</td>
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<tr>
<td>MPTP</td>
<td>1-methyl-4-phenyl-1,2,3,6-tetrahydropiridine</td>
</tr>
<tr>
<td>ms</td>
<td>Milli Second</td>
</tr>
<tr>
<td>mV</td>
<td>Millli Volt</td>
</tr>
<tr>
<td>MVC</td>
<td>Maximal Voluntary Contraction</td>
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<td>PET</td>
<td>Positron Emission Tomography</td>
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<td>PD</td>
<td>Parkinson’s Disease</td>
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<td>PDQ</td>
<td>Parkinson’s Disease Questionnaire</td>
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<td>Description</td>
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<td>PRE</td>
<td>Progressive Resistance Exercise</td>
</tr>
<tr>
<td>$Q_{30}$</td>
<td>Magnitude of the First 30ms of the Agonist Burst</td>
</tr>
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<td>$Q_{ag}$</td>
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<td>$Q_{ag1}$</td>
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<td>$Q_{ag1A1}$</td>
<td>Magnitude of the First Agonist Burst Normalized to Burst Duration</td>
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<td>$Q_{ant}$</td>
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<td>SNpc</td>
<td>Substantia Nigra Pars Compacta</td>
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<td>STN</td>
<td>Subthalamic Nucleus</td>
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<tr>
<td>tEMG</td>
<td>Time of EMG Response</td>
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<td>TMS</td>
<td>Transcranial Magnetic Stimulation</td>
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<td>tPkAcc</td>
<td>Time to Peak Acceleration</td>
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<tr>
<td>tPkTrq</td>
<td>Time to Peak Torque</td>
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<tr>
<td>tPkVel</td>
<td>Time to Peak Velocity</td>
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<tr>
<td>UPDRS</td>
<td>Unified Parkinson’s Disease Rating Scale</td>
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<tr>
<td>UPDRS-III</td>
<td>Unified Parkinson’s Disease Rating Scale, Part III, Motor Subscale</td>
</tr>
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SUMMARY

The effect of 24 months of progressive resistance exercise (PRE) on movement and cognition was examined in patients with mild to moderate Parkinson’s disease (PD) using a randomized, controlled, 24-month clinical trial. The dissertation consists of a general introduction and four papers that are intended for publication as independent articles. The general introduction discusses PD in detail, i.e., its etiology, diagnosis, and treatment. The first paper is a mechanistic review of PRE and PD. The second paper reports electromyographic (EMG) activation during fast and moderate speed point-to-point elbow flexion movements. The methodology used in the second paper, i.e., EMG activation, forms the methodological basis for the third paper. The third paper reports the effect of PRE on fast point-to-point elbow flexion movements in subjects with PD. Finally, the fourth paper reports the effects of PRE on cognitive functions including attention and working memory in subjects with PD. The third and the fourth papers of this dissertation report outcomes obtained from the first clinical trial to examine the effects of progressive resistance exercise in Parkinson’s disease. The findings provide the strongest evidence to date for the efficacy of PRE in mitigating motor and non-motor symptoms observed in PD. The findings of the experiments in this dissertation show that PRE improves bradykinesia and strength. In addition, PRE is capable of causing central changes that favorably alter the corticospinal output arriving at the muscle. Furthermore, physical activity, i.e., PRE or FC, can also improve cognition and offset the cognitive decline that is often observed in PD. In conclusion, engaging in twice a week of high intensity PRE with a personal trainer can provide improvement in bradykinesia and strength, while engaging in either FC or PRE can provide improvement in cognitive function. The findings also provide strong evidence for the use of PRE as an adjunct treatment in PD.
1. INTRODUCTION

Movement is a fundamental aspect of human life. Several systems are involved in achieving purposeful movement. The sensory system forms internal representations of the external environment. The motor system uses this internal representation as the basis to plan and execute purposeful movement. However, the motor system does not act in isolation. It requires the integrative action of higher order cognitive processes, so that sensory and motor information can be integrated. Additionally, these higher order cognitive areas are also involved in updating the internal representation of the environment and movement. For instance, a simple reach to an object requires the integrated action of several systems. The visual system is required to locate, perceive, and estimate the distance of the object from the eye. The proprioceptive system is required to identify the location of the limb in space. Sensory associative areas are required to integrate visual information with proprioceptive information and estimate the distance of the object from the limb. Sensory motor associative areas are required to integrate the sensory and the motor system. The motor system is required to plan and execute the reach towards the object. This culminates in the execution of the movement by signals traveling from the primary motor cortex to the muscle via the spinal cord. It does not end here, in fact sensory systems work together to update and refine the internal representation of the environment and the completed movement. Thus, even the simplest movements recruit several neural systems.

Studying these neural systems in health and disease provides vital insights into how the brain controls movement. Studying healthy human movement provides many fundamental insights into movement control. Studying movement in disease provides an association between neural impairment and movement dysfunction. For example, studying subjects with Parkinson’s
disease (PD) provides an association between dopaminergic loss in the basal ganglia and movement dysfunction observed in PD.

Parkinson’s disease is an ideal pathological model for studying the various neural systems involved in purposeful movement. Dopaminergic deficits in PD impair both motor and cognitive function. The motor signs of the disease include tremor, rigidity, bradykinesia, and impaired gait and posture. The cognitive impairments reported in the disease include impairments in attention and working memory. Current treatment options for PD include dopamine replacement therapy and brain surgery. More recently, progressive resistance exercise (PRE) along with medication has been suggested as an adjunct treatment for patients with PD (Bloomer et al., 2008; Dibble et al., 2006; Falvo, Schilling, & Earhart, 2008). However, the long term effects of PRE on movement and cognitive outcomes in PD are yet to be determined.

My dissertation examined the effects of 24 months of PRE on movement and cognition in PD. The dissertation consists of a general introduction and four papers that are intended for publication as independent articles. The general introduction discusses PD in detail, i.e., its etiology, diagnosis, and treatment. The first paper is a mechanistic review of PRE and PD. It reviews the underlying mechanisms of bradykinesia and muscle weakness, the central adaptations that accompany PRE, and provides a rationale for PRE in PD. It also reviews some of the research that has investigated the effect of PRE in PD and lists knowledge gaps and proposes ideas for future research. The second paper examines proprioceptive feedback control in healthy individuals. Specifically, it examines electromyographic (EMG) activation during fast and moderate speed point-to-point elbow flexion movements. The methodology used in the second paper, i.e., EMG activation, forms the methodological basis for the third paper. The third paper examines the effect of PRE on fast point-to-point elbow flexion movements in subjects
with PD. Finally, the fourth paper examines the effects of PRE on cognitive functions including attention and working memory in subjects with PD.

1.1.  **PARKINSON’S DISEASE**

1.1.1. **PREVALENCE AND ETIOLOGY**

Parkinson’s disease is the second most common neurodegenerative disease next to Alzheimer’s disease (de Lau & Breteler, 2006). Age is the most consistent risk factor for PD and its prevalence significantly increases with age. The prevalence of PD in industrialized countries is estimated to be approximately 0.3% of the general population, 1% for those between 65 and 69, and up to 3% for those over the age of 80 (de Lau & Breteler, 2006; Nussbaum & Ellis, 2003; Tanner & Goldman, 1996). In the US, prevalence of PD among Medicare beneficiaries was 0.6% in the 65-69 age range and 3.2% for those over 85 (Wright Willis, Evanoff, Lian, Criswell, & Racette, 2010). Several studies report that the age-adjusted prevalence rates in males is modestly increased when compared to females, however this is not supported by all studies (Tanner & Goldman, 1996; Wright Willis et al., 2010). PD incidence rates range from 8-18 per 100,000 person-years (de Lau & Breteler, 2006).

Parkinson’s disease is characterized by a significant loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) (Ehringer & Hornykiewicz, 1960; Gerfen et al., 1990) and the presence of Lewy body inclusions in the surviving nigral neurons (Creese, Sibley, Hamblin, & Leff, 1983). Lewy bodies are cytoplasmic inclusions that contain alpha-synuclein and ubiquitin (Baba et al., 1998). The exact cause for the degeneration of the dopaminergic neurons in the substantia nigra pars compacta is not yet known. One possible cause of the dopaminergic cell degeneration in PD is nigral mitochondrial dysfunction (Dauer & Przedborski, 2003; Lin & Beal, 2006; Schapira et al., 1989). Among the many factors that have been
associated with nigral mitochondrial dysfunction, environmental and genetic factors have significantly contributed to our understanding of the etiology of PD (Blandini, Nappi, Tassorelli, & Martignoni, 2000; Lang & Lozano, 1998a). The next two paragraphs discuss the environmental and genetic contributions to nigral mitochondrial dysfunction in PD.

One known environmental factor that causes Parkinsonism is 1-methyl-4-phenyl-1,2,3,6-tetrahydropiridine (MPTP). MPTP is a byproduct of illicit synthesis of meperidine analogs (narcotic analgesic used by recreational drug users). It selectively damages cells in the substantia nigra pars compacta and results in rapid onset of Parkinsonism (Davis et al., 1979; Langston, Ballard, Tetrud, & Irwin, 1983). MPTP itself is non-toxic; however once it crosses the blood brain barrier it oxidizes into 1-methyl-4-phenylpyridinium (MPP⁺), the active toxin. MPP⁺ is taken up via the dopamine uptake system by nigral neurons and accumulates in the mitochondria (Kopin & Markey, 1988; Nicklas, Vyas, & Heikkila, 1985). Here, it blocks mitochondrial respiration by inhibiting mitochondrial complex I and causes oxidative stress that leads to nigral cell death (Kopin & Markey, 1988; Nicklas et al., 1985). Another toxin, rotenone, a natural pesticide, is also linked to increased oxidative stress through the inhibition of mitochondrial complex I (Betarbet et al., 2000).

Until the 1990s when the first gene, alpha-synuclein, for familial PD was identified (Polymeropoulos et al., 1997), PD was largely considered the prototypical non-genetic disorder. Since then studies attempting to identify other PD genes have increased dramatically. Currently, 16 loci have been described in the database of Online Mendelian Inheritance in Man from the National Center for Biotechnology Information. Six of these loci, including alpha-synuclein, parkin, UCHL-1, PINK1, DJ1, and LRRK2 have been extensively studied (Xie, Wan, & Chung, 2010). Often these genes affect or regulate different mitochondrial functions. For example,
studies have shown that mutant alpha-synuclein, a presynaptic protein, can increase mitochondrial permeability and affect components of the electron transport chain resulting in oxidative stress (Xie et al., 2010). PINK1, a mitochondrial protein, functions to prevent oxidative stress and apoptosis. Deletion of PINK1 in Drosophila (fruit fly) results in the loss of the ability to prevent oxidative stress and apoptosis, leading to eventual nigral cell death (Xie et al., 2010). Thus, mitochondrial dysfunction is at the core of the etiology of PD. There is a remarkable similarity in the cascade of events that eventually lead to nigral cell death in sporadic and familial variants of PD (Moore, West, Dawson, & Dawson, 2005).

1.1.2. PATHOPHYSIOLOGY

The dopaminergic deficit that is observed in PD alters basal ganglia circuitry and results in the motor and non-motor symptoms observed in PD (Ehringer & Hornykiewicz, 1960; Hornykiewicz, 2002). In order to understand the pathophysiology of PD, one should have a thorough understanding of basal ganglia anatomy, its circuitry, and the effect that dopamine has on this circuitry.

The basal ganglia include four major nuclei that are involved in multiple cortical circuits. The basal ganglia nuclei include: 1) the striatum, which includes the caudate, the putamen, and the ventral striatum, 2) the globus pallidus, which is divided into the internal and external globus pallidus, 3) the substantia nigra, which includes the pars compacta and the pars reticulata, and 4) the subthalamic nucleus (DeLong, 2000). The cortical circuits that the basal ganglia are involved in include the motor circuit, the oculomotor circuit, dorsolateral prefrontal circuit, the lateral orbitofrontal circuit, and the anterior cingulate/medial orbitofrontal circuit (Alexander, Delong, & Strick, 1986). The striatum and the subthalamic nucleus are the major input nuclei of the basal ganglia. They receive input from various cortical regions, the thalamus, and the brain stem. The
internal globus pallidus and the substantia nigra pars reticulata are the major output nuclei of the basal ganglia. The targets of these nuclei are several cortical areas via the thalamus and the brain stem. The output of the basal ganglia is purely inhibitory.

The basal ganglia output is modulated by two parallel pathways, the direct and the indirect pathway. The direct pathway facilitates movement while the indirect pathway inhibits movement. The direct pathway projects from the striatum to the internal segment of the globus pallidus and the substantia nigra pars reticulata. Striatal output neurons in the direct pathway have a predominance of D1 receptors (Gerfen et al., 1990; Lang & Lozano, 1998b). The indirect pathway projects from the striatum to the external globus pallidus, which projects to the subthalamic nucleus. The subthalamic nucleus projects to the internal segment of the globus pallidus and the substantia nigra pars reticulata. Striatal output neurons in the indirect pathway have a predominance of D2 receptors (Gerfen et al., 1990; Lang & Lozano, 1998b). Dopamine has different effects on D1 and D2 receptors (Creese et al., 1983). Dopamine excites those striatal neurons with D1 receptors and inhibits those striatal neurons with D2 receptors (Creese et al., 1983). This forms the basis of the direct and the indirect basal ganglia pathways.

When dopamine enters the D1 receptors, the striatum is transiently stimulated. This results in the inhibition of the internal globus pallidus and the substantia nigra pars reticulata. Thus, through disinhibition the thalamus and selected brain stem nuclei are released from the tonic inhibitory effect of the internal globus pallidus and substantia nigra pars reticulata. This results in movement being facilitated. On the other hand, when dopamine enters the D2 receptors, the striatum is transiently inhibited. This results in the external globus pallidus exerting its inhibitory effect on the subthalamic nucleus, thus reducing/eliminating the excitatory effect the subthalamic nucleus has on the internal globus pallidus and the substantia nigra pars
reticulata. This in turn allows the internal globus pallidus and the substantia nigra pars reticulata to inhibit the thalamus and selected nuclei of the brain stem. Thus, there is a delicate balance of excitation and inhibition between the direct and indirect pathway for optimal motor control.

In PD, the balance between the direct and the indirect pathway is affected by the loss of dopaminergic neurons in the substantia nigra pars compacta. Dopaminergic deficit results in under activity of the direct pathway and over activity of the indirect pathway (Lang & Lozano, 1998b). The resultant effect is an increased inhibitory output from the output nuclei of the basal ganglia. Thus the thalamus and selected brain stem nuclei are tonically inhibited and this is associated with the motor symptoms observed in PD.

1.1.3. **CARDINAL SIGNS AND DIAGNOSIS**

The three cardinal signs of PD include bradykinesia, tremor, and rigidity. The Parkinson’s Disease Society Brain Bank defines bradykinesia as ‘slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions’ (Gibb & Lees, 1988, p.746). Tremor is defined as ‘an involuntary oscillatory movement produced by contractions of reciprocally innervated antagonistic muscles’ (Jankovic & Fahn, 1980, p. 460). Tremor is observed in approximately 70% of patients with PD (Hughes, Daniel, Blankson, & Lees, 1993). Tremor in PD typically occurs at rest, at a frequency of 4-6 Hz (Gibb & Lees, 1988). Additionally, some patients present with postural tremor at a frequency of 4-12 Hz (Andrews, Burke, & Lance, 1973; Lance, Schwab, & Peterson, 1963). Rigidity is defined as ‘a continuous and uniform increase in muscle tone felt as a constant resistance to passive movement’ (Broussolle et al., 2007, p. 909). In PD, both ‘lead pipe’ and ‘cog wheel’ types of rigidity are observed. Lead pipe rigidity is uniform resistance to passive movement through the entire range of movement. Cog wheel rigidity is non-uniform resistance, interrupted at a
frequency of 4-6Hz or 8-9Hz. The frequencies of interruption correspond to the most commonly observed resting and postural tremor frequencies respectively (Broussolle et al., 2007; Lance et al., 1963).

The diagnosis of PD is primarily clinical, based on history and examination. Currently there are no laboratory tests that can diagnose PD. Significant loss of dopaminergic neurons in the substantia nigra pars compacta and the presence of Lewy bodies are the defining features of the disease, which can only be confirmed using a post-mortem examination of the brain.

The gold standard for the diagnosis of PD is the guideline put forth by the Parkinson’s Disease Society Brain Bank (Gibb & Lees, 1988). The guideline follows a three step approach. Step 1 is the diagnosis of Parkinson’s syndrome. For a diagnosis of Parkinson’s syndrome, Bradykinesia must be accompanied with rigidity or 4-6 Hz rest tremor or postural instability not caused by visual, vestibular, cerebellar, or proprioceptive dysfunction. Step 2 is a list of exclusionary criteria. The most common exclusionary criteria include repeated strokes, repeated head injury, history of encephalitis, cerebellar signs, early severe dementia with disturbances in memory, language, and praxis, more than one affected relative, and MPTP exposure. Finally, step 3 is list of supportive criteria. These must include at least three of the following, unilateral onset, persistent asymmetry affecting the side of onset most, presence of rest tremor, progressive disorder, response to levodopa, levodopa induced dyskinesias, continued response to levodopa for at least five years, and a clinical course greater than 5 years. It should be noted that even with the use of these criteria, post mortem analysis has revealed an 18% misdiagnosis rate (Hughes, Daniel, Kilford, & Lees, 1992).

Even though the diagnosis of PD is primarily based on motor symptoms, recent studies have reported the presence of non-motor symptoms in PD. Non-motor symptoms include
neuropsychiatric symptoms (such as cognitive impairment, depression, and dementia), sleep disorders (such as restless legs, insomnia, and excessive daytime somnolence), autonomic symptoms (such as bladder disturbances, constipation, and sexual dysfunction), and sensory symptoms (such as pain and paraesthesia) (Chaudhuri, Healy, & Schapira, 2006; Olanow, Watts, & Koller, 2001; Owen, 2004). Most of the non-motor symptoms appear either later in the disease or in more severe instances of the disease. However, symptoms such as constipation and depression can appear early in the disease. Thus PD is a complex disease and the dopaminergic deficits associated with PD has a pervasive effect throughout the nervous system and beyond.

1.1.4. COGNITIVE IMPAIRMENT

In his original description of PD in 1817, James Parkinson stated that, ‘the senses and intellect are uninjured’ (Parkinson, 2002, p. 223). However, as early as 1882, Benjamin Ball observed impaired intellectual functioning in PD (Ball, 1882). Since then several studies have confirmed the presence of cognitive impairment in PD (for a recent review see (Owen, 2004)). Recent reports estimate that up to 80% of patients with PD will develop dementia (Aarsland, Andersen, Larsen, Lolk, & Kragh-Sorensen, 2003; Hely, Reid, Adena, Halliday, & Morris, 2008). Currently, it is accepted that cognitive impairment is frequently observed in PD along with the classic motor symptoms of bradykinesia, tremor, and rigidity (R. G. Brown & Marsden, 1990; Cooper, Sagar, Jordan, Harvey, & Sullivan, 1991; Lees & Smith, 1983; Owen, 2004; Sawamoto et al., 2007; Taylor, Saintcyr, & Lang, 1986). The pattern of cognitive dysfunction observed in PD is characterized by deficits in executive function (Owen, 2004). Specifically, deficits in spatial working memory, planning, and attentional set shifting (Owen et al., 1992; Sawamoto et al., 2008).
The neural basis for the associated cognitive impairment in PD is twofold. First, anatomical evidence shows that the basal ganglia are involved in non-motor loops with the dorsolateral prefrontal cortex, the medial and lateral orbitofrontal cortex, and the anterior cingulate cortex (Alexander et al., 1986). These areas are known to be involved in planning, working memory, attention, and rule-based learning (Goldman-Rakic, 1987; Middleton & Strick, 2000). And second, neurophysiologic evidence from single cell recordings have shown several populations of neurons in the internal globus pallidus and the substantia nigra pars compacta to be associated with cognitive function, higher order visual function, and performance of tasks requiring sequential memory (Hikosaka & Wurtz, 1983; Hikosaka, Sakamoto, & Miyashita, 1993). Findings from human positron imaging studies have supported the aforementioned single cell recordings. Patients with PD when compared to age matched controls have shown reduced activity of the internal globus pallidus during the performance of tasks involving planning and spatial working memory (Owen, Doyon, Dagher, Sadikot, & Evans, 1998).

1.1.5. TREATMENT

The treatment of PD includes pharmacologic management, surgical management, and non-pharmacologic management. Levodopa, a precursor to dopamine, has been the mainstay of pharmacologic management for PD since the 1960s. Even though dopamine was first synthesized in 1910 by George Barger and James Ewens (Hornykiewicz, 2002), only in 1958 did reports start emerging that dopamine was present in the brain (rabbit). Kathleen Montagu, in her seminal 1957 report in Nature, discovered the presence of an unidentified catechol compound in the rabbit brain and suggested that it was dopamine (Montagu, 1957). Six months later, in 1958, dopamine’s presence in the brain (rabbit) was confirmed by Arvid Carlsson (Carlsson, Lindqvist, Magnusson, & Waldeck, 1958). Additionally, Arvid Carlsson also found that in the rabbit brain,
reserpine depleted dopamine, while levodopa, a dopamine precursor, increased dopamine (Carlsson et al., 1958). Shortly thereafter, in 1959, Bertler and Rosengren in Carlsson’s laboratory and Sano and colleagues in Japan showed that the bulk of the dopamine in the brain of the dog and healthy humans was concentrated in the striatum (Bertler & Rosengren, 1959; Sano et al., 1959). A year later, in 1960, Ehringer and Hornykiewicz, showed that dopamine was significantly and consistently depleted in post mortem brains of 6 individuals with PD (Ehringer & Hornykiewicz, 1960). The events listed above initiated the era of dopamine replacement therapy for individuals with PD. In 1968, Cotzias successfully developed a chronic high dose oral levodopa regimen for treatment of PD (Cotzias, 1968). Since then levodopa has been the standard pharmacologic treatment for PD.

Over the past several decades refinements in the pharmacologic treatment of PD have occurred. In the early 1970s levodopa was administered in combination with carbidopa, a decarboxylase inhibitor to prevent the peripheral conversion of levodopa to dopamine and consequently prevent side effects such as nausea and vomiting (Olanow et al., 2001). In the 1990s sustained and controlled release versions of the drug were formulated (Olanow et al., 2001; Olanow, Obeso, & Stocchi, 2006). Additionally, liquid preparations and parenteral forms were also developed (Olanow et al., 2001). In addition to levodopa other drugs used to treat PD include dopamine agonists (such as Apomorphine and Pergolide), catechol-O-methyltransferase inhibitors (such as Entacapone), monoamine oxidase B inhibitors (such as Selegiline), and anticholinergic agents (such as Benzotropine) (Goetz, Poewe, Rascol, & Sampaio, 2005; Lang & Lozano, 1998b; Poewe, 2009).

Continued treatment with levodopa is associated with motor side effects, such as dyskinesias and motor fluctuations. The underlying mechanisms for levodopa induced motor side
effects are not completely understood. The suggested mechanisms include fluctuating plasma levels of dopamine and discontinuous delivery of levodopa to the brain. This results in intermittent pulses of striatal dopaminergic receptor stimulation initiating the cascade of events that eventually manifest as dyskinesias and motor fluctuations (Olanow et al., 2006). It must be noted that the drugs used to treat PD neither treat the non-motor symptoms, such as dementia and autonomous dysfunction, nor prevent disease progression (Goetz et al., 2005; Olanow et al., 2001). In fact, some of the drugs like levodopa, amantadine, and benzotropine might have non-motor side effects including cognitive decline, confusion, psychosis, hallucinations, and sedative effects (Lang & Lozano, 1998b; Olanow et al., 2001).

Until a long acting oral formulation of levodopa without the accompanying motor side effects is formulated, surgical options might offer some relief. Typically, surgery is reserved for patients with severely disabling disease that is sub-optimally managed by traditional pharmacologic options. Surgical options can be broadly divided into two categories. First are surgeries that cause lesions in specific nuclei in the basal ganglia either through ablation or stimulation. Second, those that attempt to restore striatal dopaminergic neurons through autologous or allogeneic transplantation. The sites for lesions/stimulation include the internal globus pallidus, the thalamus, and the subthalamic nucleus, while the site for transplantation is the striatum, especially the post-commissural portion of the putamen (Olanow et al., 2001).

The finding that high frequency deep brain stimulation has the same effect as ablation, is quasi-reversible, and can be performed bilaterally with minimal risk, currently makes deep brain stimulation the preferred neurosurgical option for patients with severely disabling PD (Benabid, Pollak, Louveau, Henry, & Derougemont, 1987). Deep brain stimulation of the ventral intermediate nucleus of the thalamus ameliorates tremor, however its effect on rigidity is
minimal, and it has no effect on bradykinesia or gait (Benabid et al., 1996). Given that resting tremor does not cause functional disability in PD, functional benefits due to deep brain stimulation of the ventral intermediate nucleus of the thalamus are minimal (Benabid et al., 1996; Limousin, Speelman, Gielen, & Janssens, 1999; Olanow et al., 2001). On the other hand, bilateral deep brain stimulation of the internal globus pallidus provides a 35 to 45% improvement in function as quantified by the Unified Parkinson’s Disease Rating Scale, part III, the motor subscale (UPDRS-III) in the off medicated state (Moro et al., 2010; Obeso et al., 2001; Olanow et al., 2001). The Unified Parkinson’s Disease Rating Scale (UPDRS) is the gold standard for assessing the severity and the progression of symptoms in PD and for evaluating novel therapies. Bilateral deep brain stimulation of the internal globus pallidus improves the UPDRS-III by improving the cardinal signs of PD and reduces dopamine dosage, consequently reducing dyskinesias while on medication. Yet another site for deep brain stimulation is the subthalamic nucleus because of its unique location and involvement in modulating skeletomotor, ocularmotor, and frontal lobe function. Clinical trials examining the therapeutic benefits of deep brain stimulation of the subthalamic nucleus have demonstrated a 40-60% improvement in the UPDRS, activities of daily living, and motor scores, upwards of 75% improvement in dyskinesia scores in the off medicated state (Moro et al., 2010; Obeso et al., 2001; Olanow et al., 2001). A recent multi center clinical trial compared deep brain stimulation of the internal globus pallidus and the subthalamic nucleus on the long term change in the UPDRS-III (Follett et al., 2010). They found no differences between deep brain stimulation of internal globus pallidus and subthalamic nucleus on the UPDRS-III change scores. On average, they reported an improvement of 28% for pallidal stimulation and 25% for subthalamic stimulation in the UPDRS-III in the off medicated state (Follett et al., 2010). Yet another benefit of deep brain
stimulation is that the duration of good motor function while ‘on’ medication is prolonged in both, deep brain stimulation of the internal globus pallidus, as well as the subthalamic nucleus (Follett et al., 2010; Rodriguez-Oroz et al., 2005).

Autologous transplantation of adrenal medulla has been abandoned (Lang & Lozano, 1998b), due to its inefficacy in treating the symptoms of PD, partly due to poor survival of the implanted tissue (Olanow et al., 1990). On the other hand allogeneic transplantation of fetal mesencephalon showed initial promising results (Olanow et al., 2001). The idea that degenerating neurons can be made to regenerate and reverse impaired function without additional surgical procedures is indeed appealing. However, in a recently concluded clinical trial, patients demonstrated short term clinical benefits, but these benefits were not maintained 2 years after surgery (Olanow et al., 2003). Owing to the conclusions of this study, The Movement Disorder Society Task Force’s 2005 update on the evidence based review on pharmacological and surgical treatment for PD concluded that allogeneic transplantation is clinically inefficacious and deemed it to be an investigational treatment (Goetz et al., 2005).

All of the above mentioned treatment options have complications. As mentioned earlier, prolonged pharmacologic therapy results in severely disabling motor and non-motor side effects. Side effects of surgical options include adverse events related to the surgical procedure itself, such as intracerebral hemorrhage with persistent neurologic deficit, device related infections and mechanical complications, and stimulation related side effects, such as contra lateral transient facial muscle twitch and paresthesias (Olanow et al., 2001). Also, long term effects of surgery are yet to be completely determined, although the initial five year studies are very promising, in that there is no evidence of long term negative side effects such as dyskinesias (Follett et al., 2010; Moro et al., 2010; Obeso et al., 2001; Olanow et al., 2001) and there is even evidence that
long term subthalamic deep brain stimulation can improve simple movement tasks (Sturman, Vaillancourt, Metman, Bakay, & Corcos, 2010). Non-pharmacologic treatment options, namely exercise can possibly provide relief for some of the symptoms observed in PD. The next section will review the current findings that are related to PRE in PD.

1.1.6. PROGRESSIVE RESISTANCE EXERCISE AND ITS EFFECTS IN PARKINSON’S DISEASE

Patients with PD exhibit muscle weakness, especially in the extensor muscles (Corcos, Chen, Quinn, McAuley, & Rothwell, 1996; Robichaud, Pfann, Comella, Brandabur, & Corcos, 2004). Weakness in PD has been reported in the trunk (Bridgewater & Sharpe, 1998), upper limb (Corcos et al., 1996), and lower limbs (Durmus et al., 2010; Kakinuma, Nogaki, Pramanik, & Morimatsu, 1998). The central mechanisms that contribute to muscle weakness in PD include reduced central drive to the muscle (Albin, Young, & Penney, 1989; Salenius, Avikainen, Kaakkola, Hari, & Brown, 2002; Valls-Sole et al., 1994), action tremor (P. Brown, Corcos, & Rothwell, 1997), and reduction in the CNS oscillations that generate EMG Piper frequency (40Hz) (McAuley, Corcos, Rothwell, Quinn, & Marsden, 2001). All of the above mentioned mechanisms are associated with striatal dopaminergic deficit. This dopaminergic deficit can be treated with drugs and surgery, as outlined in the previous section. The goal of these treatment strategies is to reduce the inhibitory effect the basal ganglia have on the motor cortex, thereby increasing motor cortical drive (Hershey et al., 2003; Salenius et al., 2002; Williams et al., 2002). However, pharmacologic and surgical treatments do not normalize the cortical drive to muscle (Robichaud, Pfann, Comella, & Corcos, 2002; Vaillancourt, Prodoehl, Verhagen Metman, Bakay, & Corcos, 2004), nor do they bring about any peripheral changes in the muscle itself. An
additional strategy is to consider interventions that can directly influence motor cortical areas and the target of their output, the muscle. One such intervention is PRE.

The rationale for PRE in patients with PD is twofold. First, the basal ganglia are involved in the modulation of force, both the amplitude and the rate of force generation. In the healthy, the blood-oxygen-level-dependent signal in the internal globus pallidus and the subthalamic nucleus scales with the amplitude and rate of change of force (Spraker, Yu, Corcos, & Vaillancourt, 2007). Additionally, evidence from ensemble recordings from the human subthalamic nucleus extends support for the basal ganglia’s involvement in force modulation (Patil, Carmena, Nicolelis, & Turner, 2004). Second, PRE has been shown to increase cortical activity and increase force generating capacity of the muscle (Falvo, Sirevaag, Rohrbaugh, & Earhart, 2010). Therefore, it is not unreasonable to hypothesize that PRE will benefit patients with PD.

Prior studies demonstrate that PRE has been shown to improve motor function in subjects with PD. The motor benefits observed include muscle hypertrophy and increased strength (Dibble et al., 2006; Dibble, Hale, Marcus, Gerber, & LaStayo, 2009; Hirsch, Toole, Maitland, & Rider, 2003; Scandalis, Bosak, Berliner, Helman, & Wells, 2001). Additionally, improvements in neuromuscular functioning have also been observed. These include increased latency to fall, reduced percentage of falls, improved ability to maintain balance during destabilizing conditions (Hirsch et al., 2003), longer stride length, increased velocity, and increased shoulder velocity during gait (Scandalis et al., 2001), improvements in functional mobility as quantified by the six-minute-walk and the timed-up-and-go (Dibble et al., 2006; Dibble et al., 2009), and the five times sit-to-stand (Allen et al., 2010). It should be noted that the above-mentioned studies only examined the short term (8-24 weeks) effects of PRE. The long term effects (beyond 24 weeks) of PRE are yet to be determined.
Another benefit of PRE is that it improves cognitive function in elderly healthy individuals. Cassilhas et al. (2007) demonstrated improved performance on measures of working memory and attention for those assigned to 24 weeks of PRE. More recently, Liu-Ambrose et al. (2010) have demonstrated beneficial cognitive effects of 52 weeks of PRE in community dwelling elderly women. They showed improvements in attention and conflict resolution. Thus, PRE appears to have cognitive benefits, yet no study to date has examined the effects of PRE on cognitive function in subjects with PD. Thus, there are gaps in the literature that need to be addressed with regard to the long term use of PRE in subjects with PD. A randomized clinical trial provides the most robust experimental design to address the gaps in the literature by assessing the short and long term effects of PRE in patients with PD.

1.1.7. RANDOMIZED CLINICAL TRIAL

The experiments presented in chapter 4 and 5 of this dissertation were part of a randomized, controlled, 24-month clinical trial examining the effect of PRE in subjects with PD. This clinical trial was designed to evaluate the effects of PRE on the following 5 domains: 1) Unified Parkinson’s Disease Rating Scale, a measure of clinical function in PD, 2) neurophysiological and behavioral motor deficit, 3) overall physical function, 4) quality of life, and 5) long term effects of PRE. Prior to commencing data collection, a sixth domain, cognitive function, was added. Aims 1 through 4 and aim 6 were proposed to examine the 6 month effect of PRE, while the 5th aim examined the 24 month effect of PRE on all the outcomes used in the clinical trial. The clinical trial employed a parallel group design with a 1:1 allocation ratio. Patients with PD were randomized to the PRE program or the Fitness Counts (FC) exercise program (R. Wichmann, Walde-Douglas, & Harris, 2002). The FC exercise program is recommended by the National Parkinson’s Disease Foundation and was used as an analogue for
current ‘standard exercise treatment’ for patients with PD (R. Wichmann et al., 2002). A healthy age and gender matched control group was also used to provide normative data; however, they did not participate in any form of exercise. The study commenced in October of 2007 and was completed in June of 2011 with 5 measurement points (baseline, 6, 12, 18, and 24 months).

The experiments presented in chapter 4 and 5 are both part of aim 5, i.e., examining the long term effects of PRE. Chapter 4 reports the long term effects of PRE on a subset of the outcomes used to evaluate the effect of PRE on neurophysiological and behavioral motor deficit in patients with PD. And Chapter 5 reports the long term effects of PRE on all the cognitive outcomes used to evaluate cognitive function in patients with PD.

**Consolidated Standards of Reporting Trials Flowchart**

The Consolidated Standards of Reporting Trials (CONSORT) flowchart in figure 1.1 shows the number of subjects in each intervention arm in each stage of the clinical trial. The experiments presented in chapter 4 and 5 will contain their own CONSORT flowcharts for the clinical trial and subject flow will be discussed in detail in the respective chapters.

**Sample Size Calculation**

The required sample size for the clinical trial was estimated by conducting an a priori power analysis. The sample size calculation was driven by the hypotheses that compare changes in the UPDRS-III score in Aim 1 and Aim 5. The UPDRS-III, the current “gold standard” to measure symptomatic effects, was used to drive our sample size estimations. We chose to power our study using the UPDRS-III score since this is the variable that must change in order to impact clinical practice. Thus, based on our pilot data, the required sample size with 80% power to detect a mean difference of 5 (at $\alpha = 0.05$) with a SD of 5 on the UPDRS-III, and an assumed attrition rate of 30% was estimated to be 25 subjects per group.
1.2. **ORGANIZATION OF DISSERTATION**

Paper 1 was completed and published in the journal Parkinson’s Disease in 2012. Paper 2 was completed and published in Experimental Brain Research in 2009. Paper 3 and 4 are yet to be published.
Figure 1.1. The CONSORT (Consolidated Standards of Reporting Trials) flowchart. * Persons who withdrew before the 6-month evaluation were replaced by persons who matched the off-medication UPDRS-III scores, age, and sex.
2. PAPER 1


2.1. INTRODUCTION

The standard treatment for Parkinson’s disease (PD) is pharmacologic treatment with levodopa, a precursor to dopamine. However, continued treatment with levodopa is associated with motor side effects, such as dyskinesias and motor fluctuations. Until an oral formulation of levodopa without the accompanying motor side effects is formulated, surgical options offer some relief. Typically, surgery is reserved for when the disease and the side effects due to medication are severely disabling. Currently, the most common surgical option is high frequency deep brain stimulation of the subthalamic nucleus or the internal globus pallidus (Follett et al., 2010; Moro et al., 2010; Obeso et al., 2001; Olanow et al., 2001). Despite the substantial clinical benefits of surgery, surgical treatment is not without complications, which occur in up to 50% of individuals with PD who undergo deep brain stimulation (Follett et al., 2010; Rodriguez-Oroz et al., 2005). These complications include device/surgery-related infections, cognitive decline, depression, speech difficulties, gait disorders, and postural instability (Follett et al., 2010; Rodriguez-Oroz et al., 2005). Therefore, there is merit to exploring treatment options that may be used as adjuncts to pharmacologic and surgical treatments prescribed in PD. One such option is exercise, specifically progressive resistance exercise (PRE).

This review paper will first discuss the rationale for PRE in PD specifically related to bradykinesia and muscle weakness. Within the first section, the review will discuss the central
mechanisms that underlie bradykinesia and muscle weakness. Then it will highlight findings related to the central changes that accompany PRE in healthy young and elderly individuals and extend these findings to PD. Finally, it will illustrate the hypothesized positive effects of PRE on nigro-striatal-thalamo-cortical activation and connectivity. Second, it will review recent findings related to the use of PRE in individuals with PD. Third, it will identify gaps in knowledge of using PRE in individuals with PD and makes suggestions for future research.

2.2. RATIONALE FOR PROGRESSIVE RESISTANCE EXERCISE

This section will set up the basis for PRE as a therapeutic intervention in PD. To do so, we will outline the underlying mechanisms for the motor symptoms that can be treated with PRE. We will focus primarily on the central mechanisms that underlie bradykinesia and muscle weakness in PD. Then we will discuss the central changes that accompany PRE and hypothesize as to how these changes might modify the central mechanisms that underlie bradykinesia and muscle weakness. We will conclude this section with our rationale for PRE in PD.

2.2.1. BRADYKINESIA AND MUSCLE WEAKNESS

Bradykinesia refers to the slowness of a performed movement (Berardelli, Rothwell, Thompson, & Hallet, 2001). Bradykinesia is a primary motor symptom of PD, which is also considered the most functionally debilitating symptom and is a consistent feature of the disease (Hallett & Khoshbin, 1980). Muscle weakness, which is a reduction in the amount of force generated by muscle contraction, is often observed in individuals with PD. In fact, several studies have demonstrated that individuals with PD exhibit muscle weakness (Allen, Canning, Sherrington, & Fung, 2009; Bridgewater & Sharpe, 1998; P. Brown et al., 1997; Durmus et al., 2010; Kakinuma et al., 1998; Koller & Kase, 1986; Robichaud et al., 2004; Schilling et al., 2010). We have shown that this weakness is exaggerated in the extensor muscles, specifically
extensors of the elbow (Corcos et al., 1996; Robichaud et al., 2004). Additionally, muscle weakness has also been observed across various muscle groups in the trunk (Bridgewater & Sharpe, 1998), upper limbs (Koller & Kase, 1986), and lower limbs (Allen et al., 2009; Durmus et al., 2010; Kakinuma et al., 1998; Koller & Kase, 1986).

In PD, the idea that bradykinesia and weakness are related can be derived from the fact that bradykinesia and muscle weakness might share common underlying mechanisms. Central to the pathophysiology of PD is the known nigral dopaminergic deficit that results in an increase in tonic inhibition of the thalamus and reduction in the excitatory drive to the motor cortex (Lang & Lozano, 1998b). This, in turn, may result in disruption of the cortical activation of the muscle (DeLong & Wichmann, 2010; DeLong, 1990; T. Wichmann & DeLong, 2003; T. Wichmann & DeLong, 2007) and may manifest as bradykinesia and muscle weakness. Further, muscle power, the product of movement velocity and muscle torque, is reduced in individuals with PD (Allen et al., 2009). Also, torque production during isokinetic muscle strength testing in individuals with PD has been shown to vary with movement velocity. Nogaki et al. found that in individuals with PD, no difference was observed in peak torque between the more and the less affected side for slower movements, while for faster movements the more affected side was significantly weaker than the less affected side (Nogaki, Kakinuma, & Morimatsu, 1999). Therefore, reduction in muscle power is indicative of deficits in either strength, movement speed, or both, and strengthens the proposed relationship between bradykinesia and muscle weakness.

Given that the muscle is the final target of cortical output during movement and force production, analyzing the electromyographic (EMG) activation patterns can provide insight into hypothesized impairments that underlie bradykinesia and muscle weakness. Therefore, we have extensively analyzed muscle EMG activation patterns in individuals with PD and have shown
that EMG activation patterns during ballistic movements and isometric actions are abnormal and reflect impaired activation of the muscle. During ballistic movement, first, muscle activation patterns show increased variability when compared to age- and sex-matched controls (Pfann, Buchman, Comella, & Corcos, 2001; Robichaud et al., 2002). Second, in contrast to healthy individuals, the first agonist burst duration does not systematically increase with movement distance (Pfann et al., 2001). Third, the magnitude of the first agonist burst, early in the disease, is similar to that observed in healthy individuals; however, as the disease progresses, the magnitude of the first agonist burst is modulated less with increasing movement distance (Pfann et al., 2001). Fourth, multiple agonist bursting is observed during the acceleration phase of movement and the number of agonist bursts increases with increasing movement distance (Pfann et al., 2001; Robichaud et al., 2002). During isometric actions, individuals with PD manifest deficits throughout the task. At the very beginning of the task, they exhibit decreased rate of torque generation and decreased initial phasic agonist EMG activation, which results in prolonged torque rise times and delayed peak torque (Corcos et al., 1996). In the middle of the task, during steady state contraction at 25%, 50%, and 75% of maximal voluntary contraction (MVC), the dominant frequency in the EMG spectrogram in individuals with PD stays fairly constant at ~10Hz (Chen, Sun, Lin, & Lin, 1997). In healthy individuals, however, the dominant frequency is higher and increases with increase in isometric torque generation, i.e., the dominant frequency shifts from ~18 to 25 Hz when isometric torque generation increases from 25% to 75% of MVC (Chen et al., 1997). At the end of the task, the rate of release of muscle contraction is also prolonged and torque fall times are increased in individuals with PD (Robichaud, Pfann, Vaillancourt, Comella, & Corcos, 2005).
The abnormal EMG activation patterns discussed above can be partly explained in terms of an impairment in the corticospinal activation of the muscle; specifically, impairments in variability, intensity, and frequency of the corticospinal activation of the muscle. Increased variability in the corticospinal activation of the muscle could lead to variability in motor unit recruitment and result in increased EMG variability (Miller, Thaut, McIntosh, & Rice, 1996). This increased variability in motor unit recruitment could impair coordinated relaxation of actively contracting motor units, contributing to prolonged deceleration phases during movement and prolonged relaxation times during isometric torque generation. Reduction in the intensity of the corticospinal activation of the muscle (Valls-Sole et al., 1994) may result in impaired motor unit recruitment and could contribute both to bradykinesia and muscle weakness. For instance, impaired motor unit recruitment during movement could result in reduced angular impulse during the acceleration phase of a movement and contribute to bradykinesia, and impaired motor unit recruitment during isometric torque generation could result in reduced peak torque and contribute to muscle weakness.

Alterations in the frequency of the corticospinal activation of the muscle could also explain some of the abnormal EMG patterns observed in individuals with PD. In healthy subjects the corticospinal activation to the muscle is characterized by three primary frequencies, i.e., 10Hz, 20Hz, and 40Hz (McAuley et al., 2001; Salenius et al., 2002). The magnetoencephalic (MEG) power spectrum is dominated by ~20 Hz oscillations during weak contractions and ~40Hz oscillation during strong contractions (Salenius et al., 2002). Similarly, the mean power in the EMG power spectrum increases from 10Hz to 25Hz with increase in percent MVC from 10% to 80% of MVC (Qi, Wakeling, Green, Lambrecht, & Ferguson-Pell, 2011). In untreated (de novo) individuals with PD relative to age- and sex-matched controls, resting state cortical
activity in the 8-10Hz band is increased, while activity in the 30-48Hz band is reduced (Stoffers et al., 2007). Further, in individuals with PD, the EMG power spectrum is dominated by power in the low frequency band (~10-15Hz) (Chen et al., 1997; Robichaud et al., 2005; Salenius et al., 2002), and the MEG-EMG coherence is strong in this low frequency band with the MEG signal leading the EMG signal by ~15-38ms (Salenius et al., 2002). Thus, one could hypothesize that, if the cortical signal to the muscle is dominated by low frequency oscillations, then this limits the ability to recruit larger, high frequency motor units, which are required to rapidly generate torque during ballistic movements, as well as generate maximal torque during isometric torque generation. The evidence reviewed in this and the previous two paragraphs suggests that EMG patterns are abnormal in individuals with PD, and one likely explanation for these observed EMG abnormalities is deficits in the variability, intensity, and frequency of the corticospinal activation of the muscle.

Another factor that could contribute to muscle weakness in individuals with PD is reduced muscle mass. Evidence that muscle mass is reduced in PD is provided by Petroni and colleagues (Petroni et al., 2003). They reported that mid arm muscle circumference was below the 10th percentile in 23% of individuals with advanced PD between 65 and 75 years of age (Petroni et al., 2003). On the other hand, evidence that this is not the case is provided by Markus and colleagues (Markus, Tomkins, & Stern, 1993). They found that even though body mass index and skin fold thickness, relative to age- and sex- matched controls, were reduced in individuals with PD, mid-arm circumference was not different from controls. Thus, the authors concluded that decrease in body mass index was due to a loss of fat and not due to a loss of muscle mass.
It is important to note that not only does PD cause weakness, but it is highly likely that muscle weakness and functional limitations such as postural instability and gait disturbances lead to reduced physical inactivity as a compensatory mechanism to minimize the likelihood of falls (Pickering et al., 2007). Therefore, physical inactivity can contribute to muscle weakness and lead to a vicious cycle between muscle weakness and physical inactivity (Speelman et al., 2011).

Even though we cannot discount muscle mass and changes in muscle properties as likely contributors to muscle weakness, it is our stand that the primary contributors to muscle weakness are central in origin and are related to dopaminergic deficits. This is evidenced by the fact that both anti-Parkinsonian medication and deep brain stimulation result in significant improvement in movement speed (Robichaud et al., 2002; Vaillancourt et al., 2004) and significant gains in muscle strength in relatively short amounts of time (no longer than 90 minutes) (Corcos et al., 1996; Sturman et al., 2010; Vaillancourt et al., 2006). Given that the minimum amount of time required to notice appreciable hypertrophy is at least 20 days (Seynnes, de Boer, & Narici, 2007), it is highly unlikely that the strength gains brought about by anti-Parkinsonian medication or deep brain stimulation are caused by gains in muscle mass.

The question that remains is the extent to which bradykinesia and weakness can be compensated for. We have shown that levodopa and/or deep brain stimulation of the subthalamic nucleus improves bradykinesia and/or muscle strength (Robichaud et al., 2002; Sturman et al., 2010; Vaillancourt et al., 2006), however, bradykinesia is not normalized (Robichaud et al., 2002; Vaillancourt et al., 2004). Moreover, surgical interventions carry significant risks, while medication becomes progressively less effective over time even as the side effects of medication get progressively worse. Therefore, until a cure for PD can be identified, there is a compelling need to develop interventions that improve the signs and symptoms of the disease, as well as
slow down the rate at which the signs and symptoms of the disease worsen. One such intervention is PRE, which may be a beneficial and cost effective adjunct treatment in managing PD. As such, if PRE is to be beneficial for individuals with PD, it should bring about central changes that must potentially alter nigro-striatal-thalamo-cortical activation and connectivity. This is not yet known; therefore, we will discuss the central changes that accompany PRE in healthy young and elderly individuals, and extend these findings to individuals with PD.

2.2.2. CENTRAL CHANGES THAT ACCOMPANY PROGRESSIVE RESISTANCE EXERCISE

The evidence for the central changes that accompany PRE is threefold (Enoka, 1997). First, gains in muscular strength appear before noticeable muscle hypertrophy (Enoka, 1997; Gabriel, Kamen, & Frost, 2006). After commencing a PRE protocol, strength gains appear as early as 5 days (Holtermann, Roeleveld, Vereijken, & Ettema, 2005), but muscle hypertrophy appears no earlier than 20 days (Seynnes et al., 2007). Therefore, the initial gains in muscle strength cannot be explained by measurable muscle hypertrophy. Instead, a likely explanation for the observed strength gains is the central changes that accompany PRE. Second, cross-education (i.e., improved performance in the untrained limb) is often observed (Enoka, 1997). Munn and colleagues, in their meta-analysis that included 13 studies, concluded that unilateral PRE brings about a 7% increase in strength in the untrained contra lateral limb (Munn, Herbert, & Gandevia, 2004). Given that this cross-education effect is accompanied by increase in muscle surface EMG, but is not accompanied by gains in muscle size, it is likely to be brought about by the central changes that accompany PRE (Gabriel et al., 2006; Hortobagyi, Lambert, & Hill, 1997). Third, improvements in performance following PRE are both, specific and generalized. The argument for specificity arises from the fact that short-term dynamic strength training results in
significantly greater gains in dynamic strength, while isometric strength gains are marginal (Rutherford & Jones, 1986). While the argument for generalizability arises from the fact that short-term strength training that focuses on increasing isometric strength also improves movement coordination during an untrained task (Carroll, Barry, Riek, & Carson, 2001). Thus, both specific and generalizable motor learning effects of PRE provide a third line of evidence for the central changes that accompany PRE.

Further evidence for the central changes that accompany PRE comes from studies employing transcranial magnetic stimulation (TMS), electroencephalography (EEG), functional magnetic resonance imaging (fMRI), and muscle EMG activation patterns. Using TMS, Carroll and colleagues found that for the same level of torque, the amplitude of the motor evoked potential was significantly reduced following a 4-week PRE program (Carroll, Riek, & Carson, 2002). They concluded that resistance training altered the functional properties of the spinal cord circuitry and fewer motor neurons were recruited for similar levels of pre-training torque. Using EEG, Falvo and colleagues found that the movement related cortical potentials were significantly attenuated following a 3-week PRE program (Falvo et al., 2010). They concluded that PRE reduced the neural effort required to move similar levels of pre-training loads. Using fMRI, Liu-Ambrose and colleagues found that in elderly women, following PRE, percent signal change significantly increased in the left anterior insula and the anterior portion of the left middle temporal gyrus (Liu-Ambrose, Nagamatsu, Voss, Khan, & Handy, 2011). They concluded that PRE could facilitate functional plasticity in the cortex. Using EMG, several studies have shown that the muscle activation patterns change after PRE (Falvo et al., 2010; Gabriel et al., 2006; Hakkinen & Komi, 1983b; Moritani & Devries, 1979; Pucci, Griffin, & Cafarelli, 2006; Sale, 1988). These muscle activation changes following PRE include an increase in the EMG
(Moritani & Devries, 1979; Sale, 1988; Seynnes et al., 2007), possibly due to increased motor unit recruitment (Akima et al., 1999; Enoka, 1988; Patten, Kamen, & Rowland, 2001), firing rate (Del Balso & Cafarelli, 2007; Patten et al., 2001), and synchronization (Kamen, 2005; Pucci et al., 2006); a reduction in the EMG activity to torque ratio, i.e., reduction in EMG activity relative to the amount of torque produced (Hakkinen & Komi, 1983a); a reduction in the variability associated with the timing, amplitude, and duration of muscle activity (Carroll et al., 2001); and a reduced agonist-antagonist co-activation (Carolan & Cafarelli, 1992). In addition, motor neuron excitability using the H-reflex could be used to infer central changes that accompany PRE. Using the H-reflex, Holtermann and colleagues found that the amplitude of the H-reflex increased following a 3-week PRE program (Holtermann, Roeleveld, Engstrom, & Sand, 2007). Further, they found that the H-reflex increase in amplitude was associated with an increased rate of force development. This could provide a neurophysiological basis for PRE improving bradykinesia in PD. The exact mechanisms underlying the observed increase of the H-reflex amplitude are not yet known. The authors suggested that one possibility is that the excitability of the motor neuron pool may be enhanced following PRE.

It should be noted that some of the neural changes discussed in the preceding paragraphs may be affected by factors such as age, sex, the muscle group trained and their interactions (Lemmer, Martel, Hurlbut, & Hurley, 2007; Martel et al., 2006). For instance, following PRE, upper and lower body strength gains are greater in the young than in the elderly (Lemmer et al., 2007). Also, upper body strength gains are greater in men than in women; however, lower body strength gains are not different between men and women (Lemmer et al., 2007).

In summary, PRE can bring about changes throughout the neural axis. Currently, none of the central changes that accompany PRE discussed previously in this section, have been
researched in individuals with PD. Even though improvements in neuromuscular function have been observed in individuals with PD, from a physiological perspective, further research is required to elucidate the central changes that accompany PRE and might mitigate the motor and non-motor symptoms observed in PD.

Brain regions where PRE could alter activity include the motor cortex, the posterior putamen, the internal globus pallidus (GPi), and the subthalamic nucleus (STN) (Figure 2.1). A recent study demonstrated motor cortical changes following exercise in individuals with PD. Fisher and colleagues have shown that cortical hyper-excitability, which is consistently observed in individuals with PD, is reversed following body-weight supported treadmill training (Fisher et al., 2008). Petzinger and colleagues have also shown an increase in the stimulus-evoked dopamine release within the dorsolateral striatum following intensive treadmill training in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) lesioned mice (Petzinger et al., 2007). Because the dorsolateral striatum is engaged to a high degree during fore- and hind-limb movements during treadmill exercise, they attributed the observed striatal plasticity to use-dependent synaptic plasticity.

Similarly, there may also be use-dependent synaptic plasticity in the putamen, the GPi, and the STN following PRE. Our lab has conducted a series of studies in which we have shown that nuclei within the basal ganglia scale with the performance of different force producing tasks in both healthy individuals and those with PD. Specifically, we have shown that both the globus pallidus and the STN increase percent signal change when generating progressively larger forces in healthy subjects (Spraker et al., 2007). We have also shown that individuals with PD have a reduced percent signal change in all nuclei of the basal ganglia during an isometric force production task, even early in the disease process when individuals have not yet been medicated
In addition, activity in the nuclei of the basal ganglia is correlated to the motor section of the Unified Parkinson’s Disease Rating Scale (UPDRS) (Prodoehl, Spraker, Corcos, Comella, & Vaillancourt, 2010). The symptom with the highest correlation with basal ganglia activity is bradykinesia. Thus, if PRE were shown to alter the motor section of the UPDRS and bradykinesia, then it is possible that the neuronal activity of the basal ganglia would also be altered by PRE.

Figure 2.1 illustrates the hypothesized positive effects PRE training might have in individuals with PD by possibly altering activity and connectivity in cortical and sub-cortical regions. It must be noted that the effect of PRE on activity and connectivity in cortical and sub-cortical regions is purely speculative, as there are no in vivo studies that have examined this relationship. As can be clearly seen from the figure the basal ganglia are strategically positioned to influence cortical output and modulate control of movement and force. As such, we suggest that one potential reason for why PRE training could be therapeutically beneficial for individuals with PD is that it may alter activity in the cortex and the basal ganglia, and connectivity between and within these regions. Advances in experimental techniques, such as TMS, EEG, fMRI, positron emission tomography (PET), diffusion tensor imaging (DTI), and EMG and reflex analyses, afford the possibility of testing hypotheses related to the effect of PRE on neural activity, neural connectivity, and structural integrity in vivo, in humans. Figure 2.1 lists the outcomes and the tools that can be used to empirically determine the effects of PRE in specific brain regions. To elaborate, changes in cortical excitability can be measured using TMS, while changes in cortical activity and intra cortical connectivity can be measured using EEG. Functional MRI can be used to identify blood oxygenation level dependant signal changes in cortical and sub cortical regions following PRE. PET can be used to investigate the effect of PRE
on dopamine synthesis, transport, and usage. DTI can help elucidate hypotheses related to the changes in structure in cortical and sub-cortical regions, namely the substantia nigra, the STN, and the thalamus. Reflex and EMG analyses can be used to identify reflex changes, such as change in H-reflex amplitude, and changes in EMG activation patterns to infer central changes following PRE. Prior to embarking on empirical verification of some of the ideas presented in this paragraph, researchers are cautioned on the technical difficulties, limitations, and the complications of the above-mentioned methods (for a recent detailed review see Carroll et al. (Carroll, Selvanayagam, Riek, & Semmler, 2011)).

In conclusion, the rationale for PRE is four-fold. First, as discussed above, individuals with PD exhibit muscle weakness. PRE can significantly increase the torque- and power-generating capacity of the muscle, thus directly affecting muscle weakness. Even though other forms of exercise such as aerobic exercise provide substantial benefits, they do not improve muscle strength by design. Improvements in muscle strength and power have significant impact on bradykinesia (Dibble et al., 2009) and could also facilitate independence in the community, improve functional mobility, and may reduce the risk of falls (Allen, Sherrington, Canning, & Fong, 2010). Second, exercise interventions in general have been shown to enhance cortical activity, possibly beneficially altering variability, intensity, and frequency components of the corticospinal activation of the muscle (Carroll et al., 2001; Carroll et al., 2002; Falvo et al., 2008; Falvo et al., 2010). This could significantly impact bradykinesia (Fisher et al., 2008). Third, exercise may slow down the rate at which the UPDRS scores increase. The UPDRS is the gold standard for assessing the severity and the progression of symptoms in PD and for evaluating novel therapies. Reuter and colleagues have shown that a 14-week, intense, multimodal exercise training program can bring about ~12 point reduction in the motor UPDRS scores (Reuter,
Engelhardt, Stecker, & Baas, 1999). Additionally, physical activity has been associated with increasing the survival rate of individuals with PD (Kuroda, Tatara, Takatorige, & Shinsho, 1992). Finally, there may well be additional benefits for the non-motor symptoms of PD, such as executive function, mood, and quality of life.

2.3. **PROGRESSIVE RESISTANCE EXERCISE IN PD**

Rehabilitation research studies in individuals with PD demonstrate that PRE can have a positive effect on muscle size (Dibble et al., 2006), muscle strength (Dibble et al., 2006; Dibble et al., 2009; Hass, Collins, & Juncos, 2007; Hirsch et al., 2003; Schilling et al., 2010), muscular endurance (Hass et al., 2007; Scandalis et al., 2001) and neuromuscular function (Dibble et al., 2006; Dibble et al., 2009; Hass et al., 2007; Hirsch et al., 2003; Scandalis et al., 2001). To date, only one study (Dibble et al., 2006) has quantified changes in muscle size in individuals with PD. Dibble and colleagues observed a 6% increase in muscle volume, measured using volumetric magnetic resonance imaging, after a 12-week eccentric PRE program (Dibble et al., 2006). Eccentric PRE training involves the use of eccentric muscle activity, i.e., the active lengthening of muscles when an external load is imposed; consequently, work is done on the muscle (Lindstedt, LaStayo, & Reich, 2001). The rationale for Dibble and colleagues using eccentric PRE is that for the same amount of work (i.e., force x distance), high levels of force are generated with minimal oxygen consumption (Bigland-Ritchie & Woods, 1976).

With regard to muscle strength, several studies have demonstrated significant gains in muscle strength following PRE in PD (Dibble et al., 2006; Dibble et al., 2009; Hass et al., 2007; Hirsch et al., 2003; Schilling et al., 2010). For instance, improvements in strength were observed by Hirsch and colleagues in a randomized controlled trial that compared a 10-week balance training protocol to a 10-week balance training plus PRE protocol (Hirsch et al., 2003). At the
end of 10 weeks, they observed significant improvements in strength in knee extension, knee flexion, and ankle plantar flexion in the balance plus PRE group. When the strength measures were combined across the knee and ankle, they observed a 52% increase in strength from pre to post treatment in the balance plus PRE group. In another randomized placebo controlled trial, Hass and colleagues, demonstrated significant gains in strength and endurance in upper body muscles, following a 12-week PRE program supplemented with creatine monohydrate (Hass et al., 2007). Improvement in endurance was observed by Scandalis and colleagues following an 8-week PRE program that was geared toward the lower body (Scandalis et al., 2001). They found improvements in the total number of abdominal crunches that could be performed at one time. They also observed improvements in lower limb performance, which was quantified as a product of repetitions and weight. Next, we will review the evidence that supports positive changes in neuromuscular function that accompany strength gains following PRE in PD.

From a rehabilitation perspective, it is critical that strength gains bring about corresponding improvements in neuromuscular function, such as gait, stair climbing, timed-up-and-go, and postural stability. To this end, recent studies have shown significant improvement in neuromuscular function following PRE interventions in PD. First, improvements in gait have been reported. Three dimensional gait analyses following an 8-week PRE program demonstrated that individuals with PD increased their gait velocity, stride length, and head angle relative to the floor during midstride (Scandalis et al., 2001). Similar findings of increased gait velocity were also reported by Dibble and colleagues following a 12-week eccentric PRE intervention (Dibble et al., 2006; Dibble et al., 2009). The functional gait outcomes included the six-minute-walk, ten-meter-walk, timed-up-and-go, and stair ascent and descent times. They observed that individuals with PD significantly improved gait velocity and increased the distance walked in six-minutes,
reduced the time taken to walk ten meters, reduced the time taken to complete the timed-up-and-go, and reduced stair descent times. Their findings led them to conclude that progressive resistance eccentric exercise could significantly impact bradykinesia. Second, improvement in postural stability has been reported. Hirsch and colleagues showed that individuals with PD demonstrated an improved ability to maintain balance during destabilizing conditions following a 10-week balance plus PRE intervention (Hirsch et al., 2003). Third, improvement in patient-perceived quality of life has been reported. Even though quality of life is not a direct measure of neuromuscular function, it is reasonable to assume that improved neuromuscular function might contribute to improved quality of life. Dibble and colleagues found that eccentric, PRE significantly improved patient-perceived quality of life as measured by the Parkinson’s Disease Questionnaire (PDQ-39) (Dibble et al., 2009).

In summary, PRE can significantly improve muscle size, muscle strength, muscle endurance, and neuromuscular function, and can significantly impact areas often reported to be problematic in individuals with PD, such as bradykinesia, postural instability, and patient-perceived quality of life.

2.4. LIMITATIONS OF CURRENT RESEARCH AND RECOMMENDATIONS FOR FUTURE RESEARCH

The few studies that have examined the effect of PRE in PD are no doubt vital to our continued understanding of the effect of PRE, and the pursuit of adjunct treatments for PD; however, they are not without limitations. First, it is not clear how anti-Parkinsonian medications interact with PRE. To ascertain the unique contribution of PRE on strength and functional outcomes in PD, it is essential to examine individuals while off anti-Parkinsonian medications. Also, if changes to the underlying disease process are to be evaluated, this is best done while off
medication. Among the studies reviewed, all except for Scandalis et al. (2001) tested individuals with PD while on medication. Thus, more research is required to investigate the unique effect of PRE on outcomes of strength, neuromuscular function, and the underlying disease process.

Second, the motor UPDRS, which is the gold standard of assessing severity of motor deficits in PD, has rarely been used as an outcome measure while evaluating the effects of PRE. In order to convince neurologists who manage individuals with PD to prescribe exercise as an adjunct therapy, it is vital to demonstrate clinically important change on the motor UPDRS as a result of PRE. Minimal clinically important change on the motor UPDRS is based on the effect of anti-Parkinsonian medication and is defined as a 5-point reduction on the motor UPDRS score (Schrag, Sampaio, Counsell, & Poewe, 2006). The scores on the motor UPDRS range from 0 to 108 and higher scores indicate more severe motor symptoms. Thus, if exercise can bring about at least a 5-point reduction in the motor UPDRS, one can make a compelling case to include PRE as an adjunct to the standard management of PD. Future research should include the motor UPDRS as an outcome measure while evaluating the effects of PRE. To date, Dibble et al. (2009) and Hass et al. (2007) have used the motor UPDRS as an outcome measure, however, they both failed to show any clinically relevant change following PRE. This could have been due to the fact that these studies tested individuals with PD while on medication and/or due to the short duration of the PRE intervention.

Third, long-term effects of PRE are yet to be determined. All of the studies conducted to date evaluate the effect of PRE over 8 to 24 weeks. Given that PD is a progressive neurodegenerative disorder and is further affected by the process of aging, which is accompanied by decline in strength and neuromuscular function (Jankovic & Kapadia, 2001), it is vital that the long-term effects of PRE are thoroughly understood. For instance, continued benefit of PRE over
the long-term could reduce the rate at which the disease progresses. This is significant, especially because recent exciting epidemiological research has concluded that moderate to vigorous levels of physical activity in mid or later life may be associated with a 40% reduction in the future risk of being diagnosed with PD (Xu et al., 2010). Additionally, PRE over the long term could reduce the rate at which dosage of medication is increased and possibly delay the onset of dyskinesias, as well as surgical interventions. Thus, it is essential that future studies evaluate the effects of PRE over the long-term in PD.

Fourth, even though it is accepted that cognitive impairment is frequently observed in PD (R. G. Brown & Marsden, 1990; Cooper et al., 1991; Lees & Smith, 1983; Owen, 2004; Sawamoto et al., 2007; Taylor et al., 1986), the effect of PRE on cognitive function in PD is not well researched. The rationale for PRE as a therapeutic intervention for cognitive dysfunction is threefold. First, PRE has been found to improve cognitive function in healthy subjects between the age of 65 and 75. Cassilhas et al. (2007) demonstrated improved performance on measures of working memory and attention for those assigned to 24 weeks of PRE. More recently, Liu-Ambrose and colleagues (2010) demonstrated beneficial cognitive effects of 52 weeks of PRE in community dwelling elderly women. They showed improvements in attention and conflict resolution. Additionally, in a subsequent study with the same sample, they demonstrated changes in percent signal change in brain areas that correspond to conflict resolution (Liu-Ambrose et al., 2011). Second, even though aerobic training provides cognitive benefits, a combination of aerobic and PRE has been evidenced to render the greatest cognitive benefits (Colcombe & Kramer, 2003). Recently, two studies have evaluated the combined effect of PRE and aerobic exercise on executive function in PD (Cruise et al., 2011; Tanaka et al., 2009). Both studies concluded that PRE combined with aerobic exercise improved executive function. Third, there is
a strong biological basis for the cognitive benefits gained from PRE. These include the reduction in serum levels of homocysteine (Vincent, Braith, Bottiglieri, Vincent, & Lowenthal, 2003) and the increase in serum levels of insulin like growth factor I (Borst et al., 2001), following PRE, which are both known to be associated with cognitive function (Garcia-Segura, Arevalo, & Azcoitia, 2010; Seshadri et al., 2002). Thus, there is evidence in the literature to support the beneficial effects of PRE on cognitive function and future research should address this in PD.

Fifth, the diverse experimental designs employed in the studies reviewed may be less than ideal. Given the realities of conducting research with a patient population, the studies reviewed provide an excellent basis for large scale, long-term prospective randomized clinical trials. However, the small sample sizes used (between 6-14 per group, with a total sample size not exceeding 20), the lack of rater blinding (only Hass et al. (2007) was a randomized, double-blinded, placebo-control trial; while Hirsh et al. (2003) was a randomized control trial, the raters were unblinded), and not employing the intent-to-treat principle in statistical analysis lead to biases that could question the validity of some of the conclusions. Thus, future studies should be blinded, randomized clinical trials, which will provide the most robust experimental design to address the gaps in the literature by assessing the short and long-term effects of PRE in individuals with PD.

Sixth, the optimal PRE prescription for individuals with PD is yet to be established. There are two aspects of treatment optimization. The first aspect is the optimization of PRE parameters, such as the frequency, the intensity, the duration, and the mode of exercise (i.e., strength and power training). The second aspect is the optimization of PRE with regards to the various clinical sub-types of PD. Within the general diagnosis of PD, distinct clinical sub-types have been identified based in part on the age of onset, the predominant motor sign (e.g. tremor
dominant, non-tremor dominant akinetic-rigid etc.), and the clinical course of the disease (Jellinger & Paulus, 1992). There is evidence in the literature that suggests that these different PD sub-types may respond differently to interventions and may progress at different rates (Rajput, Pahwa, Pahwa, & Rajput, 1993; Ransmayr et al., 1986; Zetusky, Jankovic, & Pirozzolo, 1985). For example, individuals who begin with significant rest tremor may not respond as well to levodopa and may progress at a slower rate compared to individuals who present with a non-tremor dominant, akinetic-rigid form of the disease. It is likely that the effect of PRE may vary with the clinical sub-type of PD. In addition, the effect of PRE on tremor and rigidity is not yet known. Thus, future research should identify the optimal PRE prescription in the context of the different clinical sub-types of individuals with PD and empirically verify hypotheses related to tremor and rigidity as well.

2.5. CONCLUSION

In PD, bradykinesia and muscle weakness are primarily due to nigral dopaminergic deficits that alter corticospinal activation. Given the wide array of neural changes that accompany PRE that we have summarized in this review, the potential to slow the rate of the progression of the symptoms of PD, the improvement in strength and function, and the positive effects on non-motor symptoms of PD, there is a strong rationale for the use of PRE as an adjunct treatment in PD.
Figure 2.1. Hypothesized central effects progressive resistance exercise training might have in the cortex, basal ganglia, and spinal cord and the tools that can be used to examine these hypothesized changes. TMS, Transcranial Magnetic Stimulation; EEG, Electroencephalography; fMRI, functional Magnetic Resonance Imaging; PET, Positron Emission Tomography; DTI, Diffusion Tensor Imaging; EMG, Electromyography; SNC, Substantia Nigra Pars Compacta; GPe, External Globus Pallidus; GPi, Internal Globus Pallidus; STN, Subthalamic Nucleus.
3. PAPER 2

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3.1. INTRODUCTION

Humans routinely make fast and slow movements when reaching for an object or when moving various objects. The object’s inertia is never known exactly and has to be guessed or estimated based on previous experience. A wrong estimation or guess, as well as when the limb encounters external disturbances, may lead to errors in movement that can be minimized by the intrinsic damping and muscle elasticity, and can be actively corrected using proprioceptive feedback. While the mechanical feedback due to the intrinsic muscle properties is virtually instantaneous (Partridge, 1966; Partridge, 1967), the neural feedback based on proprioception is associated with conduction and processing delays that may lead to instability (Prochazka & Trend, 1988; Rack, 1981).

Neural pathways that mediate proprioceptive feedback include spinal pathways with a loop delay of less than 50 ms and supra-spinal pathways with a loop delay of greater than 50 ms (Hammond, 1956; Lee & Tatton, 1975; Lewis, Polych, & Byblow, 2004). The way in which these proprioceptive pathways are utilized during movement remains unclear. One possibility is that the motor system uses all proprioceptive signals for continuous feedback control throughout the movement duration. However, the analysis of the responses in muscle surface electromyograms (EMGs) to unexpected perturbations or changes in load during point-to-point elbow flexion movements indicates that proprioceptive feedback control is suppressed in the beginning of the movement (S. H. Brown & Cooke, 1981; Gottlieb & Agarwal, 1980; Hallett &
Marsden, 1979; Hayashi, Becker, & Lee, 1990; Shapiro, Gottlieb, Moore, & Corcos, 2002; Shapiro, Gottlieb, & Corcos, 2004).

Shapiro et al. (2004) manipulated movement duration by instructing the subjects to move “as fast as possible” over a short or long distance against a light or heavy inertial load. In random trials, a viscous load was unexpectedly applied. It was found that the EMG response to unexpected changes in load was delayed in movements with longer expected duration and the response time was correlated with the expected time to peak velocity. They suggested that proprioceptive feedback control is centrally suppressed at the beginning of the movement, and the duration of initial suppression is determined by the expected time course of movement kinematics. Note that in inertial loaded movements the time to peak velocity is correlated with the time to peak acceleration which is in turn coincides with time of peak inertial torque. It was later found in an experiment that included inertial and viscous loaded movements that the duration of initial feedback suppression had a higher correlation with the expected time of peak inertial torque than the time of peak acceleration or velocity (Shapiro, Niu, Poon, David, & Corcos, 2009). In all conditions, the duration of initial feedback suppression increased in longer movements.

The duration of a movement can be prolonged by increasing movement distance, external load, or by instructing the subjects to make slower movements (Corcos, Gottlieb, & Agarwal, 1989; Hoffman & Strick, 1986a; Mustard & Lee, 1987). In the previous experiments by Shapiro and colleagues the subjects were asked to move either with maximal speed (Shapiro et al. 2004) or with a comfortable speed (Shapiro et al. 2009). Each movement task was performed with a single speed instruction, and the movement duration was determined by the task parameters, i.e., distance and load. The hypothesis proposed in these previous studies was that the duration of the
initial suppression of proprioceptive feedback depends on the timing parameters of the movement. However, these previous results cannot be generalized to conditions when an individual intentionally makes movements of different speeds over the same distance against the same load. In the current experiment we sought to directly test the idea that the intended movement speed affects the duration of initial suppression of proprioceptive feedback control.

The feedback activity was tested by unexpectedly altering the movement kinematics in a small subset of randomly chosen trials. It has been observed in previous experiments that an unexpected change in a dynamic load produces kinematic deviations that vary across subjects and across movement conditions (Gottlieb, 1996; Shapiro et al., 2002; Shapiro et al., 2004). This was due to subject specific differences in arm inertia, apparent visco-elastic properties of the muscles that scale with muscle activation (Gasser & Hill, 1924), and because of inherent variability of the neural responses to perturbations. Since the feedback response depends on both the kinematic deviation and feedback gains, it is desirable to apply similar kinematic deviations in order to test the effect of movement task on the feedback gains. We used a servo-controlled motor to control the onset and magnitude of the kinematic deviation across the subjects and across the conditions. We instructed the subjects to make movements either with maximal speed or with 70% of maximal speed. Our experimental protocol included inertial loaded movements, so the time of peak torque coincided with the peak acceleration and was delayed in slower movements. If the duration of initial suppression of proprioceptive feedback is determined by the time parameters of the expected movement, then the initial feedback suppression should be prolonged in slower movements. This prediction was tested by unexpectedly changing the movement kinematics within the first 100 ms from the onset of the agonist muscle EMG and analyzing the time of the EMG responses in the agonist and antagonist muscles. Specifically, we
predicted that the EMG responses to the unexpected perturbation will appear later in movements made under the instruction “move with 70% of maximal speed” than in movements made with maximal speed.

3.2. METHODS

3.2.1. SUBJECTS

Eleven neurologically normal volunteers (six males and five females, aged 19–44 years) participated in the study. All subjects gave informed consent according to a University approved protocol.

3.2.2. APPARATUS

The apparatus was a manipulandum which consisted of a metal bar with a handle (combined moment of inertia 0.14 kg m$^2$), freely rotating in a horizontal plane around a pivot centered at the elbow joint. The seated subject abducted the shoulder 90° and rested the forearm on the bar with the elbow joint aligned with the pivot. A computer monitor in front of the subject showed markers indicating the initial and target positions and a cursor indicating the current joint angle. The pivot was attached to a shaft of a torque motor (JR25 ServoDisk, Kollmorgen). The torque motor was used to perturb the movement in a small subset of trials. The torque applied by the motor was measured by a torque transducer positioned between the bar axis and motor shaft. Joint angle and acceleration signals were measured by the angle transducer and accelerometer; the velocity signal was obtained from the angle signal using an analog differentiating circuit. All mechanical signals were low-pass filtered using an analog third-order Bessel filter with a 60 Hz cutoff frequency. Surface EMGs in biceps, brachioradialis, triceps lateralis, and triceps longus were recorded using Delsys electrodes (gain 1,000, 20–450 Hz built-in analog band-pass filter, Bagnoli EMG system, Boston, MA). All data were digitized at 1,000 samples/s (National
Instruments). The mechanical channels were digitally low-pass filtered with a two-way second-order Butterworth filter with 20 Hz cutoff frequency, the EMG signals were digitally full-wave rectified and then low-pass filtered with the two-way second-order Butterworth filter with 50 Hz cutoff frequency.

3.2.3. EXPERIMENTAL PROTOCOL

Subjects were asked to align the cursor with an initial position marker, wait for a GO beep, make an elbow flexion movement to the target, remain at the target until the END beep, and return to the initial position. Only the movements from the initial position to the target were recorded and analyzed.

Previous research has shown that the movement time and time to peak velocity increase with movement distance and/or load (Gottlieb, Corcos, & Agarwal, 1989; Hoffman & Strick, 1986b; Mustard & Lee, 1987; Pfann, Hoffman, Gottlieb, Strick, & Corcos, 1998). Therefore, we manipulated the movement duration by varying both the instruction on movement speed and changing the movement distance and load. Movement speed was either maximal or 70% of maximal speed. We will refer to a combination of movement distance and load as “extent”, the term that was introduced by Gottlieb (1993). The low extent task was a 30° distance without an additional load, so in the low-extent condition the inertia was 0.14 kg m² of the manipulandum bar. The high-extent task was a 50° distance with an additional inertial load of 0.12 kg m² attached to the manipulandum bar, so the combined inertia was 0.26 kg m². The two independent variables, speed and extent, were combined to produce four movement conditions: (1) max speed, low extent, (2) 70% max speed, low extent, (3) max speed, high extent, and (4) 70% max speed, high extent. In all movement conditions, the subject received feedback on peak velocity
after each trial. This was done to help the subject maintain the desired movement speed in each condition.

Prior to collecting data, maximal speed was established for each extent by asking the subject to perform 20 practice trials “as fast as possible”. The peak velocity in each trial was determined, and the average peak velocity from the last ten practice trials was calculated. In the maximal-speed conditions (1 and 3), the subject made a test series of 50 movements after the first series of practice trials. In the 70% maximal speed conditions (2 and 4), the averaged peak velocity in the first series of practice trials was used to determine the desired movement speed. The subject made a second series of practice movements at 70% of maximal peak velocity. Next, the subject made a test series of 50 movements at 70% of maximal peak velocity. In all conditions, a perturbation was applied in ten trials chosen pseudorandomly out of the 50 trials in the test series. The order of extent was counterbalanced between subjects and the order of speed was randomized within extent.

The target was 6° wide, movement accuracy was not stressed. We were interested in the proprioceptive feedback during movement against known loads when perturbations are not expected; therefore, we instructed the subjects to make one smooth movement and not to correct the final position if they missed the target. In the first ten practice trials in each condition, the cursor that indicated the joint angle was shown during movement. In the remaining practice trials, as well as during the subsequent series of 50 movements, the cursor was extinguished when the velocity exceeded 20°/s at the beginning of movement and reappeared when the velocity fell below 20°/s at the end of movement. Thus, the computer screen did not provide visual feedback during movement but showed the final position at the end of each trial.
3.2.4. SERVO CONTROL OF KINEMATIC DEVIATION

We tested the activity of proprioceptive feedback by unexpectedly perturbing the movement. A servo-controlled torque motor was used to apply a velocity deviation of a desired magnitude and duration. This method required computing a set of reference velocity trajectories prior to the experiment.

In preparation for this study we had collected data in movements over 30° and 50° distances made with different speeds. The peak velocities ranged from 150°/s to 550°/s, in increments of 25°/s. For each peak velocity, we averaged 25 trials and obtained a velocity time profile of the unperturbed movement. Thus, we created a set of velocity time profiles that covered a range of possible unperturbed movements that can be made by the subjects during the experiment. Next, we calculated a set of reference velocities that were used to servo control the motor in order to perturb the movement. A desired velocity deviation, 50°/s for condition (2) and 100°/s for conditions (1, 3, 4), was subtracted from the first 200 ms of each averaged unperturbed velocity time profile. Thus, we created a set of reference velocity time profiles that could be used to apply similar velocity deviations in movements made with a range of peak velocities. Figure 3.1 illustrates one such unperturbed averaged velocity profile with corresponding reference velocity and velocity deviation.

Each reference velocity was slower than the corresponding unperturbed velocity for at least the first 200 ms from the beginning of the movement. We chose to subtract 50°/s from the unperturbed velocity in condition (2) because the overall velocity in this condition was low and subtracting 100°/s would effectively block the movement. Also, since the unperturbed velocity vel(t) was less than 50°/s at the beginning of the movement, subtracting 50°/s would produce an initial negative reference velocity. We found in a pilot study that this reference velocity signal
resulted in an excessively large torque that the motor produced in order to impose an initial perturbation into the extension which is opposite to the intended flexion movement. In order to avoid a large initial torque spike, the reference velocity was made non-negative in all conditions $\text{vel.ref} = \max[0, \text{vel.ref}(t)]$. We directly controlled the onset, duration, and magnitude of the velocity deviation from the unperturbed trajectories. The perturbation was triggered early in the movement when the velocity reached $6^\circ/s$. This occurred at less than 100 ms after the biceps EMG onset across all conditions. It should be noted that the servo control of the perturbed movement was maintained for the entire duration of the movement. The servo-control of a pre-computed reference trajectory allowed us to reduce the variability of perturbed trial. This reduction in variability can be seen in Figure 3.2 in which we compare the trajectory variability of a servo perturbation with that of a torque pulse perturbation. The motor was turned off during the unperturbed movements.

In order to prevent adaptation to the perturbation (Weeks, Aubert, Feldman, & Levin, 1996), a pseudo-random sequence of perturbed trials in each condition was generated such as to have at least two unperturbed trials follow each perturbed trial. The subject made 50 trials in each condition, of which ten randomly chosen trials were perturbed. A new pseudorandom sequence was computer generated for each test series of 50 movements.

3.2.5. DATA ANALYSIS

All ten perturbed trials were accepted for further analysis. Of the 40 unperturbed trials, we rejected between 10 and 15 trials in which the peak velocity deviated by more than $25^\circ/s$ from the mean peak velocity or missed the target by more than $5^\circ$. Most of these excluded trials immediately followed the perturbed trials. This was expected since the control of the impending movement is most affected by the last movement conditions (Scheidt, Dingwell, & Mussa-Ivaldi,
Therefore, 24 to 30 unperturbed trials were accepted for further analysis. The data were aligned on the biceps (agonist) EMG onset. The onset of the biceps EMG was determined as the time when the biceps EMG exceeded three standard deviations above the baseline EMG. This point was set as the point of alignment \((t = 0)\). The aligned EMG signals for the unperturbed and perturbed trials were compared in order to determine the time of EMG response.

Because of the high variability of the EMG signal, the task of identifying the EMG responses to the unexpected load presents a major methodological problem. We determined the time intervals when the difference between the EMG signals in the movements against the expected and unexpected loads was statistically significant (cf. Fig. 1 in Shapiro et al. 2002). For each muscle, two sets of the EMG values from the trials against the expected and unexpected loads were compared using Satterthwaite’s modified t-test (Armitage & Berry, 1994). The test was repeated for every sample point, for a time interval \(t = 0–0.5\) s to generate a \(p(t)\) time series. The EMGs in movements against the expected and unexpected loads were considered statistically different if the \(p<0.05\) for at least 10 ms. The response latency was calculated as the difference between the time of EMG response and the time of perturbation onset. In the following, the time of the EMG response in all muscles is reported with respect to the biceps EMG onset \((t = 0)\).

Our primary dependent variables included the time of EMG response and the latency of the EMG response. We performed a 2 x 2 repeated measures ANOVA on these dependent variables. The two factors were speed (70% of maximum and maximum) and extent (low and high). Our experimental protocol included inertial loaded movements in which the time of peak acceleration was delayed in slower movements. Therefore, mixed regression modeling was used
to analyze the relation of the time of EMG response (tEMG) and the time of peak acceleration (tPkAcc) in the unperturbed movement (PROC MIXED, SAS version 9.2).

\[ t_{EMG}(i) = \alpha(j) + \beta_i t_{PkAcc}(i) + \varepsilon(i) \]

where \( i = 1, \ldots, 44 \) for four conditions and 11 subjects, \( j = 1, \ldots, 11 \) for each subject. This model included a random subject effect for the intercept.

3.3. RESULTS

First, we had to confirm that the movement condition affected the time parameters of the unperturbed movements. We measured the time to peak acceleration (tPkAcc) and time to peak velocity (tPkVel). The main effect of speed, extent, and the interaction between speed and extent were significant (results of repeated measures ANOVA are given in Table 3.1). The group means indicated that a decrease in the peak velocity to 70% of maximal speed was accompanied by an increase in the time to peak acceleration on average by 17 ms in the low-extent conditions and by 36 ms in the high-extent conditions.

The novel finding in this study is that the planned movement speed affects the time of the EMG responses to unexpected perturbations. In particular, the EMG responses were delayed when movement speed decreased from maximal to 70% of maximal speed. Figure 3.3 shows the data for a representative subject for all four conditions. The perturbation was triggered at the beginning of the movement at 60 ms in condition 1; at 62 ms in condition 2; at 68 ms in condition 3; and at 78 ms in condition 4 (Figure 3.3, small vertical line). The velocity in the perturbed movement became slower than in the unperturbed movement (Figure 3.3, Velocity). The response was an increase in the biceps EMG and decrease in the triceps EMG (Figure 3.3, EMG panels) which occurred more than 100 ms after the perturbation onset. Moreover, the biceps response was delayed by 38 ms in the low-extent and by 14 ms in the high-extent
conditions as the movement speed decreased from maximal to 70% of the maximal speed. These results indicate that the time of the EMG response to unexpected perturbation is affected by the instruction on movement speed.

The effects of movement speed and extent on the time of the EMG response for the biceps brachii and triceps longus muscles across all subjects are shown in Figure 3.4, and the results of repeated measures ANOVA for all four muscles are given in Table 3.1. The responses were delayed with a decrease in intended movement speed and increase in extent. The main effects of speed and extent were significant for the biceps and triceps lateralis. Only the main effect of extent was significant for the brachioradialis and triceps longus. The interaction terms were not significant for all four muscles. It must be noted that although 11 subjects participated in the study, responses were not always observed. We did not observe the response in one condition in the biceps, in three conditions in the brachioradialis, in four conditions in the triceps lateralis, and in four conditions in the triceps longus. These responses were missing in different subjects and different conditions. The earliest agonist response was not always in the biceps. In 5 out of the 11 subjects the earliest agonist response was observed in the brachioradialis. Given the individual differences in responding to an unexpected perturbation, we also analyzed the earliest response in the agonist and antagonist muscles (Table 3.1). The earliest response in the agonist muscles was significantly delayed with a decrease in the intended movement speed and increase in extent (Figure 3.5a). In the antagonist muscles, only the main effect of extent was significant (Figure 3.5a). The interaction between speed and extent was not significant.

We also analyzed the latency of the earliest EMG response measured from the perturbation onset (Figure 3.5b). The latency was not constant across the conditions (main effect of extent $F_{1,10} = 5.96$, $p = 0.035^*$, repeated measures ANOVA). This result rules out the
possibility that the time of the EMG response was determined by the fixed loop delay of a particular feedback pathway that mediated the response.

The mixed regression model analysis showed that $t_{PkAcc}$ was significant predictor of the time of EMG response ($b = 0.58$, $F_{1, 31} = 18.68, p \lt 0.0001^\#$). Since in the present experiment the time of peak torque coincided with the peak acceleration, our result is compatible with a recent finding that the time to peak torque in the unperturbed movement ($t_{PkTrq}$) was the best predictor of the time of EMG response to perturbations (Shapiro et al., 2009). The relation between $t_{PkTrq}$ and time of EMG response in individual subjects is shown in Figure 3.6.

Since the velocity deviations were not identical across experimental conditions, it is possible that the tEMG could be related to a threshold of the velocity deviation. If that were the case, then the velocity deviation traces should reach a threshold at a similar time prior to tEMG. The threshold effect should become evident when the velocity deviations are re-aligned on the respective tEMG, i.e., the deviation traces should all intersect at some point. We plotted the original and re-aligned velocity deviations for one subject (Figure 3.7a, b) as well as the re-aligned data for all subjects (Figure 3.7c). We did not find evidence for a threshold effect.

Next, we considered whether the time of EMG response can be related to the ongoing level of EMG activity, in particular whether a higher level of ongoing muscle activation at the time of response explains the earlier response to the perturbation. We calculated the mean EMG in the interval of 20–40 ms (EMG20) prior to the detected response. A repeated measures ANOVA indicated that the EMG20 was significantly higher in the maximal-speed movements (effect of speed $F_{1, 9} = 7.2, p \lt 0.05$) and in the high-extent movement (effect of extent $F_{1, 9} = 6.3, p \lt 0.05$). On the other hand, an increase in movement speed was associated with an earlier response, while an increase in the extent was associated with a delayed response. Since speed
and extent had the opposite effects on the EMG20 and time of response, we conclude that the ongoing level of muscle activation could not explain the observed effect of the movement condition on the time of response.

3.4. **DISCUSSION**

The main finding in this study was that the EMG responses to unexpected changes in movement kinematics were delayed both in movements in which subjects intentionally slowed their movements as well as when load and distance increased. This result supports the hypothesis that proprioceptive feedback control during point-to-point movement is suppressed during the initial part of the movement for a period of time that is determined by the expected time course of the movement. Unlike previous studies in which the time course of the expected movement was set indirectly by the parameters of movement task, e.g., distance and load (Shapiro et al., 2004; Shapiro et al., 2009), the movement time course in the present experiment was manipulated directly by instructing subjects to move either with maximal speed or slower than maximal speed (Corcos et al., 1989). It has been suggested that movement speed is a global movement parameter that is different from other task parameters, e.g., expected distance (Gottlieb, Corcos, & Agarwal, 1991), and appreciable variability in intended movement speed may be related to activity in premotor cortex during movement planning (Churchland, Santhanam, & Shenoy, 2006). The fact that the duration of the initial suppression of the response to perturbations has been shown to be affected by distance and load does not necessarily imply that it must be also affected by intentional changes in movement speed. Taken together, the results of this study and that of previous studies (Shapiro et al., 2004; Shapiro et al., 2009) can be best explained by a hypothesis that the duration of the feedback suppression is determined by
timing parameters of the expected movement, e.g., expected time of peak joint torque, whether the latter is in turn determined by the planned speed, movement distance, or expected load.

The hypothesis that the expected movement duration determines the initial suppression of the proprioceptive feedback control is based on two observations. First, the EMG responses to a perturbation appeared at the similar times in movements that had similar duration while the movement distance and expected load was different, i.e., long-distance movements against a light inertial load and short-distance movements against a heavy inertial load (Shapiro et al., 2002). Second, the EMG responses were delayed when either the same inertial load was moved over a longer distance or a heavier load was moved over the same distance (Shapiro et al., 2004). This latter observation, however, does not exclude other factors that correlate with the expected movement time, such as the magnitude and duration of the first agonist burst.

The acceleration duration and duration of the first agonist burst are often correlated (S. H. Brown & Cooke, 1984), the burst duration increases with distance (Mustard & Lee, 1987) and both its magnitude and duration increase with the inertial load (Gottlieb et al., 1989). In the present study, the response was always observed after the peak of the agonist burst, and it could be argued that the response did not appear earlier because the agonist activation was at its maximum and could not be further increased. For the same extent, the burst magnitude in the slower movements was lower than in maximal speed movements, so the response would be expected to appear earlier in the slower movements if it was related to the magnitude of the agonist EMG. However, the response appeared later in slower movements. This suggests that the burst magnitude does not determine the time of EMG response. The analysis of the level of muscle activation just prior to the response across the conditions suggested that the time of response was not determined by the ongoing level of EMG which is compatible with the results.
of the previous studies (Johnson, Kipnis, Lee, & Ebner, 1993; Nakazawa, Yamamoto, & Yano, 1997).

Thus, we found no evidence that the time of EMG response to perturbations was determined by the ongoing level of activity of the motoneuron pool. Instead, we suggest that the dependence of the time of the response on the expected task is a manifestation of a central command that includes both the feedforward muscle activation and descending suppression of the proprioceptive feedback control. We can only speculate about the neural substrate that realizes this gain suppression as well as why its time course correlates with the expected movement duration. Kimura and colleagues (Kimura, Haggard, & Gomi, 2006) showed that when subjects expected a force field the reflex gains were modulated depending on the direction of the field, and a TMS applied over the primary motor cortex disrupted the anticipatory gain modulation, but did not abolish the reflex. This clearly demonstrated that the sensorimotor cortex is involved in modulation of proprioceptive feedback gains. Other brain regions are likely to be involved as well. Major cerebellar influence on reflex gain regulation was emphasized by MacKay and Murphy (1979). Further support for the role of the cerebellum in modulating reflex gain comes from studies in which inactivation of the interposed and dentate cerebellar nuclei in cats prevented the animals from adapting on-line corrective responses to an unexpectedly applied elastic load (Shimansky, Wang, Bauer, Bracha, & Bloedel, 2004). The elastic load was applied frequently, in 50% of the trials, and Shimansky and colleagues suggested that cerebellum primes the spinal circuitry at a particular time when the perturbation is likely to be present (Fig. 15 in Shimansky et al., 2004)). This implies that the response itself must be generated by the spinal circuitry which is compatible with our results. Our results suggest, however, that the time course of gain modulation is determined by the expected movement task rather than the time of
perturbation. We found that the EMG response was delayed with an increase in extent and
decrease in speed despite the fact that the perturbation was applied at about the same time early
in the movement. In our experiment, the perturbations were unexpected and infrequent, and our
results should not be generalized to conditions when a perturbation is expected (Bonnard, de
Graaf, & Pailhous, 2004).

In order to use proprioceptive feedback control during movement, the reference
kinematic time profile(s) must be computed by the CNS. This points to the intimate relation
between proprioceptive feedback control during movement and movement planning. It is
possible that the reference kinematic profile(s) are being computed during the planning stage of
movement, possibly in a faster time scale, and this process is not completed by the time of the
movement onset. The internal simulation may take longer for the movement of a longer duration
which will make the feedback control available later in longer movements. Another possibility is
that the CNS simply uses the same sequence of feedforward, feedback, and end-point adjustment
control modes (Sainburg, Ghez, & Kalakanis, 1999) and stretches the duration of each mode
with an increase in the expected movement duration. Proprioceptive feedback control is both
computationally and metabolically expensive and the CNS may have to judiciously choose the
time to facilitate the feedback gains based on the task requirements. Proprioceptive feedback
may also be involved in dynamic modulation of hand stiffness (Kimura et al., 2006; Lacquaniti
& Maioli, 1989; Nichols & Houk, 1976). In this case the feedback gains may be facilitated at the
time of peak torque during movement as was suggested in a previous study (Shapiro et al.,
2009). Further studies are required to identify whether the factors that govern the descending
suppression and subsequent facilitation of the gains of the proprioceptive feedback control
during voluntary movement are related to movement dynamics, movement kinematics, or other specific task requirements.
Table 3.1. Effect of the task on the time of EMG response

<table>
<thead>
<tr>
<th></th>
<th>Speed main effect</th>
<th>Extent main effect</th>
<th>Speed-extent interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>( t_{pk\text{Acc}} )</td>
<td>( F_{1,10} = 60.30 )</td>
<td>( F_{1,10} = 236.06 )</td>
<td>( F_{1,10} = 7.95 )</td>
</tr>
<tr>
<td></td>
<td>( p &lt; 0.001^* )</td>
<td>( p &lt; 0.001^* )</td>
<td>( p = 0.018^* )</td>
</tr>
<tr>
<td>( t_{pk\text{Vel}} )</td>
<td>( F_{1,10} = 114.34 )</td>
<td>( F_{1,10} = 99.60 )</td>
<td>( F_{1,10} = 12.27 )</td>
</tr>
<tr>
<td></td>
<td>( p &lt; 0.001^* )</td>
<td>( p &lt; 0.001^* )</td>
<td>( p = 0.006^* )</td>
</tr>
<tr>
<td>Agonist muscles</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biceps</td>
<td>( F_{1,9} = 5.64 )</td>
<td>( F_{1,9} = 14.16 )</td>
<td>( F_{1,9} = 1.14 )</td>
</tr>
<tr>
<td></td>
<td>( p = 0.042^* )</td>
<td>( p = 0.004^* )</td>
<td>( p = 0.314 )</td>
</tr>
<tr>
<td>Brachioradialis</td>
<td>( F_{1,7} = 0.21 )</td>
<td>( F_{1,7} = 14.66 )</td>
<td>( F_{1,7} = 0.55 )</td>
</tr>
<tr>
<td></td>
<td>( p = 0.660 )</td>
<td>( p = 0.006^* )</td>
<td>( p = 0.481 )</td>
</tr>
<tr>
<td>Earliest agonist</td>
<td>( F_{1,10} = 6.51 )</td>
<td>( F_{1,10} = 21.77 )</td>
<td>( F_{1,10} = 1.34 )</td>
</tr>
<tr>
<td></td>
<td>( p = 0.029^* )</td>
<td>( p &lt; 0.001^* )</td>
<td>( p = 0.274 )</td>
</tr>
<tr>
<td>Antagonist muscles</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triceps lateralis</td>
<td>( F_{1,6} = 12.89 )</td>
<td>( F_{1,6} = 28.00 )</td>
<td>( F_{1,6} = 3.32 )</td>
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<tr>
<td></td>
<td>( p = 0.012^* )</td>
<td>( p = 0.002^* )</td>
<td>( p = 0.12 )</td>
</tr>
<tr>
<td>Triceps longus</td>
<td>( F_{1,6} = 0.90 )</td>
<td>( F_{1,6} = 45.54 )</td>
<td>( F_{1,6} = 0.42 )</td>
</tr>
<tr>
<td></td>
<td>( p = 0.381 )</td>
<td>( p = 0.001^* )</td>
<td>( p = 0.541 )</td>
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<tr>
<td>Earliest antagonist</td>
<td>( F_{1,8} = 4.93 )</td>
<td>( F_{1,8} = 24.99 )</td>
<td>( F_{1,8} = 2.04 )</td>
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<tr>
<td></td>
<td>( p = 0.068 )</td>
<td>( p &lt; 0.001^* )</td>
<td>( p = 0.191 )</td>
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Table 3.2. Regression coefficients for individual subjects

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<th>Subject</th>
<th>Intercept</th>
<th>Slope</th>
<th>$R^2$</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>0.063</td>
<td>0.88</td>
<td>0.18</td>
</tr>
<tr>
<td>2</td>
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Figure 3.1. A reference velocity for servo control of perturbed movement (dashed) was calculated by subtracting 50°/s from the averaged velocity time profile of an unperturbed movement (solid) with a peak velocity of 150°/s recorded prior to the experiment. The ramps in the desired velocity deviation (dotted) before and after the 50°/s plateau were introduced in order to avoid excessive torque spikes at the beginning and end of the velocity deviation.
Figure 3.2. Average velocity profile of the unperturbed (solid) and perturbed (dashed) movements in servo mode and torque pulse mode of delivering the perturbation. The standard deviation of the perturbed velocity (shaded in gray) is also shown. The velocity variability is small in the servo-controlled perturbed movement.
Figure 3.3. The effect of movement speed on the time of EMG response in biceps and triceps lateralis in the four conditions. Averaged data (SD shown in gray) in unperturbed (solid) and perturbed (dashed) are shown. The velocity deviation (dotted) is also shown in the velocity panels. The short vertical lines in all panels indicate the onset of the perturbing torque, the arrows in the EMG panels indicate the time of statistically significant EMG response. Data from one representative subject are shown.
Figure 3.4. The time of EMG response in biceps and triceps lateralis (means, SD error bars)
Figure 3.5. The time of earliest EMG response in the agonist and antagonist muscles (A) and the latency of the earliest EMG response in the agonist and antagonist muscles with respect to perturbation onset (B). Means and SD (error bars) are shown.
Figure 3.6. Relation between the time of response (tEMG) in perturbed movements versus time of peak inertial torque (tPkTrq) in the unperturbed movement. Note that the inertial torque is the product of joint acceleration and the moment of inertia of the limb; thus the time of peak inertial torque coincides with the time of peak acceleration. The equation shown is for the regression line for pooled data (black). The regression lines for individual subjects (gray) are also shown. The coefficients of the regression equations for the individual subjects are given in Table 3.2
Figure 3.7. A The velocity deviations in the four conditions for one subject. The short vertical bars indicate the perturbation onset, the arrows indicate the time of response. B The same velocity deviations as in A realigned on the respective tEMG. Time t = 0 is the point of realignment (vertical gray line). C Data for all eight subjects in the four conditions.
4. PAPER 3

4.1. INTRODUCTION

Bradykinesia, the slowness of a performed movement (Berardelli et al., 2001), is a primary motor symptom of Parkinson’s disease (PD). Bradykinesia is also considered the most functionally debilitating symptom in PD, and is a consistent feature of PD (Hallett & Khoshbin, 1980). Additionally, muscle weakness, the reduction in the amount of force generated by muscle contraction, is observed quite often in individuals with PD (Allen et al., 2009; Bridgewater & Sharpe, 1998; P. Brown et al., 1997; Durmus et al., 2010; Kakinuma et al., 1998; Koller & Kase, 1986; Robichaud et al., 2004; Schilling et al., 2010). Nigral deficits result in a reduction in the excitatory drive to the motor cortex (Lang & Lozano, 1998b) that may disrupt cortical activation of the muscle (DeLong & Wichmann, 2010; DeLong, 1990; T. Wichmann & DeLong, 2003; T. Wichmann & DeLong, 2007), which could contribute to bradykinesia and muscle weakness. Because the muscle is a target of cortical output during movement and force production, EMG analysis of muscle activation patterns can provide insight to the control signal that arrives at the muscle.

In PD, muscle activation patterns during ballistic movements are abnormal (Berardelli et al., 1996; Hallett & Khoshbin, 1980; Pfann et al., 2001). In healthy subjects, ballistic movements exhibit a characteristic triphasic EMG pattern (Hallett, Shahani, & Young, 1975). The first phase is the first agonist burst that accelerates the limb. The amplitude of the first agonist burst scales with movement speed, thus larger amplitudes correspond to faster movement speeds. The second phase is the antagonist burst that decelerates the limb. The third phase is the second agonist burst that clamps the limb at the end of the movement (Hannaford & Stark, 1985). Subjects with PD do not exhibit this
triphasic pattern; instead they exhibit a fractionated bursting pattern (Hallett & Khoshbin, 1980). Specifically, the amplitude and duration of the first agonist burst are reduced, the number of agonist bursts during the acceleration phase of the movement is increased, and the amplitude of the antagonist burst is reduced (Pfann et al., 2001; Teasdale, Phillips, & Stelmach, 1990).

Treatments aimed at modifying basal ganglia output such as anti-Parkinsonian medication and deep brain stimulation of the subthalamic nucleus favorably alters muscle activation patterns and increases first agonist EMG magnitude and duration, reduces the number of first agonist bursts during the acceleration phase of movement, increases antagonist magnitude, and brings about improvement in bradykinesia (Vaillancourt et al., 2004). However, neither medication nor deep brain stimulation of the subthalamic nucleus normalizes the abnormal muscle activation pattern observed in PD. Furthermore, pharmacological treatment is accompanied with side effects, such as, dyskinesias, cognitive decline, confusion, psychosis, hallucinations, and sedative effects, (Lang & Lozano, 1998b; Olanow et al., 2001) that reduce tolerance of such treatment. Similarly, brain surgery poses serious side effects that include adverse events related to the surgical procedure itself, such as intracerebral hemorrhage with persistent neurologic deficit, device related infections and mechanical complications, and stimulation related side effects, such as contra lateral transient facial muscle twitch, speech impairments, and paresthesias (Olanow et al., 2001). Therefore, there is a need for exploring adjunct treatments that could possibly modify basal ganglia output and mitigate bradykinesia.

Recently, progressive resistance exercise (PRE) has been suggested as a therapeutically beneficial adjunct treatment for PD. Over the past decade several studies have
examined the effects of PRE in PD (Falvo et al., 2008). The consensus is that PRE in PD improves muscle size and strength (Dibble et al., 2006). In addition, PRE improves whole body bradykinesia as measured by functional measures, such as gait speed, timed-up-and-go, and the six-minute-walk (Dibble et al., 2006; Hirsch et al., 2003; Scandalis et al., 2001). However, prior research has had the following limitations. First, most of the studies tested subjects with PD while on their anti-Parkinsonian medication (Dibble et al., 2006; Hirsch et al., 2003), and therefore it is not clear the extent to which the benefits of PRE have been masked by the benefits of anti-Parkinsonian medication. Second, most of the previous research examined the effect of 8-24 weeks of PRE; the effect of PRE beyond 24 weeks is yet to be determined. This is of particular importance, especially because PD is a progressive neurodegenerative disease. Reported average rates of clinical progression as assessed by the off medication Unified Parkinson’s Disease Rating Scale, part III, motor subscale (UPDRS-III) varies from 3.5 to 8.9 points per year (Evans et al., 2011). Thus, if PRE is to be used as an adjunct treatment, its therapeutic benefit should be investigated beyond 24 weeks. Third, even though PRE has been shown to improve bradykinesia, the underlying mechanisms that mediate this improvement are yet to be determined.

The primary purpose of this study was to determine the efficacy of a 24-month PRE program compared to a non-progressive exercise program on upper limb bradykinesia while simultaneously addressing some of the limitations of previously conducted research. To this end, the current study was a 24-month prospective, rater-blinded, randomized control trial, with data being collected while patients were off their anti-Parkinsonian medication. A second purpose was to determine the underlying mechanisms that mediate improvement in upper limb bradykinesia following PRE. In previous studies, bringing about changes in
muscle activation patterns in PD due to medication and deep brain surgery have been used as evidence for modifying basal ganglia output. Therefore, in addition to examining movement velocity, we examined muscle activation patterns as well, in order to make inferences about the control signal that arrives at the muscle.

4.2. METHODS

4.2.1. TRIAL DESIGN

The study design was a matched pairs, randomized, controlled, rater blinded, 24-month prospective clinical trial, examining the effect of PRE in subjects with PD. It employed a parallel group design with a 1:1 allocation ratio. A healthy age and gender matched control group was also used to provide normative data; however, they did not participate in any form of exercise. The study commenced in and was completed in June of 2011 with 5 measurement points (baseline, 6, 12, 18, and 24 months).

4.2.2. SUBJECTS

Three groups of subjects were tested. They were: 1) subjects with PD who were assigned to the PRE program, 2) subjects with PD who were assigned to the Fitness Counts (FC) exercise program (R. Wichmann et al., 2002), and 3) an age and sex matched healthy control group who did not participate in either exercise program. Subjects were recruited through the Movement Disorders Center at Rush University Medical Center. Inclusion criteria for subjects with PD were: 1) a diagnosis of PD (Hughes et al., 1992) 2) no other neurological disorder as determined by medical history and neurological exam, 3) no other known injury, disease, or other disorder that might interfere with motor function in the proposed experiments, 4) no medications that might interfere with neuromuscular junction function such as D-penicillamine and aminoglycoside antibiotics, 5) a score greater than 23
on the Mini-Mental State Examination to exclude the role of neuropsychiatric dysfunction in problems with performing the various tasks, and complying with the exercise programs, 6) not actively engaged in a formal exercise program, 7) between the ages of 50 and 67, 8) and not have deep brain stimulation surgery.

The healthy age and sex matched controls were recruited by flyers placed in and around the University of Illinois at Chicago’s campus and by word of mouth. The inclusion criteria for healthy controls were: 1) no neurological disorder as determined by medical history, 2) no known injury, disease, or other disorder that might interfere with function in the proposed experiments, 3) no medications that might interfere with neuromuscular junction function such as D-penicillamine and aminoglycoside antibiotics, 4) a score greater than 23 on the Mini-Mental State Examination to exclude the role of neuropsychiatric dysfunction, 5) and between the ages of 45 and 72 (control subjects were matched ±5 years of the subjects with PD).

Institutional Review Boards for the protection of research subjects of the University of Illinois at Chicago and Rush University Medical Center approved the research protocol. All subjects provided written informed consent.

4.2.3. INTERVENTIONS

Subjects participated in one of two-prescribed exercise programs, PRE or FC, twice a week for two years. One-on-one training, with a certified personal trainer was provided for both exercise programs twice a week during the first six months. This was done to help subjects become comfortable with the training regimen, and because there is documented evidence of greater strength gains when training with a personal trainer (Mazzetti et al., 2000). For the remaining 18 months, one-on-one training was provided once a week and
subjects performed the second session each week on their own. If a subject missed a session, they were instructed to make it up. Thus, at the study end-point of 24 months, a subject who completed the entire 24-month protocol would have attended 208 exercise sessions. In order to maximize compliance we did the following: 1) subjects were supervised (one-on-one training) twice a week for the first six months and then once a week until completion of the study by a personal trainer who was paid for by the study, 2) exercise sessions were held at a gym facility close to the subject’s home which was paid for by the study, 3) exercise sessions were scheduled at the subject’s convenience, 4) subjects were asked to exercise only twice a week, 5) if subjects missed two consecutive sessions, immediate action was taken by the exercise coordinator to resolve any issues, and 6) the exercise coordinator contacted the subjects’ trainer every 2-3 months to check on the subject’s compliance with the protocol.

Both exercise programs had the same warm up and cool down phases that each lasted up to 10 minutes. These exercises included 3 minutes of walking followed by 5 repetitions of the following 5 stretching exercises: 1) neck circles to both directions, 2) trunk rotation while lying down to both directions, 3) arm circles in both directions, 4) hamstring stretches while sitting and 5) ankle stretches while standing. The total duration for each exercise session in both programs was approximately 60-90 minutes. Subjects performed the exercise programs while on their anti-Parkinsonian medication.

*Progressive Resistance Exercise Program*

The PRE program consisted of a general strengthening program targeting all major muscle groups. The following specific exercises were used: 1) Chest press (modified), 2) Latissimus pull downs, 3) Reverse flys, 4) Double leg press, 5) Hip extension, 6) Shoulder press, 7) Biceps curl, 8) Rotary calf (ankle plantar flexion), 9) Triceps extension, 10) Seated
quad and 11) Back extension. Exercise sessions were separated by at least 48 hours (Feigenbaum & Pollock, 1999). Photographs of the exercises are included in the appendix.

At baseline a one-repetition maximum (1RM), i.e., the greatest resistive load that can be moved through the full range of motion in a controlled manner with good posture (American College of Sports Medicine, 2010), was established for the above exercises. Resistance was set at approximately 40-50% of the baseline 1RM (30-40% for upper body exercises; 50-60% for lower body exercises) during the first week of training. As soon as the subject was able to perform a set of the exercises using good form and perceive the exercise to be somewhat easy, the resistance was increased by at least 5% (Feigenbaum & Pollock, 1999) or as allowed by the equipment. Each repetition lasted six to nine seconds. Subjects raised the weight over 2-3 seconds, paused briefly (2-3 seconds), and slowly lowered the weight (3-4 seconds) (Pollock et al., 2000). Subjects performed three sets of 8 repetitions for each exercise starting with just one set and working up to three sets as they progressed. After 8 weeks on the strength program, subjects switched to a power (speed) program. Here the emphasis was on speed with which each repetition was completed. The resistance was set at 70-80% of their 1RM and each subject performed 2 sets of 12 repetitions. Every 8 weeks subjects alternated between the strength and power (speed) training programs and the resistance was set at where they left off for the respective programs.

**Fitness Counts Exercise Program**

The FC exercise program is recommended by the National Parkinson Foundation (R. Wichmann et al., 2002) and was used as a comparative intervention. It consists of low intensity stretching, non-progressive strengthening, breathing, and balance exercises. There are 12 stretching exercises which consist of: neck stretch, chest stretches, rotation stretch,
overhead stretch, hamstring stretch, side stretch, ankle circles, back stretch, shoulder stretch, calf stretch, shoulder circles, and trunk rotation stretch. Except for the ankle and shoulder circles, all other stretching exercises were performed 3 times while holding the stretch for 3-5 breath counts. The 7 strengthening exercises consisted of the following: wall slides, bridging, shoulder blade squeeze (sitting and standing with a resistance tube), quadriceps strengthening, quadraped trunk, and prone on elbows. Three sets of 10 repetitions were performed for all strengthening exercises. There was also a 2 to 3 seconds of rest (or more if needed) between all stretching and strengthening exercises. The last set of exercises, balance exercises consisted of the following two exercises: weight shifts forward and backward 10 to 20 times while standing with feet placed hip width apart and single leg stance on each leg for 5-10 seconds. Photographs of the exercises are included in the appendix.

4.2.4. APPARATUS

Isometric Task

The apparatus used to test maximal voluntary contraction during elbow flexion was a rigid, light-weight manipulandum that was locked in place with the elbow flexed at 90°. The axis of rotation was aligned with the elbow joint. Joint torque was measured by a strain gauge torque transducer mounted on the shaft at the axis of rotation. The subject viewed a computer monitor, which displayed a red cursor that reflected joint torque. A small stationary marker was displayed that corresponded to the initial torque (0 Nm).

Ballistic Movement Task

The apparatus used to test point-to-point ballistic movements was a single degree of freedom manipulandum which consisted of a metal bar with a handle (combined moment of inertia 0.14 kg m²), freely rotating in a horizontal plane around a pivot centered at the elbow
joint. For the right (left) elbow, full extension was defined as 90° (-90°), elbow flexion was in the negative (positive) direction, and the initial position for the experiments was 35° (-35°). The movement amplitude was 72° (-72°), thus the target location was set at 37° (-37°). The width of the target corresponded to 6° of angular elbow movement. Joint angle was measured by a capacitive transducer mounted on a shaft at the axis of rotation. Joint angle was digitally differentiated to generate joint velocity. Joint acceleration was measured by a piezoresistive accelerometer mounted 47.6 cm from the center of rotation. Surface electromyograms (EMG) were recorded from the biceps brachii, brachioradialis, and the lateral and long heads of the triceps brachii. The EMG signals were band pass filtered between 20-450 Hz using built-in Bagnoli filters and then amplified (gain 1,000) (Delsys Inc.). All signals were digitized at 1000 Hz using a 16-bit analogue to digital converter.

4.2.5. EXPERIMENTAL PROTOCOL

Isometric Task

The isometric task measured maximal voluntary contraction (MVC) elbow flexion. Subjects were seated with their arm abducted between 75° and 90°, their elbow flexed at 90°, and their forearm supported by the rigid manipulandum, which was locked at 90° of elbow flexion. Subjects were instructed to bend their elbow and contract their muscles as hard as possible after the “go” beep and to continue until they heard the “end” beep. Subjects were given on-line visual feedback and instructed that contracting their arm moved the red cursor that they viewed on the computer screen. On-line visual feedback was used to help with subject motivation. Three trials were collected for MVC elbow flexion.
Ballistic Movement Task

The ballistic movement task measured peak elbow velocity. Subjects were seated with their arm abducted between 75° and 90° and their forearm supported by the manipulandum. The subjects viewed a computer monitor that displayed the initial position, the target, and a vertical cursor that corresponded to the angular displacement of the elbow. The threshold for visual feedback of the vertical cursor was set at 100°/s, i.e., when the movement velocity exceeded 100°/s, the vertical cursor was extinguished. Thus, the vertical cursor was only visible at the beginning and at the end of the movement. At the start of each trial the subject was asked to line up the vertical cursor with the initial position. When the subject heard a ‘GO’ beep he/she was asked to move the vertical cursor to the target as fast as possible in one smooth movement. Both speed and accuracy were stressed. At the end of the trial, when the subject heard an ‘END’ beep, he/she was asked to return to the initial position. Data was collected only when the subject moved from the initial position to the target. Each subject was given 10-20 practice trials and 30 test trials. Practice trials were not analyzed.

At each time point, MVC elbow flexion and point-to-point movement data were collected from the more affected upper limb when the subjects were off and on anti-Parkinsonian medications. Because a 12-hour withdrawal from anti-Parkinsonian medications is recommended (Langston et al., 1992), off-medication testing always preceded the on-medication testing session. When required, a car service was used to pick them up and drop them off. If travel time from their home to the laboratory was substantial, then subjects were housed in a hotel close to our laboratory. The progression of testing at each evaluation time point was as follows: First, off medication testing was completed. Second, subjects ingested their medication. Third, a 60-90 minute lunch break was taken to provide sufficient
time for the medications to begin having an effect (Robichaud et al., 2002). Fourth, after confirming from the subject that the medication was in effect, the on medication testing was completed. It should be noted that the morning session was always off medication and the post lunch session was always on medication. The healthy group was tested in the morning. This paper only reports the results of the off-medication testing in patients with PD. We chose to test individuals off medication because medication may mask the underlying changes induced by participation in the PRE program along with masking “true” disease progression. Procedural fidelity was maintained between time points by ensuring the following biomechanical configurations were adjusted between subjects to ensure within subject consistency: 1) elbow and shoulder angle were kept constant for each time point, 2) seat height was kept constant.

4.2.6. DATA ANALYSIS

Data processing was performed offline and with the investigator blinded to group allocation. The kinetic and kinematic signals were low pass filtered at 20 Hz (2nd order Butterworth dual pass filter). The EMG signals were full wave rectified and then low pass filtered at 50 Hz.

4.2.7. OUTCOMES

It should be noted that all of the outcomes described below were determined by raters who were blinded to group allocation.

Isometric Task

*MVC Elbow Flexion (Nm)*

The trial with the maximal elbow flexion torque was used to calculate MVC elbow flexion. First, the maximal elbow flexion torque was indentified. Second, elbow flexion
torque 100ms prior to, and 100ms after maximal elbow flexion torque were averaged to calculate MVC elbow flexion.

**Ballistic Movement Task**

The primary outcome variables were determined from the kinematic and EMG signals. The onset and offset of the agonist EMG was critical to the calculation of many of the outcome variables, thus the first step was to determine the onset and offset of the agonist EMG. This was determined by a well trained rater using a semi-automated algorithm. 1) The algorithm identified movement onset. This was accomplished by finding peak acceleration and then searching backwards to locate the first acceleration data sample that fell below 5% of peak acceleration. 2) Due to the well-known electromechanical delay (~30 ms) between EMG and kinematic signals (Corcos, Gottlieb, Latash, Almeida, & Agarwal, 1992), the algorithm searched for the onset of the EMG signal before the onset of acceleration. Each data sample from the EMG during that period was compared with the baseline EMG activity (this was defined as mean EMG activity from -200ms to -100ms prior to acceleration onset). Because of the presence of a 4-7 Hz rest tremor in some of the subjects with PD, a notch filter (4-7 Hz) was employed while estimating mean baseline EMG activity to minimize the effect of rest tremor and obtain a stable baseline. If the EMG data sample was greater than an onset threshold (sum of 5 times the standard deviation of mean baseline EMG and the mean baseline EMG activity) for 30 consecutive samples, this was marked as the onset of the EMG burst. 3) The algorithm searched forward to find when the EMG signal fell below an offset threshold (sum of 6 times the standard deviation of mean baseline EMG and the mean baseline EMG activity) for 3 consecutive samples, this time point was set as the offset of the EMG burst. 4) Steps 2 and 3 were repeated to mark any additional EMG
bursts that occurred before peak velocity. After automated algorithm marking, each trial was visually inspected by a well trained rater to ensure EMG burst marking accuracy and adjustments were made if necessary. Approximately 20% of the trials were visually adjusted. Below are the operational definitions of each of the primary outcome variables.

*Peak Velocity (degrees/second)*

Peak velocity was defined as the maximum of the absolute value of the velocity signal.

*Time to Peak Velocity (milliseconds)*

Time to peak velocity was defined as the time period between the onset of the first EMG burst and the time of peak velocity

*Duration of the First Agonist Burst (milliseconds)*

Duration of the first agonist burst was defined as the time period between the onset and the offset of the first agonist burst.

*Q₁₉₎₁₉, Magnitude of the First Agonist Burst*

Magnitude of the first agonist burst was defined as the integral of the agonist EMG during the first agonist burst. This parameter characterized the size of the first agonist burst which is responsible for initial acceleration of the limb towards the target.

*Q₁₉₅₁₉ / t₁₉₅₁₉, Magnitude of the First Agonist Burst Normalized to Burst Duration*

Magnitude of the first agonist burst was defined as the integral of EMG activity during the first agonist burst divided by the duration of the first agonist burst.
**Q_{30}. Magnitude of the First 30 ms of the Agonist Burst**

Magnitude of the first 30 ms of the agonist burst was defined as the integral of EMG activity during the first 30 ms of the agonist burst. This parameter characterized the initial activation of the agonist EMG.

**Q_{ag}. Magnitude of the Agonist Burst**

Magnitude of the agonist burst was defined as the integral of EMG activity from the onset of the first agonist burst to the time of peak velocity.

**Number of Agonist Bursts**

Number of agonist bursts was defined as the count of the number of agonist bursts that began prior to peak velocity.

**Q_{ant}. Magnitude of the Antagonist Burst**

Magnitude of the antagonist burst was defined as the integral of the antagonist EMG activity from the onset of the first agonist burst to the end of the movement (the time when the absolute value of the deceleration signal dropped below 5% of maximum). This parameter characterized the size of the antagonist burst which is responsible for the limb decelerating as it comes closer to the target.

**Co-contraction during Limb Acceleration**

The degree of co-contraction from movement onset to peak acceleration was calculated according to the algorithm by Winter (1990). This time was chosen as we were only interested in the muscle co-contraction during limb acceleration.

\[
%\text{Cocon} = 2 \cdot \frac{\int \min[EMG_i(t), EMG_j(t)] dt}{\int EMG_i(t) dt + \int EMG_j(t) dt}
\]

Where \( \min \) is the minimum of values at time \( t \).
4.2.8. SAMPLE SIZE

The required sample size was estimated by conducting an a priori power analysis. The healthy control group was not included in our sample size estimations as they did not participate in either exercise programs and were merely used to establish norms. The UPDRS-III, the current “gold standard” to measure symptomatic effects, was used to drive our sample size estimations. Based on our pilot data, the required sample size with 80% power to detect a mean difference of 5 (at \( \alpha = 0.05 \)) with a SD of 5 on the UPDRS-III, and an assumed attrition rate of 30% was estimated to be 25 subjects per group.

4.2.9. RANDOMIZATION

All subjects were tested at baseline off and on anti-Parkinsonian medication. Matched pairs randomization was then performed according to sex and off medication UPDRS-III score to force balanced exercise groups. This was done because males are generally stronger than females and because disease severity affects motor function. Males and females were randomized separately. In each sex stratum, subjects were paired with other subjects with off medication UPDRS-III score within 5 points. One subject in each matched pair of PD subjects was randomly assigned by the statistician to one of the exercise groups. The second subject in the assigned pair was placed in the other exercise group. The first assignments in each pair were generated according to a random-length permuted block design so that the initial assignments would not become unbalanced and so that the assignment sequence would have been difficult to guess (Friedman, Furberg, & DeMets, 1998). Additionally, since we restricted age to 50 – 67 years and were using random assignment to the exercise groups, we expected the age of the exercise groups to be similar. This expected age balance was checked after half the subjects were randomized and was found to be balanced.
4.2.10. INTENTION-TO-TREAT ANALYSIS

We employed the Intent-to-Treat principle for our primary analysis. A priori, a decision was made to replace subjects with PD who might withdraw from the study prior to 6-month testing, if the reasons for dropping out were unrelated to the study and unrelated to the disease. These subjects were to be replaced by a patient who was matched for sex and off medication UPDRS-III score. No subject who withdrew after the 6-month testing was replaced and the intent-to-treat analysis was used for all statistical analyses.

4.2.11. BLINDING

The raters assessing the motor outcomes were blinded to exercise regimen. The blinding was achieved by: 1) only the statistician and exercise study coordinator were aware of group membership, 2) using random-length permuted block design for randomization, which makes guessing assignment sequence difficult (Friedman et al., 1998), and 3) prior to each testing session, study subjects were reminded not to discuss their group membership with the blinded raters. In addition, the subjects were blinded to the specific purpose of the clinical trial and the raters were instructed not to discuss the hypotheses of the clinical trial with the subjects.

4.2.12. STATISTICAL METHODS

All analyses were based on the intention-to-treat principle and missing observations for those subjects who were lost to follow-up were replaced by the last available observation being carried forward. A mixed effects regression model was used to identify the effect of group, the effect of time, and the group by time interaction on our outcome measures. Group was a between-subject variable with two levels: FC and PRE. Time was a within-subject variable. Time was treated as a categorical variable with five levels: baseline, 6, 12, 18, and
24 months. In the event of a significant group by time interaction, we performed planned comparisons that compared the change from baseline scores between groups at each time point. All statistical analyses were performed with the use of SAS software, version 9.1. The statistical tests were all two-sided, and a P value < .05 was used to determine statistical significance. There was no formal correction for the use of multiple comparisons.

4.3. RESULTS

4.3.1. RECRUITMENT

Eligible participants were recruited from September of 2007 to June of 2009. All eligible participants were tested at baseline and randomized, and then tested at 6-month intervals for 2 years. Testing the patients with PD commenced in October of 2007 and concluded in June of 2011.

4.3.2. SUBJECT FLOW

The Consolidated Standards of Reporting Trials (CONSORT) flowchart in Figure 4.1 shows the number of subjects in each intervention arm in each stage of the clinical trial. Initially, a total of 70 subjects with PD were screened for eligibility, 20 of whom were not eligible as they did not meet the inclusion criteria for the study. The remaining 50 subjects completed baseline testing, two of whom withdrew before randomization. One subject had back surgery and one subject did not want to continue in the study in the event he was randomized to the FC group. The remaining 48 subjects were pair randomized i.e., matched on off-medication UPDRS-III and sex to the intervention groups. Twenty-four subjects were allocated to the PRE group and 24 subjects were allocated to the FC group. After randomization, three subjects withdrew and were replaced. One of whom we were unable to contact and did not start exercising, one did not want to continue after 2 sessions due to
personal reasons, and one did not want to come off medication for the 6-month testing. As a result, in addition to the initial 70 subjects, medical charts of another 20 subjects were reviewed and 3 were chosen to be screened for eligibility. These three subjects were specifically identified to match the off-medication UPDRS-III and sex of those who withdrew after randomization. Consequently, their group allocations were predetermined and not randomized. At 6 months, 24 subjects in each group completed testing.

After the 6-month testing, one subject from the FC group passed away, and one subject from the PRE group withdrew as he moved to a different state. Thus, at 12 months, 23 subjects in each intervention group completed testing. After the 12-month testing, two subjects from the FC group withdrew, both of whom underwent deep brain stimulation (DBS) surgery and were no longer eligible to continue in the study, and one subject in the PRE group withdrew as he had medical complications (subject had a fall at home that required long term rehabilitation) that prevented continuation in the study. Thus, at 18 months, 21 subjects in the FC group and 22 subjects in the PRE group completed testing. After the 18-month testing, four subjects from the FC group withdrew, of whom three had medical complications (one was diagnosed with Amyotrophic Lateral Sclerosis, one had complications due to cancer, and one had a bone infection following surgery), and one had DBS surgery. One subject in the PRE group withdrew as she underwent DBS surgery. Thus, at 24 months, 17 subjects in the FC group and 21 in the PRE group completed testing. Given that the intent-to-treat principle and the last observation carried forward principle to replace missing data were used, 48 subjects were included in the final statistical analyses for each of the outcomes. Table 4.1 lists the demographic and clinical characteristics of these 48 subjects
at baseline. As can be seen in Table 4.1 the groups were equivalent at baseline with respect to
demographic and clinical characteristics.

4.3.3. OUTCOMES

Isometric Task

MVC Elbow Flexion

A non-significant effect of group (p = 0.42), a significant effect of time (p < 0.0001),
and a significant group by time interaction (p < 0.0001) were observed. As can be seen in
Figure 4.2(A) and Table 4.2, the FC group gained in isometric MVC elbow flexion by
3.96Nm at the 6-month time point and then began to decline. At the 12-month time point the
FC group returned to baseline levels and then continued to decline below baseline levels at
18 and 24 months (Figure 4.2(A)). At the study end-point of 24 months, the FC group was
4.04Nm below baseline levels. On the other hand, the PRE group was 7.7Nm above baseline
at 6 months and 8.97Nm above baseline levels at the study end-point of 24 months. Planned
comparisons revealed that the gain in MVC elbow flexion relative to baseline shown in
(Figure 4.2(B)) and Table 4.2, was significantly greater in the PRE group compared to the FC
group at 12 months (p = 0.0004), 18 months (p = 0.0001), and at the study end-point of 24
months (p < 0.0001).

Ballistic Movement Task

Figure 4.3(A) shows kinematic and EMG patterns of a 63-year old male patient with
PD randomized to the FC group during a single trial of a 72º flexion movement at baseline, 6
months, and at the study end-point of 24 months. While Figure 4.3(B) depicts the same
information at baseline, 6, and 24 months, for a 59-year old male patient with PD randomized
to the PRE group. Baseline, off medication UPDRS-III scores were 39 and 42 for the patient
in the FC and PRE group, respectively. The first columns in Figure 4.3 (A) and (B) represent data at baseline. At baseline, both subjects presented with comparable peak velocities (~335°/sec), times to peak velocity (~250ms), first agonist burst durations (~100ms), first 30ms of the agonist burst magnitudes (~1.79au), and number of agonist bursts prior to peak velocity (~2). The first agonist burst magnitude was 10.56au for the subject in the FC group and 6.04au for the subject in the PRE group. Except for the first agonist burst magnitude, the individual trial data for these two representative subjects were fairly representative of group averages reported in Table 4.2.

The second columns in Figure 4.3 (A) and (B) represent data at 6 months. At the 6-month time point, relative to baseline peak velocity improved by 71°/sec in the subject in the FC group and by 51°/sec in the subject in the PRE group, times to peak velocity decreased by 25ms in the subject in the FC group and by 38ms in the subject in the PRE group, first agonist burst durations increased by 22ms in the subject in the FC group and by 14ms in the subject in the PRE group, first agonist burst magnitude increased by 4.12au in the subject in the FC group and by 4.8au in the subject in the PRE group, first 30ms of the agonist burst magnitude increased by 1.89au in the subject in the FC group and by 2.56au in the subject in the PRE group, and the number of agonist bursts prior to peak velocity remained at 2 for both subjects. Similar to the group means listed in Table 4.2 both subjects improved on all outcome variables and there are no major differences between these two representative individuals.

The third columns in Figure 4.3 (A) and (B) represent data 24 months after the intervention. At the 24-month time point, relative to baseline peak velocity improved significantly in the subject in the PRE group by 105°/sec compared to the subject in the FC
group who only improved by $74\,^\circ/\text{sec}$. However, the reduction in time to peak velocity relative to baseline remained comparable. The subject in the PRE group reduced by 35ms, while the subject in the FC group reduced by 45ms. The duration of the first agonist burst significantly increased in the subject in the PRE group by 91ms compared to the subject in the FC group who only improved by 31ms. In addition the magnitude of the first agonist burst also significantly increased in the subject in the PRE group (20.4au) compared to the subject in the FC group (4.72au). Consequently the number of agonist bursts prior to peak velocity also differed significantly between the subjects. The subject in the PRE group presented with 1 agonist burst while the subject in the FC group presented with 2 bursts. Thus at the 24-month time point, relative to baseline, the subject in the PRE group presented with significant improvement compared to the subject in the FC group. The differences observed at the individual level paralleled the differences observed at the group level shown in Table 4.2.

Taken together, at 6 months, in these representative subjects, both FC and PRE bring about improvement in peak velocity relative to baseline. Corresponding improvements in EMG activation patterns are also observed at 6 months, namely, duration and magnitude of the first agonist burst. However, at the study end-point of 24 months the PRE group presents with greater change relative to baseline compared to the FC group. These are particularly evident in the peak velocity, duration and magnitude of the first agonist burst, and the number of agonist bursts prior to peak velocity. Next the results at the group level will be presented for each of the kinematic and EMG activation pattern variables.
**Peak Velocity (degrees/second)**

A non-significant effect of group \( (p = 0.75) \), a significant effect of time \( (p < 0.0001) \), and a significant group by time interaction \( (p = 0.02) \) were observed. Figure 4.4(A) and Table 4.2, show that the FC and the PRE groups presented with increase in peak velocity at the 6-month time point. The FC group slightly increased their peak velocity relative to baseline from 69.84°/sec at 6 months to 77.33°/sec at the study end-point (Table 4.2). On the other hand the PRE group almost doubled their peak velocity relative to baseline from 60.63°/sec at 6 months to 107.67°/sec at the study end-point (Table 4.2). Planned comparisons revealed the gain in peak velocity relative to baseline shown in (Figure 4.4(B)), was significantly greater in the PRE group compared to the FC group that at the study end-point of 24 months \( (p = 0.019) \). The FC and the PRE intervention brought about significant gains in peak velocity at 6 months. However, PRE was more efficacious than FC in continuing to improve peak velocity beyond the initial 6-month time point, through the 24-month time point.

**Time to Peak Velocity (milliseconds)**

A non-significant effect of group \( (p = 0.923) \), a significant effect of time \( (p < 0.0001) \), and a non-significant group by time interaction \( (p = 0.99) \) were observed. As can be seen in Figure 4.5(A) and (B), both, the FC and the PRE groups manifested with reductions in times to peak velocity relative to baseline from 6 through 24 months. Looking at Figure 4.5(A) and (B) and Table 4.2, it is clear that there were no difference in time to peak velocity, nor were there differences in time to peak velocity relative to baseline between the FC and PRE groups.

At the study end-point of 24 months, the time to peak velocity was similar between groups (Figure 4.5(B) and Table 4.2), but the peak velocity was significantly greater in the
PRE group compared to the FC group (Figure 4.4(B) Table 4.2). This suggests that the PRE group had a greater rate of velocity, i.e., acceleration, than the FC group. In inertially loaded movements, as was the case in movements performed in this study, acceleration is proportional to torque, therefore, the amount of torque generated in the PRE group had to be greater than the FC group. This is suggestive of the ability of PRE to improve torque production during dynamic conditions and contribute towards improving movement speed.

*Duration of the First Agonist Burst (milliseconds)*

A non-significant effect of group (\(p = 0.56\)), a significant effect of time (\(p = 0.005\)), and a significant group by time interaction (\(p = 0.03\)) were observed. As can be seen in Figure 4.6(A) and Table 4.2, the FC and the PRE groups presented with similar increase in the duration of the first agonist burst at the 6- and 12-month time point. However, at the 18- and 24-month time point the FC group started to head towards baseline levels, while the PRE group increased their first agonist burst duration at the 18-month time point and presented with a slight decrease at the 24-month time point. At the study end-point the FC group presented with a 20.99ms increase, while the PRE presented with a 61.66ms increase in the duration of the first agonist burst relative to baseline. Planned comparisons revealed that the increase in first agonist burst duration relative to baseline as shown in Figure 4.6(B) and Table 4.2, was significantly greater in the PRE group compared to the FC group at 18 months (\(p = 0.048\)), and at the study end-point of 24 months (\(p = 0.014\)). Additionally, at the study end-point of 24 months, the first agonist burst duration in the FC group trended towards baseline levels and was not significantly different from baseline (\(p = 0.12\)). PRE was more efficacious than FC in increasing the first agonist burst duration. While FC was able to bring about increase in first agonist burst duration, FC was unable to maintain or increase the first
agonist burst duration beyond the 12-month time point. On the other hand, despite disease progression, PRE was able to increase first agonist burst duration and maintain this increase beyond 12 months.

\( Q_{ag1}, \text{Magnitude of the First Agonist Burst} \)

A non-significant effect of group (p = 0.14), a significant effect of time (p = 0.003), and a significant group by time interaction (p = 0.002) were observed. As can be seen in Figure 4.7(A) and Table 4.2, the FC and the PRE groups presented with increases in \( Q_{ag1} \) at the 6- and 12-month time point. However at the 18- and 24-month time point the FC group started to head towards baseline levels. At the study end point the FC group was only 3.33au greater than baseline. On the other hand the PRE group maintained their initial increase in \( Q_{ag1} \) and was 12.12au greater than baseline at the study end-point. Planned comparisons revealed that the increase in \( Q_{ag1} \) relative to baseline as shown in Figure 4.7(B), was significantly greater for the PRE group compared to the FC group at 18 months (p = 0.014), and at the study end-point of 24 months (p = 0.001). Additionally, at the study end-point of 24 months, \( Q_{ag1} \) in the FC group trended towards baseline levels and was not significantly different from baseline (p = 0.12). PRE was more efficacious than FC in increasing \( Q_{ag1} \). While FC was able to increase in \( Q_{ag1} \), FC was unable to maintain or increase \( Q_{ag1} \) beyond the 12-month time point. On the other hand, despite disease progression, PRE was able to increase \( Q_{ag1} \) and maintain this increase beyond 12 months.

\( Q_{ag1/t1}, \text{Magnitude of the First Agonist Burst Normalized to Burst Duration} \)

A non-significant effect of group (p = 0.17), a non-significant effect of time (p = 0.07), and a significant group by time interaction (p = 0.013) were observed. As can be seen in Figure 4.8(A) and Table 4.2, the FC and the PRE groups increased \( Q_{ag1/t1} \) relative to
baseline at the 6- and 12-month time point. However, at the 18- and 24-month time point the FC group started to head towards baseline levels, while the PRE group maintained the increase in $Q_{ag1/t1}$. At the study end-point the FC group presented with an increase of 0.01au/ms, while the PRE group presented with a 0.04au/ms increase in $Q_{ag1/t1}$ relative to baseline. Planned comparisons revealed that the increase in $Q_{ag1/t1}$ relative to baseline as shown in Figure 4.8(B), was significantly greater for the PRE group compared to the FC group at 12 months ($p = 0.02$), and at the study end-point of 24 months ($p = 0.009$). Additionally, at the study end-point of 24 months, the $Q_{ag1/t1}$ in the FC group trended towards baseline levels and was not significantly different from baseline ($p = 0.12$).

Because the magnitude of the first agonist burst is calculated by integrating the EMG signal, the magnitude will increase as the duration of the first agonist burst increases. Thus, normalizing the magnitude of the first agonist burst to its duration represents the magnitude per unit time. PRE was more efficacious in increasing $Q_{ag1/t1}$ compared to FC. While FC was able to increase in $Q_{ag1/t1}$, FC was unable to maintain or increase $Q_{ag1/t1}$ beyond the 12-month time point. On the other hand, despite disease progression, PRE was able to increase $Q_{ag1/t1}$ and maintain this increase beyond 12 months.

$Q_{30}$, Magnitude of the First 30 ms of the Agonist Burst

A non-significant effect of group ($p = 0.13$), a non-significant effect of time ($p = 0.54$), and a non-significant group by time interaction ($p = 0.19$) were observed. As can be seen in Figure 4.9(A) and (B) and Table 4.2, neither PRE, nor FC had any effect on $Q_{30}$. At the study end point the PRE group presented with a higher $Q_{30}$ of 0.61au compared to 0.23au in the FC group, however, this was not statistically significant.
\( Q_{ag} \), Magnitude of the Agonist Burst

A non-significant effect of group (\( p = 0.16 \)), a non-significant effect of time (\( p = 0.12 \)), and a non-significant group by time interaction (\( p = 0.26 \)) were observed. As can be seen in Figure 4.10(A) and (B) and Table 4.2, neither PRE, nor FC had any effect on \( Q_{ag} \). At the study end point the PRE group presented with a higher \( Q_{ag} \) of 3.88au compared to 1.99au in the FC group, however, this was not statistically significant.

Number of Agonist Bursts

A non-significant effect of group (\( p = 0.56 \)), a significant effect of time (\( p < 0.0001 \)), and a significant group by time interaction (\( p = 0.003 \)) were observed. Both, the FC and the PRE groups manifested with reduction in number of agonist bursts prior to peak velocity relative to baseline from 6 through 24 months (Figure 4.11(A) and Table 4.2). As can be seen in Figure 4.11(A) and Table 4.2, the PRE group exhibited a downward trend at all study time points, while the FC group plateaued at 6, 12, and 18 months, and slightly reduced at the study end-point of 24 months. At the study end point the number of agonist burst relative to baseline reduced by 0.56 in the FC group and by 0.94 in the PRE group. PRE was able to reduce the number of agonists burst by almost 1 entire burst. Planned comparisons revealed that the reduction in the number of agonist bursts relative to baseline as shown in Figure 4.11(B) and Table 4.2, was significantly greater for the PRE group compared to the FC group at 12 months (\( p = 0.032 \)), at 18 months (\( p = 0.001 \)), and at the study end-point of 24 months (\( p = 0.001 \)). PRE was more efficacious in reducing the number of agonist bursts prior to peak velocity compared to FC.
**Q\textsubscript{ant}, Magnitude of the Antagonist Burst**

A non-significant effect of group (p = 0.40), a significant effect of time (p = 0.0005), and a non-significant group by time interaction (p = 0.12) were observed. As can be seen in Figure 4.12 Table 4.2, there were no differences in change from baseline in Q\textsubscript{ant} between the PRE and the FC groups at the study end-point of 24 months. At the study end point the PRE group presented with a higher Q\textsubscript{ant} of 3.65au compared to 3.37au in the FC group, however, this was not statistically significant.

**Co-contraction during Limb Acceleration**

A non-significant effect of group (p = 0.07), a non-significant effect of time (p = 0.78), and a non-significant group by time interaction (p = 0.79) were observed. As can be seen in Figure 4.13(A) and (B) and Table 4.2 the PRE group presented with lower co-contraction indices relative to baseline compared to the FC group across all time points. At the study end-point the co-contraction index in the FC group was 1.66 units above baseline, while it was 2.31 units below baseline in the PRE group. However none of the differences between the FC and PRE group were statistically significant.

**4.4. DISCUSSION**

This clinical trial demonstrated that 24 months of PRE is more efficacious than FC in improving bradykinesia and force production in the upper-limb in patients with PD while off their anti-Parkinsonian medication. In addition, 24 months of PRE is also more efficacious than FC in bringing about changes in muscle activation patterns in patients with PD while off their anti-Parkinsonian medication.

Our data show that, at the study end-point of 24 months, following PRE, isometric elbow flexion strength and movement velocity were significantly increased. It should be
noted, on average, the time to peak velocity was identical between groups at the study end-point of 24 months. This suggests that the increase in peak velocity observed in the PRE group at the study end-point of 24 months was brought about by a significant increase in peak acceleration in the PRE group. Given that these movements were inertially loaded, acceleration is directly related to peak torque and would imply that the peak torque generated was significantly greater in the PRE group compared to the FC group. This increase in peak torque is ultimately responsible for the greater velocity observed in the PRE group. Thus, in addition to increasing isometric strength, PRE brought about increases in dynamic strength as well.

The idea that PRE group could produce greater torque and consequently greater movement velocity is also supported by examining the results of the EMG activation patterns. Again, because the time to peak velocity between groups was identical at the study end-point of 24 months, the duration within which the first agonist burst could be modulated prior to peak velocity was also identical between groups. On average, at the study end-point of 24 months, the duration of the first agonist burst was ~150ms for the FC group and ~180ms for the PRE group. This meant that on average, the number of agonist bursts prior to peak velocity was >1 in the FC group, while it was approximately equal to 1 in the PRE group. In addition, on average, at the study end-point of 24 months, the magnitude of the first agonist, both in absolute terms and relative to the duration of the first agonist burst, was also significantly greater in the PRE group than the FC group. It is known that there is a strong relationship between first agonist magnitude and peak torque (Corcos et al., 1989). Thus, increase in the magnitude of the first agonist burst could, at least partially, contribute to the increased torque and increased velocity observed in the PRE group. Taken together, i.e.,
increased movement velocity, increased torque, increased first agonist burst magnitude and duration, and decreased number of agonist bursts are suggestive of the ability of PRE to bring about changes in the control signal that arrives at the muscle. Because it has previously been proposed that the basal ganglia are involved in modulating both the magnitude and duration of the signal arriving at the motoneuron pool, it is quite likely that the EMG activation pattern changes observed following PRE are brought about by changes in basal ganglia output.

Use dependent synaptic plasticity lends further support for the idea that in PD, PRE could possibly bring about changes in control signal that arrives at the muscle. In 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) lesioned mice, Petzinger and colleagues (2007) have shown an increase in the stimulus-evoked dopamine release within the dorsolateral striatum following intensive treadmill training. Because the dorsolateral striatum is engaged to a high degree during fore- and hind-limb movements during treadmill exercise, they attributed the observed striatal plasticity to use-dependent synaptic plasticity. Similarly, there may also be use-dependent synaptic plasticity in the putamen, the GPi, and the STN following PRE. Vaillancourt and colleagues have conducted a series of studies in which they have shown that nuclei within the basal ganglia scale with the performance of different force producing tasks in both healthy individuals and those with PD. Specifically, they have shown that both the globus pallidus and the STN increase percent signal change when generating progressively larger forces in healthy subjects (Spraker et al., 2007). They have also shown that individuals with PD have a reduced percent signal change in all nuclei of the basal ganglia during an isometric force production task, even early in the disease process when individuals have not yet been medicated (Spraker et al., 2010). In addition, activity in the
nuclei of the basal ganglia is correlated to the UPDRS-III (Prodoehl et al., 2010). The symptom with the highest correlation with basal ganglia activity is bradykinesia. Given that we have shown that 24 months of PRE improved upper limb bradykinesia, it is quite possible that the neuronal activity of the basal ganglia was also altered by PRE. It should be noted that physical activity has been linked with plastic changes in several cortical and sub-cortical regions. The aim of the current study was to show that PRE could bring about changes in the control signal that arrives at the muscle in PD. It does not aim to identify where in the neural axes these plastic changes occur. Thus the reader is cautioned that it is quite possible, that plastic changes secondary to PRE could very well occur in brain regions other than the basal ganglia.

Magnitude of the EMG signal is influenced by both central and peripheral factors and PRE has both central and peripheral effects. One reason as explained in the previous paragraph is that the control signal arriving at the muscle is altered, possibly by altering basal ganglia output. But EMG magnitude can also be affected by peripheral factors like muscle fiber diameter, amount of sub-cutaneous fat, and fiber type composition, which are altered following 24 months of exposure to PRE. However, these peripheral factors are unlikely to affect the duration modulation of the first agonist burst. This is solely amenable to modulation through central mechanisms. Therefore, it is our conclusion that the primary contributor to improvement in bradykinesia of the upper limb following 24 months of PRE is likely to be central with secondary contributions from peripheral factors.

Parkinson’s disease is a progressive neurodegenerative disease and the progression of PD differentially affected the outcomes tested in this study. Evidence for this comes from the fact that in the current study the FC group improved relative to baseline on peak velocity and
time to peak velocity, while they gradually deteriorated with respect to first agonist burst normalized to burst duration, and they rapidly deteriorated with respect to MVC elbow flexion ending up below baseline levels. Thus, strength seems to deteriorate more rapidly than movement speed, while EMG activation patterns deteriorate more gradually compared to movement speed. Despite disease progression and differential effects of disease progression in PD, our data show that PRE was able to offset these decrements in performance in most of the outcome variables tested in the current study. Viewing the trends over time for MVC elbow flexion, peak velocity, $Q_{30}$, number of agonist bursts, and $Q_{ant}$, it appears the PRE group was continuing to improve, or plateaued at levels that were significantly improved relative to baseline. $Q_{ag}$ and co-contraction were the only two variables that were trending towards baseline. Thus, it is not unreasonable to conclude that PRE was effective in offsetting decrements in performance due to disease progression that might have occurred over a 24-month period.

In conclusion, to our knowledge this is the first clinical trial to examine the effects of 24 months of PRE on bradykinesia and muscle force production in PD. At the study endpoint of 24 months, PRE brought about significant gains in upper limb movement velocity and significant gains in strength. PRE was able to significantly change the control signal arriving at the muscle and brought about increases in the first agonist burst magnitude and duration, and reduced the number of agonist bursts prior to peak velocity. Thus PRE has significant impact on bradykinesia, which is a primary feature of PD. Additionally, by positively modifying the control signal that arrives at the muscle it also shows promise in modifying cortical output. It is our view that patients with PD will achieve significant motor
benefits by engaging in PRE twice a week and that PRE should be used as an adjunct treatment.
Table 4.1. Characteristics of Patients at Baseline, by Study Group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study group*</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>FC (N = 24)</td>
<td>PRE (N = 24)</td>
<td>P Value†</td>
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<tr>
<td>Demographic or Clinical</td>
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<tr>
<td>Age in years</td>
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<td>59.04 ± 4.60</td>
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<tr>
<td>Duration of diagnosis in years</td>
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<td>Mini-Mental State Examination</td>
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<tr>
<td>Sex - no. (%)</td>
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<td>Male</td>
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<td>14 (58.3)</td>
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<tr>
<td>Ethnicity - no. (%)</td>
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<td>Hispanic or Latino</td>
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<td>1 (4.2)</td>
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<tr>
<td>Race - no. (%)</td>
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<td>White</td>
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<td>22 (91.7)</td>
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<td>Handedness - no. (%)</td>
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<td>Right</td>
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<td>23 (95.8)</td>
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<td>Most Affected Side - no. (%)</td>
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<tr>
<td>Right</td>
<td>17 (70.8)</td>
<td>13 (54.2)</td>
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<tr>
<td>Motor Status</td>
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<tr>
<td>UPDRS-III Score (range, 0-108; off medication)</td>
<td>34.67 ± 11.49</td>
<td>34.46 ± 11.94</td>
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<td>Hoehn and Yahr Scale Staging (range, 0-5)</td>
<td>2.29 ± 0.53</td>
<td>2.21 ± 0.41</td>
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<tr>
<td>Strength</td>
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<tr>
<td>Elbow Flexion Torque (Nm; off medication)</td>
<td>50.18 ± 17.83</td>
<td>47.56 ± 15.72</td>
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<tr>
<td>Speed</td>
<td></td>
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<tr>
<td>Elbow flexion velocity (deg/s; off medication)</td>
<td>330.34 ± 86.25</td>
<td>327.18 ± 79.66</td>
<td>0.90</td>
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</table>

* Plus-minus values are means ± 1SD.
† P values calculated with the use of t-tests for continuous variables and Fisher’s exact test for binary variables.
Table 4.2. Observed Means and Mean Change from Baseline for Outcome Measures

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score at visit *</th>
<th>Change from Baseline</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FC</td>
<td>PRE</td>
<td>FC</td>
</tr>
<tr>
<td>MVC Flexion (Nm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>50.18 ± 17.83</td>
<td>47.56 ± 15.72</td>
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<tr>
<td>6 Month</td>
<td>54.14 ± 21.93</td>
<td>55.26 ± 17.23</td>
<td>3.96</td>
</tr>
<tr>
<td>12 Month</td>
<td>50.29 ± 20.29</td>
<td>55.8 ± 17.83</td>
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</tr>
<tr>
<td>18 Month</td>
<td>48.43 ± 20.81</td>
<td>54.64 ± 15.45</td>
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<tr>
<td>24 Month</td>
<td>46.13 ± 18.53</td>
<td>56.53 ± 16.34</td>
<td>-4.04</td>
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<tr>
<td>Peak Velocity (%/s)</td>
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<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>330.34 ± 86.25</td>
<td>327.18 ± 79.66</td>
<td></td>
</tr>
<tr>
<td>6 Month</td>
<td>400.18 ± 99.54</td>
<td>387.81 ± 77.87</td>
<td>69.84</td>
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<td>12 Month</td>
<td>399.75 ± 100.44</td>
<td>411.51 ± 97.03</td>
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<td>18 Month</td>
<td>407.73 ± 99.46</td>
<td>424.14 ± 87.96</td>
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<td>24 Month</td>
<td>407.68 ± 90.69</td>
<td>434.85 ± 85.01</td>
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<tr>
<td>Time to Peak Velocity (ms)</td>
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<tr>
<td>Baseline</td>
<td>223.07 ± 55.36</td>
<td>221.43 ± 67.43</td>
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<tr>
<td>6 Month</td>
<td>187.57 ± 55.02</td>
<td>187.68 ± 41.22</td>
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</tr>
<tr>
<td>12 Month</td>
<td>183.21 ± 51.37</td>
<td>183.11 ± 39.20</td>
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</tr>
<tr>
<td>18 Month</td>
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<td>179.29 ± 40.00</td>
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<td>24 Month</td>
<td>182.46 ± 40.11</td>
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<td>First Agonist Duration (ms)</td>
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<tr>
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<tr>
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<td>164.30 ± 80.20</td>
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<td>12 Month</td>
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<td>24 Month</td>
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<tr>
<td>QAg₁</td>
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<tr>
<td>Baseline</td>
<td>8.84 ± 6.10</td>
<td>8.65 ± 6.47</td>
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<tr>
<td>6 Month</td>
<td>14.22 ± 9.53</td>
<td>14.08 ± 9.18</td>
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<td>12 Month</td>
<td>15.78 ± 11.73</td>
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<tr>
<td>18 Month</td>
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<td>24 Month</td>
<td>12.17 ± 8.17</td>
<td>20.77 ± 15.00</td>
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<tr>
<td>QAg₁/t₁</td>
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<td></td>
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<tr>
<td>Baseline</td>
<td>0.07 ± 0.04</td>
<td>0.08 ± 0.07</td>
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<tr>
<td>6 Month</td>
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<td>18 Month</td>
<td>0.09 ± 0.05</td>
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<td>Change from Baseline</td>
<td>P Value†</td>
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<td>2.10</td>
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<tr>
<td>6 Month</td>
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<tr>
<td>Qag</td>
<td></td>
<td></td>
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<tr>
<td>Baseline</td>
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<td>19.37</td>
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<td>19.73</td>
<td>23.97</td>
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<tr>
<td>6 Month</td>
<td>1.71</td>
<td>1.72</td>
<td>-0.44</td>
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<tr>
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<td>1.64</td>
<td>1.54</td>
<td>-0.41</td>
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<tr>
<td>18 Month</td>
<td>1.67</td>
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<td>1.28</td>
<td>-0.44</td>
</tr>
<tr>
<td>Qant</td>
<td></td>
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<tr>
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<td>9.35</td>
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<tr>
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<td>12.39</td>
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<tr>
<td>18 Month</td>
<td>12.97</td>
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<tr>
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<tr>
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<td>6 Month</td>
<td>43.25</td>
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<td>12 Month</td>
<td>42.45</td>
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<td>42.19</td>
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<tr>
<td>24 Month</td>
<td>45.78</td>
<td>37.08</td>
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FC, Fitness Counts; PRE, Progressive Resistance Exercise; MVC, Maximal Voluntary Contraction; Nm, Newton meter; ms, milliseconds; QAg1, Magnitude of the First Agonist Burst; QAg1/t1, Magnitude of the First Agonist Burst Normalized to Burst Duration; Q30, Magnitude of the First 30ms of the Agonist Burst; Qag, Magnitude of the Agonist Burst; Qant, Magnitude of the Antagonist Burst

* Mean score ± 1SD
† P values are based on t-tests comparing the PRE vs. FC on change from baseline scores
†† P values are invalid because the group by time interaction was not significant
Figure 4.1. The CONSORT (Consolidated Standards of Reporting Trials) flowchart. Dashed lines indicate replaced subject flow.
Figure 4.2. (A) Mean off-medication MVC elbow flexion at 6, 12, 18, and 24 months. (B) Mean change from baseline in the off-medication MVC elbow flexion at 6, 12, 18, and 24 months. Positive change scores indicate increase in MVC.
Figure 4.3. Kinematic and EMG time series of representative subjects from the FC group (A) and the PRE group (B) at baseline, 6, and 24 months. Each trace shows data from a single trial of a 72 degree flexion movement. Subject in FC group was a 63 year old male with an off medication UPDRS-III of 39 at baseline and the subject in the PRE group was a 59 year old male with an off medication UPDRS-III of 42 at baseline.
Figure 4.4. (A) Mean off-medication elbow peak velocity at 6, 12, 18, and 24 months. (B) Mean change from baseline in the off-medication elbow peak velocity at 6, 12, 18, and 24 months. Positive change scores indicate increase in movement velocity.
Figure 4.5. (A) Mean off-medication time to peak velocity at 6, 12, 18, and 24 months. (B) Mean change from baseline in the off-medication time to peak velocity at 6, 12, 18, and 24 months. Negative change scores indicate shorter time to peak velocity.
Figure 4.6. (A) Mean off-medication duration of the first agonist burst EMG at 6, 12, 18, and 24 months. (B) Mean change from baseline in the off-medication duration of the first agonist burst EMG at 6, 12, 18, and 24 months. Positive change scores indicate increase in first agonist burst EMG duration.
Figure 4.7. (A) Mean off-medication EMG magnitude of the first agonist burst at 6, 12, 18, and 24 months. (B) Mean change from baseline in the off-medication EMG magnitude of the first agonist burst at 6, 12, 18, and 24 months. Positive change scores indicate increase in first agonist burst EMG magnitude.
Figure 4.8. (A) Mean off-medication EMG magnitude of the first agonist burst normalized to burst duration at 6, 12, 18, and 24 months. (B) Mean change from baseline in the off-medication EMG magnitude of the first agonist burst normalized to burst duration at 6, 12, 18, and 24 months. Positive change scores indicate increase in first agonist burst EMG magnitude normalized to burst duration.
Figure 4.9. (A) Mean off-medication EMG magnitude of the first 30ms of the agonist burst at 6, 12, 18, and 24 months. (B) Mean change from baseline in the off-medication EMG magnitude of the first 30ms of the agonist burst at 6, 12, 18, and 24 months. Positive change scores indicate increase in EMG magnitude of the first 30ms of the agonist burst.
Figure 4.10. (A) Mean off-medication EMG magnitude of the agonist burst at 6, 12, 18, and 24 months. (B) Mean change from baseline in the off-medication EMG magnitude of the agonist burst at 6, 12, 18, and 24 months. Positive change scores indicate increase in EMG magnitude of the agonist burst.
Figure 4.11. (A) Mean off-medication number of agonist bursts prior to peak velocity at 6, 12, 18, and 24 months. (B) Mean change from baseline in the off-medication number of agonist bursts prior to peak velocity at 6, 12, 18, and 24 months. Negative change scores indicate reduction in number of agonist bursts.
Figure 4.12. (A) Mean off-medication magnitude of the antagonist burst at 6, 12, 18, and 24 months. (B) Mean change from baseline in the off-medication magnitude of the antagonist burst at 6, 12, 18, and 24 months. Positive change scores indicate increase in EMG magnitude of the antagonist burst.
Figure 4.13. (A) Mean off-medication co-contraction during the acceleration phase of movement at 6, 12, 18, and 24 months. (B) Mean change from baseline in the off-medication co-contraction during the acceleration phase of movement at 6, 12, 18, and 24 months. Negative change scores indicate reduction in co-contraction.
5. PAPER 4

5.1. INTRODUCTION

Cognitive impairment is frequently observed in subjects with Parkinson’s disease (PD) along with the classic motor symptoms of bradykinesia, tremor, and rigidity (R. G. Brown & Marsden, 1990; Cooper et al., 1991; Lees & Smith, 1983; Owen, 2004; Sawamoto et al., 2007; Taylor et al., 1986). The pattern of cognitive dysfunction observed in PD is characterized by deficits in executive function (Owen, 2004), specifically, deficits in attention and spatial working memory (Owen et al., 1992). Given that up to 80% of patients with PD will develop dementia (Aarsland et al., 2003; Hely et al., 2008); there is an urgent need for interventions that can delay this highly probable cognitive decline. However, interventions that can treat the cognitive impairment in PD are not well researched.

Dopaminergic medications, which are the treatment mainstay of motor symptoms in PD, have only minor clinical benefits for treating the cognitive symptoms observed in PD (Aarsland et al., 2003). Additionally, ‘over-dosing’ areas that are not dopamine depleted, such as the frontal cortical areas, which obtain their dopamine via the mesocortical pathway might contribute to, rather than alleviate cognitive symptoms (Sawamoto et al., 2008; Zahrt, Taylor, Mathew, & Arnsten, 1997). Moreover, pharmacological treatment is wrought with side effects that reduce tolerance of such treatment. One possible alternative is exercise training, specifically, progressive resistance exercise (PRE).

The rationale for PRE as an intervention for cognitive function in PD is threefold. First, PRE has been found to improve cognitive function in healthy subjects between the age of 65 and 75. Cassilhas et al. (2007) demonstrated improved performance on measures of working memory and attention for those assigned to 24 weeks of PRE. More recently, Liu-
Ambrose and colleagues (2010) demonstrated beneficial cognitive effects of 52 weeks of PRE in community dwelling elderly women. They showed improvements in attention and conflict resolution. They also demonstrated that PRE could facilitate functional plasticity in the cortex by showing an increase in percent signal change in the left anterior insula and the anterior portion of the left middle temporal gyrus following PRE (Liu-Ambrose et al., 2011). Second, even though aerobic training provides cognitive benefits, a combination of aerobic and PRE has been evidenced to render the greatest cognitive benefits (Colcombe & Kramer, 2003). Third, there is a strong biological basis for the cognitive benefits gained from PRE. These include the reduction in serum levels of homocysteine (Vincent et al., 2003) and the increase in serum levels of insulin like growth factor I (Borst et al., 2001), which are both known to be associated with cognitive function (Garcia-Segura et al., 2010; Seshadri et al., 2002). Thus, there is evidence in the literature that supports the beneficial effects of PRE on cognitive function.

What is not yet known is the effect of PRE on cognition in PD. There are no randomized controlled trials examining the long-term effects of PRE on cognitive symptoms in PD. The current study was a randomized controlled trial, which aimed to investigate the effects of 24 months of PRE in PD. Because the effects of anti-Parkinsonian medication on cognitive outcomes are not well understood, and because anti-Parkinsonian medication could possibly mask the effects of PRE, we chose to examine the effects of PRE on PD while patients were off their anti-Parkinsonian medication. The cognitive outcomes included were the Stroop test, the Brief Test of Attention, and the Digit Span Forwards and Backwards. The above-mentioned tests measure executive function, specifically, selective attention, attentional conflict, and working memory, which are known to be frequently impaired in PD.
5.2. METHODS

5.2.1. TRIAL DESIGN

The study design was a matched pairs, randomized, controlled, rater blinded, 24-month prospective clinical trial, examining the effect of PRE in subjects with PD. It employed a parallel group design with a 1:1 allocation ratio. A healthy age and gender matched control group was also used to provide normative data; however, they did not participate in any form of exercise. The study commenced in October of 2007 and was completed in June of 2011 with 5 measurement points (baseline, 6, 12, 18, and 24 months).

5.2.2. SUBJECTS

Three groups of subjects were tested. They were: 1) subjects with PD who were assigned to the PRE program, 2) subjects with PD who were assigned to the Fitness Counts (FC) exercise program (R. Wichmann et al., 2002), and 3) an age and sex matched healthy control group who did not participate in either exercise program. Subjects were recruited through the Movement Disorders Center at Rush University Medical Center. Inclusion criteria for subjects with PD were: 1) a diagnosis of PD (Hughes et al., 1992) 2) no other neurological disorder as determined by medical history and neurological exam, 3) no other known injury, disease, or other disorder that might interfere with motor function in the proposed experiments, 4) no medications that might interfere with neuromuscular junction function such as D-penicillamine and aminoglycoside antibiotics, 5) a score greater than 23 on the Mini-Mental State Examination to exclude the role of neuropsychiatric dysfunction in problems with performing the various tasks, and complying with the exercise programs, 6) not actively engaged in a formal exercise program, 7) between the ages of 50 and 67, 8) and not have deep brain stimulation surgery.
The healthy age and sex matched controls were recruited by flyers placed in and around the University of Illinois at Chicago’s campus and by word of mouth. The inclusion criteria for healthy controls were: 1) no neurological disorder as determined by medical history, 2) no known injury, disease, or other disorder that might interfere with function in the proposed experiments, 3) no medications that might interfere with neuromuscular junction function such as D-penicillamine and aminoglycoside antibiotics, 4) a score greater than 23 on the Mini-Mental State Examination to exclude the role of neuropsychiatric dysfunction, 5) and between the ages of 45 and 72 (control subjects were matched ±5 years of the subjects with PD).

Institutional Review Boards for the protection of research subjects of the University of Illinois at Chicago and Rush University Medical Center approved the research protocol. All subjects provided written informed consent. The data for each measurement point were collected at the Neural Control of Movement Laboratory at the University of Illinois at Chicago.

5.2.3. INTERVENTIONS

Subjects participated in one of two—prescribed exercise programs, PRE or FC program, twice a week for two years. One-on-one training, with a certified personal trainer was provided for both exercise programs twice a week during the first six months. This was done to help subjects become comfortable with the training regimen, and because there is documented evidence of greater strength gains when training with a personal trainer (Mazzetti et al., 2000). Then one-on-one training was provided once a week and subjects performed the second session each week on their own for the remaining 18 months. If a subject missed a session, they were instructed to make it up. Thus, at the study end-point of
24 months, each subject completed a total of ~208 exercise sessions. In order to maximize compliance we did the following: 1) subjects were supervised (one-on-one training) twice a week for the first six months and then once a week until completion of the study by a personal trainer who was paid for by the study, 2) exercise sessions were held at a gym facility close to the subject’s home which was paid for by the study, 3) exercise sessions were scheduled at the subject’s convenience, 4) subjects were asked to exercise only twice a week, 5) if subjects missed two consecutive sessions, immediate action was taken by the exercise coordinator to resolve any issues, and 6) the exercise coordinator contacted the subjects’ trainer every 2-3 months to check on the subject’s progression.

Both exercise programs had the same warm up and cool down phases that each lasted up to 10 minutes. These exercises included 3 minutes of walking followed by 5 repetitions of the following 5 stretching exercises: 1) neck circles to both directions, 2) trunk rotation while lying down to both directions, 3) arm circles in both directions, 4) hamstring stretches while sitting and 5) ankle stretches while standing. The total duration for each exercise session in both programs was approximately 60-90 minutes. Subjects performed the exercise programs while on anti-Parkinsonian medication.

**Progressive Resistance Exercise Program**

The PRE program consisted of a general strengthening program with a primary focus on strengthening extensor muscles. The following specific exercises were used: 1) chest press (modified), 2) latissimus pull downs, 3) reverse flys, 4) double leg press, 5) hip extension, 6) shoulder press, 7) biceps curl, 8) rotary calf (ankle plantar flexion), 9) triceps extension, 10) seated quad and 11) back extension. Exercise sessions were separated by at
least 48 hours (Feigenbaum & Pollock, 1999). Photographs of the exercises are included in the appendix.

At baseline a one-repetition maximum (1RM), i.e., the greatest resistive load that can be moved through the full range of motion in a controlled manner with good posture (American College of Sports Medicine, 2010), was established for the above exercises. Resistance was set at approximately 40-50% of the baseline 1RM (30-40% for upper body exercises; 50-60% for lower body exercises) during the first week of training. As soon as the subject was able to perform a set of the exercises using good form and perceive the exercise to be somewhat easy, the resistance was increased by at least 5% (Feigenbaum & Pollock, 1999) or as allowed by the equipment. Each repetition lasted six to nine seconds. Subjects raised the weight over 2-3 seconds, paused briefly (2-3 seconds), and slowly lowered the weight (3-4 seconds) (Pollock et al., 2000). Subjects performed three sets of 8 repetitions for each exercise starting with just one set and working up to three sets as they progressed. After 8 weeks on the strength program, subjects switched to a power (speed) program. Here the emphasis was on speed with which each repetition was completed. The resistance was set at 70-80% of their 1RM and each subject performed 2 sets of 12 repetitions. Every 8 weeks subjects alternated between the strength and power (speed) training programs and the resistance was set at where they left off for the respective programs.

*Fitness Counts Exercise Program*

The FC exercise program is recommended by the National Parkinson Foundation (R. Wichmann et al., 2002) and was used as a comparative intervention. It consists of low intensity stretching, non-progressive strengthening, breathing, and balance exercises. There are 12 stretching exercises which consist of: neck stretch, chest stretches, rotation stretch,
overhead stretch, hamstring stretch, side stretch, ankle circles, back stretch, shoulder stretch, calf stretch, shoulder circles, and trunk rotation stretch. All stretching exercises were performed 3 times while holding the stretch for 3-5 breath counts. The 7 strengthening exercises consisted of the following: wall slides, bridging, shoulder blade squeeze (sitting and standing with a resistance tube), quadriceps strengthening, quadraped trunk, and prone on elbows. Three sets of 10 repetitions were performed for all strengthening exercises. There was also a 2 to 3 seconds of rest (or more if needed) between all stretching and strengthening exercises. The last exercise, balance exercises consisted of the following two exercises: weight shifts forward and backward 10 to 20 times while standing with feet placed hip width apart and single leg stance on each leg for 5-10 seconds. Photographs of the exercises are included in the appendix.

5.2.4. OUTCOMES

It should be noted that the cognitive outcomes were one of 6 outcome domains that were tested. These domains consisted of clinical status, bradykinesia and strength, tremor, gait, quality of life, and cognition. This paper will report the cognitive outcomes only. Three measures of executive cognitive function were used: the Stroop Test (Golden & Freshwater, 2002), the Brief Test of Attention (Schretlen, 1997) and the Digit Span Forwards and Backwards (Wechsler, 1997). The order of administration of the cognitive outcomes was randomized both within and between outcome domains. At each time point, each cognitive test was administered by a rater blinded to group allocation when the subjects were both off and on anti-Parkinsonian medications. Because a 12 hour withdrawal from anti-Parkinsonian medications is ideal (Langston et al., 1992), off medication testing always preceded the on medication testing session. Thus, the morning session was always off medication and the
post lunch session was always on medication. At least 60-90 minutes elapsed after ingesting medication before on medication testing commenced (Robichaud et al., 2002). The healthy group was tested in the morning. It should be noted that this paper only reports the results of the off medication testing in patients with PD. Below is a brief description of the instruments used to test the above mentioned executive cognitive functions.

**Stroop Color and Word Test (Selective Attention and Conflict Resolution)**

The standardized adult version of the Stroop Color and Word Test was used to assess selective attention and conflict resolution (Golden & Freshwater, 2002). The Stroop test consists of reading from three pages: Word, Color, and Color-Word. For the ‘Word’ page, subjects were asked to read aloud printed words (e.g., blue). For the ‘Color’ page, subjects were asked to name aloud the color of colored ‘x’s. In the ‘Color-Word’ test, subjects were asked to name aloud the color of the ink of the printed word. However, the color of the print ink and the word were incongruent, i.e., the word ‘red’ printed in green ink. For each page the subject was asked to read/name aloud as many words/colors in 45 seconds. The raw score for each page was the number of words/colors the subject read/named correctly. Test administration and scoring was performed as instructed in the user manual. The Color-Word interference T-score was used as the outcome variable to measure selective attention and conflict resolution. The T-score is a standardized normative metric with a mean of 50 and a standard deviation of 10.

**Brief Test of Attention (Divided Attention)**

The Brief Test of Attention was used to assess divided attention (Schretlen, 1997). It consists of two parallel forms that are presented via audio cassette. The first is Form N (numbers); a voice reads 10 lists of letters and numbers that increase in length from 4 to 18
elements. The subject is asked to ignore the letters and count how many numbers were read aloud. The same 10 lists are presented as Form L (letters), here the subject is asked to disregard the numbers and count how many letters were read aloud. The number of correct responses on Form N and L are added to yield a raw score from 0-20. This raw score was used as the outcome variable to measure divided attention.

_The Digit Span Forwards and Backwards (Working Memory)_

The Digit Span Forwards and Backwards form the Wechsler Adult Intelligence Scale – III was used to assess working memory (Wechsler, 1997). The Digit Span Forwards consists of 8 pairs of random number sequences. The sequence begins with 2 digits and progresses to 9 digits. Each pair consists of sequences of identical length. The examiner reads out aloud each sequence at the rate of 1 digit per second and the subject is asked to repeat the sequence in the correct order. The stop rule is when the subject responds erroneously on both sequences within a pair. The Digit Span Forwards raw score ranges from 0-16. The Digit Span Backwards task consists of 7 pairs of random number sequences. The sequence begins with 2 digits and progresses to 8 digits. Here the subject is asked to repeat the sequence in the reverse order. The Digit Span Backwards raw score ranges from 0-14. Thus, the Digit Span Forwards and Backwards raw sum score ranges from 0-30. In addition, a combined Digit Span Forwards and Backwards scaled score can be calculated. The range of the scaled score is from 1-19, with 10 being indicative of average performance. The combined Digit Span Forwards and Backwards sum score was used as the outcome variable to measure working memory.
5.2.5. SAMPLE SIZE

The required sample size was estimated by conducting an a priori power analysis. The healthy control group was not included in our sample size estimations as they did not participate in either exercise programs and were merely used to establish norms. The cognitive outcome variables previously described were not used in the power analysis. The study reported here was part of a larger clinical trial, whose primary outcome was the Unified Parkinson’s disease Rating Scale, part III, the motor subscale (UPDRS-III) and cognitive outcomes were secondary outcomes. Therefore, the UDPRS-III, the current “gold standard” to measure symptomatic effects, was used to drive our sample size estimations. Based on our pilot data, the required sample size with 80% power to detect a mean difference of $5$ (at $\alpha = 0.05$) with a SD of $5$ on the UPDRS-III, and an assumed attrition rate of $30\%$ was estimated to be $25$ subjects per group.

5.2.6. RANDOMIZATION

All subjects were tested at baseline off and on anti-Parkinsonian medication. Matched pairs randomization was then performed according to sex and off-medication UPDRS-III score to force balanced exercise groups. This was done because males are generally stronger than females and because disease severity affects motor function. Males and females were randomized separately. In each sex stratum, subjects were paired with other subjects with off medication UPDRS-III score within $5$ points. One subject in each matched pair of PD subjects was randomly assigned by the statistician to one of the exercise groups. The second subject in the assigned pair was placed in the other exercise group. The first assignments in each pair were generated according to a random-length permuted block design so that the initial assignments would not become unbalanced and so that the assignment sequence would
have been difficult to guess (Friedman et al., 1998). Additionally, since we restricted age to 50 – 67 years and were using random assignment to the exercise groups, we expected the age of the exercise groups to be similar. This expected age balance was checked after half the subjects were randomized and the groups were found to be balanced.

5.2.7. INTENTION-TO-TREAT ANALYSIS

We employed the Intent-to-Treat principle for our primary analysis. A priori, a decision was made to replace subjects with PD who might withdraw from the study prior to 6-month testing, if the reasons for dropping out were unrelated to the study and unrelated to the disease. These subjects were to be replaced by a patient who was matched for sex and off medication UPDRS-III score. No subject who withdrew after the 6-month testing was replaced and the intent-to-treat analysis was used for all statistical analyses.

5.2.8. BLINDING

The raters assessing the cognitive outcomes were blinded. The blinding was achieved by: 1) only the statistician and exercise study coordinator were aware of group membership, 2) using random-length permuted block design for randomization, which makes guessing assignment sequence difficult (Friedman et al., 1998), and 3) prior to each testing session, study subjects were reminded not to discuss their group membership with the blinded raters. In addition, the subjects were blinded to the specific purpose of the clinical trial and the raters were instructed not to discuss the hypotheses of the clinical trial with the subjects.

5.2.9. STATISTICAL METHODS

All analyses were based on the intention-to-treat principle and missing observations for those subjects who were lost to follow-up were replaced by the last available observation being carried forward. A mixed effects regression model was used to identify the effect of
group, the effect of time, and the group by time interaction on our outcome measures. Group was a between-subject variable with two levels: FC and PRE. Time was a within-subject variable. Time was treated as a categorical variable with five levels: baseline, 6, 12, 18, and 24 months. In the event of a significant group by time interaction, we performed planned comparisons that compared the change from baseline scores between groups at each time point. The outcome measures were those collected in the “off medication" condition. We chose to test individuals off medication because medication may mask the underlying changes induced by participation in the PRE program along with masking “true” disease progression. All statistical analyses were performed with the use of SAS software, version 9.1. The statistical tests were all two-sided, and a P value < .05 was used to determine statistical significance. There was no formal correction for the use of multiple comparisons.

5.3. RESULTS

5.3.1. RECRUITMENT

Eligible participants were recruited from September of 2007 to June of 2009. All eligible participants were tested at baseline and randomized, and then tested at 6-month interval for 2 years. Testing the patients with PD commenced in October of 2007 and concluded in June of 2011.

5.3.2. SUBJECT FLOW

The Consolidated Standards of Reporting Trials (CONSORT) flowchart in Figure 5.1 shows the number of subjects in each intervention arm in each stage of the clinical trial. Initially, a total of 70 subjects with PD were screened for eligibility, of whom, 20 were not eligible as they did not meet the inclusion criteria for the study. The remaining 50 subjects completed baseline testing, of whom, two subjects withdrew before randomization. One
subject had back surgery, and one subject did not want to continue in the study in the event he was randomized to the FC group. The remaining 48 subjects were pair randomized i.e., matched on off-medication UPDRS-III and sex to the intervention groups. Twenty-four subjects were allocated to the PRE group and 24 subjects were allocated to the FC group. After randomization, three subjects withdrew and were replaced. One of whom we were unable to contact and did not start exercising, one did not want to continue after 2 sessions due to personal reasons, and one did not want to come off medication for the 6-month testing. As a result, in addition to the initial 70 subjects, medical charts of 20 subjects were reviewed and 3 were chosen to be screened for eligibility. These three subjects were specifically identified to match the off-medication UPDRS-III and sex of those who withdrew after randomization. Consequently, their group allocations were predetermined and not randomized. At 6 months, 24 subjects in each group completed testing.

After the 6-month testing, one subject from the FC group passed away, and one subject from the PRE group withdrew as he moved to a different state. Thus, at 12 months, 23 subjects in each intervention group completed testing. After the 12-month testing, two subjects from the FC group withdrew, both of whom underwent deep brain stimulation (DBS) surgery and were no longer eligible to continue in the study, and one subject in the PRE group withdrew as he had medical complications (subject had a fall at home that required long term rehabilitation) that prevented continuation in the study. Thus, at 18 months, 21 subjects in the FC group and 22 subjects in the PRE group completed testing. After the 18-month testing, four subjects from the FC group withdrew, of whom three had medical complications (one was diagnosed with ALS, one had complications due to cancer, and one had a bone infection following surgery), and one had DBS surgery. One subject in
the PRE group withdrew as she underwent DBS surgery. Thus, at 24 months, 17 subjects in
the FC group and 21 in the PRE group completed testing. Given that the intent-to-treat
principle and the last observation carried forward principle to replace missing data were used,
48 subjects were included in the final statistical analyses for each of the outcomes. Table 5.1
lists the demographic and clinical characteristics of these 48 subjects at baseline. As can be
seen in Table 5.1 the groups were equivalent at baseline with respect to demographic and
clinical characteristics.

5.3.3. OUTCOMES

*Stroop Color-Word Interference T-Score (Selective Attention and Conflict Resolution)*

A non-significant effect of group (p = 0.28), a significant effect of time (p = 0.032),
and a non-significant group by time interaction (p = 0.68) were observed. As can be seen in
Figure 5.2 and Table 5.1, both, the FC and the PRE groups manifested with improvements in
the Stroop color-word interference T-score relative to baseline from 6 through 24 months.

*Brief Test of Attention Raw Score (Divided Attention)*

A non-significant effect of group (p = 0.71), a significant effect of time (p = 0.031),
and a non-significant group by time interaction (p = 0.895) were observed. As can be seen in
Figure 5.3 and Table 5.2, both, the FC and the PRE groups manifested with improvements in
the Brief Test of Attention relative to baseline from 6 through 24 months.

*The Digit Span Forwards and Backwards Sum Score (Working Memory)*

A non-significant effect of group (p = 0.62), a significant effect of time (p < 0.0001),
and a non-significant group by time interaction (p = 0.055) were observed. As can be seen in
Figure 5.4 and Table 5.2, both, the FC and the PRE groups manifested with improvements in
the Digit Span Forwards and Backwards sum score relative to baseline from 6 through 24 months.

In summary, FC and PRE provided similar improvements across all cognitive domains tested. PRE and FC were equally efficacious in improving cognitive function.

5.4. DISCUSSION

This clinical trial demonstrated that 24 months of physical activity, twice a week, is effective in improving cognitive outcomes in patients with mild to moderate PD. However, no differences in efficacy between FC and PRE interventions were observed. To our knowledge this is the first clinical trial to examine the effects of 24 months of physical activity on cognitive functions in patients with mild to moderate PD while off medication.

A key finding of this clinical trial is that physical activity can improve cognitive function in previously sedentary patients with PD. This is evident from the improvement observed in both the FC and the PRE group across all the cognitive outcomes tested in the current clinical trial. At the study end-point of 24 months, relative to baseline, the effect size (cohen’s $d$) for the Stroop color-word interference was 0.47 for the FC group and 0.52 for the PRE group; the effect sizes for the BTA were 0.31 for the FC group and 0.49 for the PRE group; and the effect sizes for the Digit Span were 0.87 for the FC group and 0.56 for the PRE group. When comparing these effect sizes to previously published data, it is evident that physical activity in PD has a significant impact in maintaining or improving cognitive function. For instance, Troster and colleagues examined the test re-test reliability of several commonly used cognitive measures in patients with PD while they were on their anti-Parkinsonian medication. They found that re-testing approximately 17 months apart resulted in declines in attention ($d = -0.3$), and declines in performance in the digit span forward ($d = $
-0.21) and backward (\(d = -0.15\)) test (Troster, Woods, & Morgan, 2007). Additionally, Schmand and colleagues tested the effect of unilateral pallidotomy on patients with PD and compared their results with a wait listed control group (Schmand et al., 2000). Time to follow-up after baseline testing was 6 months. They found that the time to complete color-word interference test increased in the control group as well as in the unilateral pallidotomy group. The effect sizes calculated from the means and SD they reported are \(d = -0.03\) for the control group and \(d = -0.19\) for the unilateral pallidotomy group. It should be noted that the effect sizes published by Troster et al. (2007) and those calculated from Schmand et al. (2000) are quite small. From a descriptive perspective they are indicative of a decline, but this need not necessarily be indicative of statistical significant declines. Nevertheless, comparing the findings of the current clinical trial to those that have been previously published provides evidence for the benefit of physical activity towards maintaining or improving cognitive function.

In healthy elderly individuals, previous research has concluded that PRE is more efficacious in improving cognitive function than balance and non progressive strengthening exercises (Cassilhas et al., 2007; Liu-Ambrose et al., 2010). In the present study, PRE was only as efficacious as FC in improving cognitive function. FC was similar to balance and non progressive strengthening exercises used as ‘control’ interventions in previous studies. This could mean that with regard to cognitive function in PD, PRE is not as efficacious as in healthy elderly individuals. In addition, the current study was different from Cassilhas and colleagues in the following ways, first, Cassilhas and colleagues used subjects who ranged in age from 65-75 years, while the age range in the current study was from 50 to 67 years. Second, even though Cassilhas and colleagues measured cognitive outcomes that measured
executive function, the assessments themselves were different from those used in the current study. Third, they excluded those volunteers that attended less than 75% of their training sessions, so they did not use an intention to treat analysis. Also, they did not report the number of participants that dropped out of the study.

The current study was different from Liu-Ambrose and colleagues’ (2010) study as well. First, their subject pool was entirely comprised of females. Second, their age range was also between 65 and 75 years, similar to Cassilhas et al. (2007). Third, even though they used the Stroop test, the scoring method they used to assess selective attention and conflict resolution was different from the present study. Their outcome variable was the difference in the time taken to complete the ‘color-word’ test and the time taken to complete the ‘color’ test, whereas in the current study we used the color-word interference T-score. Thus, differences in the study population and methodology between previous studies and the current study could possibly account for differences in results.

In general, repeated administrations of cognitive assessments in healthy individuals are known to have practice effects, and these practice effects are affected by factors such as age, task difficulty (Lowe & Rabbitt, 1998; Rabbitt, 1993), and IQ (Rabbitt, 1993). In the present study, there was a significant effect of time but there were no group by time interactions, therefore it is not possible to differentiate the effects of the interventions from the effects of practice. That being said, there are two arguments that imply that the improvement in cognitive outcomes observed in this study were an effect of exercise and not an effect of practice. First, in healthy individuals the ageing process is accompanied by cognitive decline. In healthy individuals between the age of 49 and 70 years, taking into account dropouts, sex, socioeconomic status, age at entry, and practice effects, cognitive
function has been shown to decline in a quadratic fashion with increasing age (Rabbitt, Diggle, Smith, Holland, & Mc Innes, 2001). Second, in PD the neurodegenerative disease process augments the cognitive decline that accompanies the ageing process. Muslimovic and colleagues have shown that over 36 months, cognitive decline occurs at a faster rate in patients with PD when compared to age-matched controls (Muslimovic, Post, Speelman, De Haan, & Schmand, 2009). In addition, prospective follow-up of patients with PD over 6 (Schmand et al., 2000) and 17 months (Troster et al., 2007) have shown no practice effects. Thus, in the current study, if treatment was inefficacious, one should either observe maintenance of cognitive function or cognitive decline over time. However, we observed an improvement in performance across all cognitive outcomes. Thus, it is not unreasonable to conclude that in PD, there is a beneficial cognitive effect due to 24 months of exercise.

In conclusion, to our knowledge this is the first clinical trial to examine the effects of 24 months of PRE on cognitive outcomes in PD. At the study end-point of 24 months, both PRE and FC brought about significant gains across all cognitive outcomes tested. PRE and FC were able to improve selective attention and conflict resolution, divided attention, and working memory. Because PRE was only as efficacious as FC, it is our view that patients with PD will achieve cognitive benefit by engaging in either form of physical activity at least twice a week.
Table 5.1. Characteristics of Patients at Baseline, by Study Group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study group*</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><em>FC</em> (N = 24)</td>
<td><em>PRE</em> (N = 24)</td>
<td><em>P Value</em>†</td>
</tr>
<tr>
<td>Demographic or Clinical</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age in years</td>
<td>58.63 ± 5.59</td>
<td>59.04 ± 4.60</td>
<td></td>
<td>0.78</td>
</tr>
<tr>
<td>Duration of diagnosis in years</td>
<td>6.46 ± 4.68</td>
<td>6.51 ± 4.11</td>
<td></td>
<td>0.97</td>
</tr>
<tr>
<td>Mini-Mental State Examination</td>
<td>29.08 ± 1.35</td>
<td>29.29 ± 1.08</td>
<td></td>
<td>0.56</td>
</tr>
<tr>
<td>Sex - no. (%)</td>
<td></td>
<td></td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Male</td>
<td>14 (58.3)</td>
<td>14 (58.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity - no. (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.19</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>5 (20.8)</td>
<td>1 (4.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race - no. (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.49</td>
</tr>
<tr>
<td>African American</td>
<td>0 (0)</td>
<td>2 (8.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>24 (100)</td>
<td>22 (91.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Handedness - no. (%)</td>
<td></td>
<td></td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Right</td>
<td>22 (91.7)</td>
<td>23 (95.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Most Affected Side - no. (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.37</td>
</tr>
<tr>
<td>Right</td>
<td>17 (70.8)</td>
<td>13 (54.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor Status‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UPDRS-III Score (range, 0-108)</td>
<td>34.67 ± 11.49</td>
<td>34.46 ± 11.94</td>
<td></td>
<td>0.90</td>
</tr>
<tr>
<td>Hoehn and Yahr Scale Staging (range, 0-5)</td>
<td>2.29 ± 0.53</td>
<td>2.21 ± 0.41</td>
<td></td>
<td>0.43</td>
</tr>
<tr>
<td>Cognitive Status‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroop Color-Word Interference (T-Score, mean 50, SD 10)</td>
<td>45.08 ± 10.71</td>
<td>42.42 ± 11.75</td>
<td></td>
<td>0.42</td>
</tr>
<tr>
<td>Brief Test of Attention (range, 0-20)</td>
<td>15.29 ± 3.68</td>
<td>15.58 ± 3.82</td>
<td></td>
<td>0.79</td>
</tr>
<tr>
<td>Digit Span (range, 0-30)</td>
<td>17.21 ± 3.82</td>
<td>17.17 ± 3.53</td>
<td></td>
<td>0.97</td>
</tr>
</tbody>
</table>

* Plus-minus values are means ± 1SD.
† P values calculated with the use of t-tests for continuous variables and Fisher’s exact test for binary variables
‡ Off medication scores
Table 5.2. Observed Means and Mean Change from Baseline for Outcome Measures

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score at visit *</th>
<th>Change from Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FC</td>
<td>PRE</td>
</tr>
<tr>
<td>Stroop</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>45.08 ± 10.71</td>
<td>42.42 ± 11.75</td>
</tr>
<tr>
<td>6 Month</td>
<td>48.04 ± 10.03</td>
<td>44.00 ± 12.14</td>
</tr>
<tr>
<td>12 Month</td>
<td>48.63 ± 10.11</td>
<td>46.96 ± 12.27</td>
</tr>
<tr>
<td>18 Month</td>
<td>49.04 ± 10.06</td>
<td>44.79 ± 12.67</td>
</tr>
<tr>
<td>24 Month</td>
<td>48.88 ± 10.30</td>
<td>45.33 ± 12.33</td>
</tr>
<tr>
<td>BTA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>15.29 ± 3.68</td>
<td>15.58 ± 3.82</td>
</tr>
<tr>
<td>6 Month</td>
<td>16.46 ± 3.56</td>
<td>16.79 ± 3.46</td>
</tr>
<tr>
<td>12 Month</td>
<td>16.38 ± 3.02</td>
<td>16.58 ± 3.49</td>
</tr>
<tr>
<td>18 Month</td>
<td>16.96 ± 2.44</td>
<td>16.96 ± 3.34</td>
</tr>
<tr>
<td>24 Month</td>
<td>16.13 ± 3.10</td>
<td>16.88 ± 3.64</td>
</tr>
<tr>
<td>Digit Span</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>17.21 ± 3.82</td>
<td>17.17 ± 3.53</td>
</tr>
<tr>
<td>6 Month</td>
<td>19.21 ± 4.16</td>
<td>18.96 ± 3.98</td>
</tr>
<tr>
<td>12 Month</td>
<td>18.67 ± 3.96</td>
<td>19.29 ± 3.86</td>
</tr>
<tr>
<td>18 Month</td>
<td>19.54 ± 4.11</td>
<td>18.13 ± 3.64</td>
</tr>
<tr>
<td>24 Month</td>
<td>20.17 ± 4.09</td>
<td>18.75 ± 3.59</td>
</tr>
</tbody>
</table>

FC, Fitness Counts; PRE, Progressive Resistance Exercise; BTA, Brief Test of Attention
* Mean score ± 1SD
† P values are based on t-tests comparing the PRE vs. FC on change from baseline scores
Figure 5.1. The CONSORT (Consolidated Standards of Reporting Trials) flowchart. Dashed lines indicate replaced subject flow.
Figure 5.2. (A) Mean off-medication Stroop Color-Cord Interference T-score at 6, 12, 18, and 24 months. (B) Mean change from baseline in the off-medication Stroop Color-Word Interference T-score at 6, 12, 18, and 24 months. Positive change scores indicate improvement.
Figure 5.3. (A) Mean off-medication Brief Test of Attention sum score at 6, 12, 18, and 24 months. (B) Mean change from baseline in the off-medication Brief Test of Attention sum score at 6, 12, 18, and 24 months. Positive change scores indicate improvement.
Figure 5.4. (A) Mean off-medication Digit Span Forwards and Backwards sum score at 6, 12, 18, and 24 months. (B) Mean change from baseline in the off-medication Digit Span Forwards and Backwards sum score at 6, 12, 18, and 24 months. Positive change scores indicate improvement.
6. CONCLUSIONS AND DIRECTIONS FOR FUTURE RESEARCH

The experiments reported in this dissertation are parts of the first clinical trial to examine the effects of progressive resistance exercise (PRE) in Parkinson’s disease (PD). This clinical trial is a much needed first step in providing the strongest evidence to date for the efficacy of PRE in mitigating motor and non-motor symptoms observed in PD. It is clear from the experiments reported in this dissertation that PRE improves bradykinesia and strength. In addition, PRE is capable of causing central changes that favorably alter the corticospinal output arriving at the muscle. Furthermore, PRE can also improve cognition and offset the cognitive decline that is typically observed in PD. An additional finding was the efficacy of FC in improving and maintaining cognitive function. Based on our findings, engaging in twice a week of high intensity PRE with a personal trainer can provide improvement in bradykinesia and strength, while engaging in either FC or PRE can provide improvement in cognitive function. Thus, we have provided strong evidence for the use of PRE as an adjunct treatment in PD.

Several questions remain to be answered in the future. Recently, the idea of neuro-protection and exercise in general has been investigated with much vigor (see Alberts, Linder, Penko, Lowe, & Phillips, 2011 for a recent review). Given the biological changes that accompany PRE, future clinical trials could employ a wait-listed control design and answer question that are pertinent to PRE and neuro-protection. Another area that requires considerable attention is the optimal PRE prescription for individuals with PD with regard to PRE parameters, such as the frequency, the intensity, the duration, and the mode of exercise (i.e., strength and power training), as well as with regards to the various clinical sub-types of PD (e.g. tremor dominant, non-tremor dominant akinetic-rigid etc.). It is likely that the effect
of PRE may vary with the clinical sub-type of PD. In addition, the effect of PRE on tremor and rigidity is not yet known. Thus, future research should identify the optimal PRE prescription in the context of the different clinical sub-types of individuals with PD and empirically verify hypotheses related to tremor and rigidity as well. Yet another area is the combined effect of PRE with other forms of exercise namely, high intensity aerobic training. It is well known, that PRE and aerobic training provide different benefits, future research could investigate the combined benefit of PRE and aerobic exercise and provide an evidence based general exercise prescription that might serve as an adjunct treatment for patients with PD.
APPENDIX

*Warm Up and Cool Down Exercises*

1. Neck Circles

2. Trunk Rotation

3. Arm Circles
4. Hamstring Stretches

5. Ankle Stretches
**Fitness Counts**

*Stretching Exercises*

1. Neck Stretch

![Neck Stretch](image1)

2. Lying Rotation Stretch

![Lying Rotation Stretch](image2)

3. Chest Stretch

![Chest Stretch](image3)
4. Overhead Stretch
**Strengthening Exercises**

1. Quadriceps Strengthening

2. Quadruped Trunk Strengthening

3. Prone on Elbows
Balance Exercises

1. Weight Shift Forwards

2. Weight Shift Backwards

3. One Legged Standing (Holding on to Wall)
4. One Legged Standing (Not Holding on to Wall)
Progressive Resistance Exercises

1. Chest Press

2. Reverse Fly
3. Lattismus Pull Down

4. Double Leg Press
5. Hip Extension

6. Biceps Curl
7. Shoulder Press

8. Rotary Calf

9. Triceps Pull Down (standing)
10. Triceps Pull Down (seated)

11. Seated Quadriceps
12. Back Extension
CITED LITERATURE


Goldman-Rakic, P. (1987). Circuitry of primate prefrontal cortex and the regulation of behavior by representational memory. In F. Plum, & V. Mountcastle (Eds.), *Handbook of physiology, section 1, the nervous system* (pp. 373). Bethesda, MD: American Physiological Society.


Weiskrantz (Eds.), *Attention, selection, awareness and control* (pp. 197-231). Oxford: Oxford University Press.


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INSTITUTIONAL REVIEW BOARD PROTOCOL APPROVAL

Protocol approval from 2006 to 2009 for experiment reported in chapter 3
Recruitment Material(s):
   a) UIC Recruitment Flyer: Flyer #1. 5 Healthy males, Version #2, 10/31/04
   b) UIC Recruitment Flyer: Flyer #2, Healthy (neurologically normal) subjects, Version #2, 10/31/04
   c) UIC Recruitment Flyer: Research Motor Control Laboratory, Flyer #3, Version 2, 10/31/04
   d) Patient Letter, Motor Control - Statement of Interest, Version #3, 10/30/2001
   e) Follow-up Letter, Cover Letter Version #1, 1/7/04
   f) Recruitment Letter, Dear Dr. Daniel Cucos, Version #2, 1/7/2004

Informed Consent(s):
   a) Motor Deficits # 1998-1161, Version # 2, Follow Up Addendum Neurologically Normal, 1/19/2004
   b) Motor Deficits # 1998-1161, Version # 2, Follow Up Addendum Medication, 1/19/2004
   c) Motor Deficits # 1998-1161, Version # 1, Follow Up Addendum Brain Stimulation, 1/7/2004

HIPAA Authorization(s):
   a) Waiver of HIPAA authorization for recruitment purposes granted under [45 CFR 164.512(i)(1)(ii)]
   b) UIC "Motor Deficits # 1998-1161 - Authorization", Version # 1, 3/31/03

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Please remember to:

→ Use your research protocol number (1998-1161) on any documents or correspondence with the IRB concerning your research protocol.

→ Review and comply with all requirements on the enclosure.

"UIC Investigator Responsibilities, Protection of Human Research Subjects"

Please note that the UIC IRB has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.
We wish you the best as you conduct your research. If you have any questions or need further help, please contact OPRS at (312) 996-1711 or me at (312) 355-1404. Please send any correspondence about this protocol to OPRS at 203 AOB, M/C 672.

Sincerely,

[Signature]

Sherilah R. Graham, BS
IRB Coordinator, IRB # 1
Office for the Protection of Research Subjects

Enclosure(s):

1. **UIC Investigator Responsibilities, Protection of Human Research Subjects**
2. **Informed Consent Document(s):**
   a) Motor Deficits # 1998-1161, Version # 2, Follow Up Addendum Neurologically Normal, 1/19/2004
   b) Motor Deficits # 1998-1161, Version # 2, Follow Up Addendum Medication, 1/19/2004
   c) Motor Deficits # 1998-1161, Version # 1, Follow Up Addendum Brain Stimulation, 1/7/2004
3. **Recruiting Material(s):**
   a) UIC Recruitment Flyer: Flyer # 1, Healthy males, Version # 2, 10/31/04
   b) UIC Recruitment Flyer: Flyer # 2, Healthy (neurologically normal) subjects, Version # 2, 10/31/04
   c) UIC Recruitment Flyer: Recruitment - Statement of interest, Version # 2, 10/31/04
   d) Patient Letter, Motor Control - Statement of interest, Version # 3, 10/30/2001
   e) Follow-up Letter, Cover Letter Version # 1, 1/7/04
   f) Recruitment Letter, Dear Dr. Daniel Ceratos, Version # 2, 1/7/2004
4. **Optional Form 310 - Protection of Human Subjects, Assurance Identification/Certification/Declaration**

cc: Mark D. Grabiner, Department of Movement Sciences, M/C 194
December 10, 2007

Daniel Corcos, PhD
Department of Movement Sciences
Movement Sciences, A11S
808 S. Wood St., 690 CMF, MC 994
Chicago, IL 60612
Phone: (312) 355-1708 / Fax: (312) 413-3699

RE: Protocol # 1998-1161
"Motor Deficits-Experimental Correlates"

Dear Dr. Corcos:

Your Continuing Review received on November 15, 2007 was reviewed and approved by the Institutional Review Board (IRB) #1 by the Convened review process on December 5, 2007. You may now continue your research.

Please note the following information about your approved research protocol:

Approved Subject Enrollment #: 500
Additional Determinations for Research Involving Minors: These determinations have not been made for this study since it has not been approved for enrollment of minors.
Performance Sites: UIC, Rush Presbyterian St. Luke's Medical Center,
Institute of Neurology in London
Sponsor: NIH - NINDS
PA#: 2005-06809
Grant/Contract No.: R01 NS40962-08
Grant/Contract Title: STN Stimulation: Neural Control of Movement and Posture
Research Protocol:
   a) HHS-NIH-NS40962, "STN Stimulation: Neural Control of Movement and Posture", renewal dated October 26, 2004

Recruitment Materials:
   a) UIC Recruitment Flyer: Flyer # 1, 5 Healthy males, Version # 2, 10/31/04
   b) UIC Recruitment Flyer: Flyer # 2, Healthy (neurologically normal) subjects, Version # 2.

Phone: 312-996-1711 http://www.uic.edu/dept/chr/opsr/ FAX: 312-413-2929
Informed Consents:

a) Motor Deficits # 1998-1161, Version # 2, Follow Up Addendum Neurologically Normal, 1/19/2004
b) Motor Deficits # 1998-1161, Version # 2, Follow Up Addendum Medication, 1/19/2004
c) Motor Deficits # 1998-1161, Version # 1, Follow Up Addendum Brain Stimulation, 1/7/2004

HIPAA Authorizations:

a) Waiver of HIPAA authorization for recruitment purposes granted under [45 CFR 164.512(i)(1)(ii)]
b) UIC "Motor Deficits # 1998-1161 - Authorization", Version # 1, 3/31/03

Please note the Review History of this submission:

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Please remember to:

⇒ Use your research protocol number (1998-1161) on any documents or correspondence with the IRB concerning your research protocol.

⇒ Review and comply with all requirements on the enclosure.

"UIC Investigator Responsibilities, Protection of Human Research Subjects"

Please note that the UIC IRB has the right to seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

Please be aware that if the scope of work in the grant/project changes, the protocol must be amended and approved by the UIC IRB before the initiation of the change.

We wish you the best as you conduct your research. If you have any questions or need further help, please contact OPRS at (312) 996-1711 or me at (312) 413-3788. Please send any correspondence about this protocol to OPRS at 203 AOB, M/C 672.
Sincerely,

Rachel Okech
IRB Coordinator, IRB #1
Office for the Protection of Research Subjects

Enclosures:

1. **UIC Investigator Responsibilities, Protection of Human Research Subjects**

2. **Informed Consent Documents:**
   a) Motor Deficits # 1998-1161, Version # 2, Follow Up Addendum Neurologically Normal, 1/19/2004
   b) Motor Deficits # 1998-1161, Version # 2, Follow Up Addendum Medication, 1/19/2004
   c) Motor Deficits # 1998-1161, Version # 1, Follow Up Addendum Brain Stimulation, 1/7/2006

3. **Recruiting Materials:**
   a) UIC Recruitment Flyer: Flyer # 1, 5 Healthy males, Version # 2, 10/31/04
   b) UIC Recruitment Flyer: Flyer # 2, Healthy (neurologically normal) subjects, Version # 2, 10/30/04
   c) UIC Recruitment Flyer: Research Motor Control Laboratory, Flyer # 3, Version 2, 10/31/04
   d) Patient Letter, Motor Control - Statement of Interest, Version # 3, 10/30/2001
   e) Follow-up Letter, Cover Letter Version # 1, 1/7/04
   f) Recruitment Letter, Dear Dr. Daniel Cirecos, Version # 2, 1/7/2004

4. **Optional Form 310 - Protection of Human Subjects, Assurance Identification/Certification/Declaration**

cc: Mark D. Grabiner, Department of Movement Sciences, M/C 194
    OVR CR Administration, M/C 672
December 16, 2008

Daniel Corcos, PhD
Department of Kinesiology and Nutrition
Kinesiology and Nutrition
808 S. Wood St., 690 AHSB, M/C 994
Chicago, IL 60612
Phone: (312) 355-1708 / Fax: (312) 413-3699

RE: Protocol # 1998-1161
"Motor Deficits-Experimental Correlates"

Dear Dr. Corcos:

The Institutional Review Board #1 reviewed and approved your Continuing Review by the
Convened review process on December 3, 2008. You may now continue your research.

Please note the following information about your approved research protocol:

Please provide documentation of annual renewal and approval from the Institute of
Neurology in London when available.

Protocol Approval Period: December 18, 2008 - December 17, 2009
Approved Subject Enrollment #: 500 Total (223 enrolled to date)
Additional Determinations for Research Involving Minors: These determinations have not
been made for this study since it has not been approved for enrollment of minors.
Performance Sites:
- Neurology in London

Sponsor: NIH - NINDS
PAF#: 2095-06809
Grant/Contract No: R01 NS-40892-08
Grant/Contract Title: STN Stimulation: Neural Control of Movement and Posture

Research Protocols:  
- HHS-NIH-NS40892, "STN Stimulation: Neural Control of Movement and Posture", renewal dated October 26, 2004

Phone: 312-996-1711  http://www.uic.edu/depts/ocr/ops/  FAX: 312-413-2929
Recruitment Material(s):
   a) UIC Recruitment Flyer: Flyer # 1, 5 Healthy males, Version # 2, 10/31/04
   b) UIC Recruitment Flyer: Flyer # 2, Healthy (neurologically normal) subjects, Version # 2, 10/31/04
   c) UIC Recruitment Flyer: Research Motor Control Laboratory, Flyer # 3, Version 2, 11/3/04
   d) Patient Letter, Motor Control - Statement of Interest, Version # 3, 10/30/2001
   e) Follow-up Letter, Cover Letter Version # 1, 1/7/04
   f) Recruitment Letter, Dear Dr. Daniel Corcos, Version # 2, 1/7/2004

Informed Consent(s):
   a) Motor Deficits # 1998-1161, Version # 2, Follow Up Addendum Neurologically Normal, 1/19/2004
   b) Motor Deficits # 1998-1161, Version # 2, Follow Up Addendum Medication, 1/19/2004
   c) Motor Deficits # 1998-1161, Version # 1, Follow Up Addendum Brain Stimulation, 1/7/2004

HIPAA Authorization(s):
   a) Waiver of HIPAA authorization for recruitment purposes granted under [45 CFR 164.512(i)(1)(i)]
   b) UIC "Motor Deficits # 1998-1161 - Authorization", Version # 1, 3/31/03

Please note the Review History of this submission:

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Please remember to:

→ Use your research protocol number (1998-1161) on any documents or correspondence with the IRB concerning your research protocol.

→ Review and comply with all requirements on the enclosure,
   "UIC Investigator Responsibilities. Protection of Human Research Subjects"

Please note that the UIC IRB has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

Please be aware that if the scope of work in the grant/project changes, the protocol must be amended and approved by the UIC IRB before the initiation of the change.
We wish you the best as you conduct your research. If you have any questions or need further help, please contact OPRS at (312) 996-1711 or me at (312) 355-1404. Please send any correspondence about this protocol to OPRS at 203 AOB, M/C 672.

Sincerely,

[Signature]

Sheilah R. Graham, BS
IRB Coordinator, IRB #1
Office for the Protection of Research Subjects

Enclosures:

1. UIC Investigator Responsibilities, Protection of Human Research Subjects
2. Informed Consent Document(s):
   a) Motor Deficits, #1998-1161, Version #2, Follow Up Addendum Neurologically Normal, 1/19/2004
   b) Motor Deficits #1998-1161, Version #2, Follow Up Addendum Medication, 1/19/2004
   c) Motor Deficits #1998-1161, Version #1, Follow Up Addendum Brain Stimulation, 1/7/2004
3. Recruiting Material(s):
   a) UIC Recruitment Flyer: Flyer #1, 5 Healthy males, Version #2, 10/31/04
   b) UIC Recruitment Flyer: Flyer #2, Healthy (neurologically normal) subjects, Version #2, 10/31/04
   c) UIC Recruitment Flyer: Research Motor Control Laboratory. Flyer #3, Version 2, 11/13/04
   d) Patient Letter, Motor Control - Statement of Interest, Version #3, 10/30/2001
   e) Follow-up Letter, Cover Letter Version #1, 1/7/04
   f) Recruitment Letter, Dear Dr. Daniel Coreas, Version #2, 1/7/2004
4. Optional Form 310 - Protection of Human Subjects, Assurance Identification/Certification/Declaration (If federally supported)

cc: Mark D. Grabner, Department of Kinesiology and Nutrition, M/C 194
    OVCRI Administration, M/C 672
Protocol approval from 2007 to 2012 for experiments reported in chapters 4 and 5

University of Illinois
at Chicago

Office for the Protection of Research Subjects (OPRS)
Office of the Vice Chancellor for Research OBC 657B
3330 S. hooks Avenue, Willow Building
1139 W. 31st St.
Chicago, Illinois 60616-8427

Approval Notice
Initial Review (Response To Modifications)

May 3, 2007

Daniel Corcos, PhD
Department of Movement Sciences
Movement Sciences, A.H.S.
808 S. Wood St., 690 CME, M/C 994
Chicago, IL 60612
Phone: (312) 355-1708 / Fax: (312) 413-3699

RE: Protocol # 2007-0115
"Exercise and Motor Control"

Dear Dr. Corcos:

Your Initial Review (Response To Modifications) was reviewed and approved by members of IRB #1 under the Expedited review process on May 3, 2007. You may now begin your research.

Please note the following information about your approved research protocol:

This study has been approved by the UIC IRB; however, patient recruitment cannot begin without approval from the Rush University Medical Center IRB. Such approval should be submitted to the UIC IRB via amendment upon availability.

Protocol Approval Period:

Approved Subject Enrollment #: 75

Performance Sites: UIC, Rush University Medical Center

Sponsor: NIMH-National Institutes of Health

Research Protocols:

a) Grant Application: Motor Deficits - Experimental and Clinical Correlates

b) Appendix 1 - Exercise and Motor Control: Testing Protocols; Version 3, 5-1-07

c) Appendix 2 - Exercise and Motor Control: Recruitment, Testing and Exercise Protocols; Version #3, 5-1-07

Recruitment Materials:

a) Flyer: Volunteers Needed; Version 2, 5-1-07

b) Phone Screening Script, Exercise and Motor Control; Version #1, 4-6-07

Informed Consents:

a) UIC Consent: Exercise and Motor Control - Neurologically Normal; Version #3, 5-1-07

Phone: 312-696-4711
http://www.mc.edu/depts/ops/irb
FAX: 312-413-2929
b) UIC Consent: Exercise and Motor Control - Neurologically Involved; Version #3, 5-1-07

HIPAA Authorization:

a) The UIC IRB determined that HIPAA Authorization is not required when subjects are enrolled at UIC, as no PHI will be collected from medical records following enrollment. Additionally, any PHI collected from patients at Rush during the recruitment process must be approved by the Rush IRB.

Additional Determinations for Research Involving Minors:

These determinations have not been made for this study since it has not been approved for enrollment of minors.

Please note the Review History of this submission:

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<td>05/03/2007</td>
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Please remember to:

→ Use your research protocol number (#2007-0115) on any documents or correspondence with the IRB concerning your research protocol.

→ Review and comply with all requirements on the enclosure.

"UIC Investigator Responsibilities, Protection of Human Research Subjects"

Please note that the UIC IRB has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

We wish you the best as you conduct your research. If you have any questions or need further help, please contact OPRS at (312) 996-1711 or me at (312) 413-3202. Please send any correspondence about this protocol to OPRS at 203 AOB, M/C 672.

Sincerely,

[Signature]

Teresa D. Johnston, B.S.
Assistant Director, IRB #1
Office for the Protection of Research Subjects

Enclosures:

1. UIC Investigator Responsibilities, Protection of Human Research Subjects
2. Informed Consent Documents:
   a) UIC Consent: Exercise and Motor Control - Neurologically Normal; Version #3, 5-1-07
   b) UIC Consent: Exercise and Motor Control - Neurologically Involved; Version #3, 5-1-07
3. **Recruiting Materials:**
   a) Flyer: Volunteers Needed; Version 2, 5-1-07
   b) Phone Screen Script, Exercise and Motor Control; Version #1, 4-6-07

4. **Optional Form 310 - Protection of Human Subjects, Assurance Identification/Certification/Declaration**

cc: Mark D. Grabiner, Department of Movement Sciences, M/C 194
March 11, 2008

Daniel Coreas, PhD
Department of Kinesiology and Nutrition
Kinesiology and Nutrition
808 S. Wood St., 690 AltSB, MC 994
Chicago, IL 60612
Phone: (312) 355-1708 / Fax: (312) 413-3699

RE: Protocol # 2007-0115
“Exercise and Motor Control”

Dear Dr. Coreas:

The Institutional Review Board #1 reviewed and approved your Continuing Review by the Convened review process on March 5, 2008. You may now continue your research.

Please note the following information about your approved research protocol:

**Protocol Approval Period:** March 5, 2008 - March 4, 2009

**Approved Subject Enrollment #:** 75 Total (18 enrolled)

**Additional Determinations for Research Involving Minors:** These determinations have not been made for this study since it has not been approved for enrollment of minors.

**Performance Sites:** UIC; Rush Presbyterian St. Luke’s Medical Center; Provena Mercy Medical Center Health and Wellness Center; Edward Health and Fitness Centers; Taylor Family Branch YMCA; Fitness Formula Clubs; Cardinal Fitness of Des Plaines; Wheaton Park District; Parks Plus Fitness Center; Governor’s State University’s Recreation and Fitness Center; Northwest Athletic Club; Woodstock Recreation Department; Lockport Chiropractic; 9th Street Fitness, Addison Park District

**Sponsor:** NIH-National Institutes of Health

**PAF #:** 2007-02014

**Grant/Contract No:** RO1-NS028472

**Grant/Contract Title:** Motor Deficits - Experimental Correlates

**Research Protocol(s):**

a) Grant Application; Motor Deficits - Experimental and Clinical Correlates
b) Appendix 1 - Exercise and Motor Control: Testing Protocols; Version 4, 7-13-07
c) Appendix 2 - Exercise and Motor Control: Recruitment, Testing and Exercise Protocols; Version 64, 7-13-07

Phone: 312-996-1711 http://www.uic.edu/depts/ocrer regs FAX: 312-413-2429
Recruitment Material(s):
  a) Flyer: Volunteers Needed; Version 2, 5-4-07
  b) Phone Screening Script, Exercise and Motor Control; Version #1, 4-6-07

Informed Consent(s):
  a) UIC Consent: Exercise and Motor Control - Neurologically Normal; Version #5, date 2-20-08
  b) UIC Consent: Exercise and Motor Control - Neurologically Involved; Version #5, date 2-20-08

HIPAA Authorization(s):
  a) The UIC IRB determined that HIPAA Authorization is not required when subjects are
     enrolled at UIC, as no PHI will be collected from medical records following enrollment.
     Additionally, any PHI collected from patients at Rush during the recruitment process must
     be approved by the Rush IRB.

Please note the Review History of this submission:

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Please remember to:

→ Use your research protocol number (2007-0115) on any documents or correspondence with
  the IRB concerning your research protocol.

→ Review and comply with all requirements on the enclosure.
  "UIC Investigator Responsibilities, Protection of Human Research Subjects"

Please note that the UIC IRB has the prerogative and authority to ask further questions,
seek additional information, require further modifications, or monitor the conduct of your
research and the consent process.

Please be aware that if the scope of work in the grant/project changes, the protocol must be
amended and approved by the UIC IRB before the initiation of the change.

We wish you the best as you conduct your research. If you have any questions or need further
help, please contact OPRS at (312) 996-1711 or me at (312) 355-1404. Please send any
correspondence about this protocol to OPRS at 203 AOB, M/C 672.

Sincerely,

Sheilah R. Graham, BS
IRB Coordinator, IRB # 1
Office for the Protection of Research Subjects
Enclosure(s):

1. UIC Investigator Responsibilities, Protection of Human Research Subjects
2. Informed Consent Document(s):
   a) UIC Consent: Exercise and Motor Control - Neurologically Normal; Version #5, date 2-20-08
   b) UIC Consent: Exercise and Motor Control - Neurologically Involved; Version
3. Recruiting Material(s):
   a) Flyer: Volunteers Needed; Version 2, 5-1-07
   b) Phone Screening Script: Exercise and Motor Control; Version 61, 4-6-07
4. Optional Form 310 - Protection of Human Subjects, Assurance
   Identification/Certification/Declaration (If federally supported)
5. VA Form 10-1223 - Report of Subcommittee on Human Studies (If JBVAMC)

cc: Mark D. Grabiner, Department of Kinesiology and Nutrition, M/C 194
    OVCRA Administration, M/C 672
March 3, 2009

Daniel Coreos, PhD
Department of Kinesiology and Nutrition
Kinesiology and Nutrition
808 S. Wood St., 690 AHSB, M/C 994
Chicago, IL 60612
Phone: (312) 355-1708 / Fax: (312) 413-3699

RE: Protocol # 2007-0115
“Exercise and Motor Control”

Please note that the recruitment flyer (version #3, dated 02/27/2009) was modified with Amendment #10 and is included with this approval letter.

Dear Dr. Coreos:

Your Continuing Review (Response To Modifications) was reviewed and approved by the Expedited review process on February 27, 2009. You may now continue your research.

Please note the following information about your approved research protocol:

Protocol Approval Period: March 5, 2009 - March 4, 2010
Approved Subject Enrollment #: 75 (51 enrolled to date)
Additional Determinations for Research Involving Minors: These determinations have not been made for this study since it has not been approved for enrollment of minors.
Performance Sites: UIC, Rush Presbyterian St. Luke’s Medical Center, Provena Mercy Medical Center Health and Wellness Center, Edward Health and Fitness Centers, Taylor Family Branch YMCA, Fitness Formula Clubs, Cardinal Fitness of Des Plaines, Wheaton Park District Parks Plus Fitness Center, Governor’s State University’s Recreation and Fitness Center, Northwest Athletic Club, Woodstock Recreation Department, Lockport Chiropractic, 9th Street Fitness, Addison Park District, Gottlieb Fitness Center, Life Fitness, Inc., Lake Forest Health and Fitness Center, Valpo Athletic Club, Schaumburg Park District, Skokie Park District, Tinley Park Fitness, Lifetime Fitness, Sports Medicine Performance, Body Tech Total Fitness, Lakeshore Athletic Club, Bally Total Fitness, FVC- Evanston Athletic Club, Creative Common Sense, J.L.C.
Sponsor: NIH-National Institutes of Health
PAF#: 2007-02634
Grant/Contract #: RO1-NR028127-12
Phone: 312-996-1711 http://www.uic.edu/depts/over oprs/ FAX: 312-413-2929
Grant/Contract Title: Motor Deficits - Experimental Correlates

Research Protocols:

a) Grant Application: Motor Deficits - Experimental and Clinical Correlates
c) Appendix 2 - Exercise and Motor Control: Recruitment, Testing and Exercise Protocols: Version #5. 2-26-09

Recruitment Materials:

a) Phone Screening Script, Exercise and Motor Control; Version #1. 4-6-07

Informed Consent(s):

a) UIC Consent: Exercise and Motor Control - Neurologically Normal: Version #5. date 2-20-08
b) UIC Consent: Exercise and Motor Control - Neurologically Involved: Version #6. date 2-24-09

HIPAA Authorization(s):

a) The UIC IRB determined that HIPAA Authorization is not required when subjects are enrolled at UIC, as no PHI will be collected from medical records following enrollment. Additionally, any PHI collected from patients at Rush during the recruitment process must be approved by the Rush IRB.

Please note the Review History of this submission:

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Please remember to:

\[\rightarrow\] Use your research protocol number (2007-0115) on any documents or correspondence with the IRB concerning your research protocol.

\[\rightarrow\] Review and comply with all requirements on the enclosure.

*UIC Investigator Responsibilities, Protection of Human Research Subjects*

Please note that the UIC IRB has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

Please be aware that if the scope of work in the grant/project changes, the protocol must be amended and approved by the UIC IRB before the initiation of the change.
We wish you the best as you conduct your research. If you have any questions or need further help, please contact OPRS at (312) 996-1711 or me at (312) 413-7323. Please send any correspondence about this protocol to OPRS at 203 AOB, M/C 672.

Sincerely,

/Jennifer Joaquin, MPH
IRB Coordinator, IRB #1
Office for the Protection of Research Subjects

Enclosures:

1. UIC Investigator Responsibilities, Protection of Human Research Subjects
2. Informed Consent Document(s):
   a) UIC Consent: Exercise and Motor Control - Neurologically Normal; Version 
      #5, date 2-20-08
   b) UIC Consent: Exercise and Motor Control - Neurologically Involved; Version 
      #6, date 2-24-09
3. Recruiting Material(s):
   a) Phone Screening Script, Exercise and Motor Control; Version #1, 4-6-07
   b) Flyer: Volunteers Needed; Version 3, 2-27-2009
4. Optional Form 310 - Protection of Human Subjects, Assurance
   Identification/Certification/Declaration

cc: Mark D. Graber, Department of Kinesiology and Nutrition, M/C 194
    OVCRR Administration, M/C 672
Approval Notice

Continuing Review (Response to Modifications)

February 12, 2010

Daniel Corcos, PhD
Department of Kinesiology and Nutrition
Kinesiology and Nutrition
808 S. Wood St., 690 AHSB, M/C 994
Chicago, IL 60612
Phone: (312) 355-1708 Fax: (312) 355-2305

RF: Protocol # 2007-0115
“Exercise and Motor Control”

Dear Dr. Corcos:

Your Continuing Review (Response to Modifications) was reviewed and approved by the Expedited review process on February 11, 2010. You may now continue your research.

Please note the following information about your approved research protocol:

Protocol Approval Period:
February 11, 2010 - January 19, 2011

Approved Subject Enrollment #: 75 Total (61 enrolled to date)

Additional Determinations for Research Involving Minors: These determinations have not been made for this study since it has not been approved for enrollment of minors.

Performance Sites: UIC, Rush Presbyterian St. Luke’s Medical Center, Provena Mercy Medical Center, Health and Wellness Centers, Edward Health and Fitness Centers, Taylor Family Branch YMCA, Fitness Formula Clubs, Cardinal Fitness of Des Plaines, Wheaton Park District Parks Plus Fitness Center, Governor’s State University’s Recreation and Fitness Center, Northwest Athletic Club, Woodstock Recreation Department, Lockport Chiropractic, 9th Street Fitness, Addison Park District, Gottlieb Fitness Center, Life Fitness, Inc., Lake Forest Health and Fitness Center, Valpo Athletic Club, Schaumburg Park District, Skokie Park District, Tinley Park Fitness, Lifetime Fitness, Sports Medicine Performance, Body Tech Total Fitness, Lakeshore Athletic Club, Barry Total Fitness, EVC - Evanston Athletic Club, Creative Common Sense, L.L.C., Elmhurst Park District - Courts Plus, Bartlett Park District

Sponsor: NIH-National Institutes of Health

PA#: 2007-02034

Grant/Contract No: RO1-NS028127-12

Grant/Contract Title: Motor Deficits - Experimental Correlates
**Research Protocol(s):**
- a) Grant Application: Motor Deficits - Experimental and Clinical Correlates
- c) Appendix 2 - Exercise and Motor Control: Recruitment, Testing and Exercise Protocols: Version #5, 2-26-09

**Recruitment Material(s):**
- a) Phone Screening Script, Exercise and Motor Control; Version #1, 4-6-07
- b) Flyer: Volunteers Needed; Version 3, 2-27-2009

**Informed Consent(s):**
- a) UIC Consent: Exercise and Motor Control - Neurologically Normal; Version #5, date 2-20-08
- b) UIC Consent: Exercise and Motor Control - Neurologically Involved; Version #6, date 2-24-09

**HIPAA Authorization(s):**
- a) The UIC IRB determined that HIPAA Authorization is not required when subjects are enrolled at UIC, as no PHI will be collected from medical records following enrollment. Additionally, any PHI collected from patients at Rush during the recruitment process must be approved by the Rush IRB.

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Please remember to:

→ Use your research protocol number (2007-0115) on any documents or correspondence with the IRB concerning your research protocol.

→ Review and comply with all requirements on the enclosure, "UIC Investigator Responsibilities, Protection of Human Research Subjects"

Please note that the UIC IRB has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

Please be aware that if the scope of work in the grant/project changes, the protocol must be amended and approved by the UIC IRB before the initiation of the change.

We wish you the best as you conduct your research. If you have any questions or need further help, please contact OPRS at (312) 996-1711 or me at (312) 355-1404. Please send any correspondence about this protocol to OPRS at 203 AOB, M/C 672.
Sincerely,

[Signature]

Sheila R. Graham, BS
IRB Coordinator, IRB #1
Office for the Protection of Research Subjects

Enclosures:

1. UIC Investigator Responsibilities, Protection of Human Research Subjects

2. Informed Consent Document(s):
   a) UIC Consent: Exercise and Motor Control - Neurologically Normal; Version #5, date 2-20-08
   b) UIC Consent: Exercise and Motor Control - Neurologically Involved; Version #6, date 2-24-09

3. Recruiting Material(s):
   a) Phone Screening Script, Exercise and Motor Control; Version #1, 4-6-07
   b) Flyer: Volunteers Needed; Version 3, 2-27-2009

4. Optional Form 310 - Protection of Human Subjects, Assurance Identification/Certification/Declaration

cc: Charles B. Walter, Department of Kinesiology and Nutrition, MC 317
    OVCR Administration, MC 672
Approval Notice
Continuing Review

January 11, 2011

Dr. Corcos, PhD
Department of Kinesiology and Nutrition
Kinesiology and Nutrition
620 S. Wood St., 600 NHSB, MC 994
Chicago, IL 60612
Phone (312) 252-1708, Fax (312) 252-2308

IRB: Protocol # 2007-0115
"Exercise and Motor Control"

Dear Dr. Corcos:

Your Continuing Review was reviewed and approved by the Convened review process on January 5, 2011. You may now continue your research.

Please note the following information about your approved research protocol:

Approved Subject Enrollment: 400 Total (70 enrolled to date)

Additional Determinations for Research Involving Minors: These determinations have not been made for this study since it has not been approved for enrollment of minors.

Performance Sites:
- UIUC, Rush Presbyterian St. Luke's Medical Center,
- Provena Mercy Medical Center, Health and Wellness Center, Edward Health and Fitness Centers,
- Taylor Family Branch YMCA, Fitness Formula Clubs, Cardinal Fitness of Des Plaines, Wheaton
- Park District Parks Plus Fitness Center, Governor's State University's Recreation and Fitness Center, Northwest Athletic Club, Woodstock Recreation Department, Lockport Chiropractic, 9th Street Fitness, Addison Park District, Gottlieb Fitness Center, Life Fitness, Inc., Lake Forest Health and Fitness Center, Valpo Athletic Club, Schaumburg Park District, Skokie Park District
- Fitch Park, Fitness, Lifetime Fitness, Sports Medicine Performance, Body Tech Total Fitness, Laskin Athletic Club, Bally Total Fitness, FVC- Expansion Athletic Club, Creative Common Sense, L.L.C., Elmhurst Park District - Courts Plus, Bartlett Park District, Greenbury YMCA, Fitness Zone

Sponsor: NIH-National Institutes of Health
PAR#: 2007-02034
Grant Contract No: RO1-NS028127-12
Grant Contract Title: Motor Deficits - Experimental Correlates

http://www.arl.edu/crpts/overopts FAX 312-413-2029
Research Protocol(s):

- Grant Application: Motor Deficits - Experimental and Clinical Correlates
- Appendix 2 - Exercise and Motor Control: Recruitment, Testing and Exercise Protocols; Version #6, 5-15-10
- Appendix 1 - Exercise and Motor Control: Testing Protocols; Version 5, 5-15-2010

Investigational Device:
- Kinesa (ID#: KO383872)

Device Risk Determination:
- Non-significant Risk

Recruitment Material(s):
- Phone Screening Script, Exercise and Motor Control; Version #1, 4-6-07
- Flyer: Volunteers Needed; Version 4, 5-15-2010

Informed Consent(s):
- UIC Consent: Exercise and Motor Control - Neurologically Normal; Version #6, date 5-15-10
- UIC Consent: Exercise and Motor Control - Neurologically Involved; Version #7, date 5-15-2010
- Exercise and Motor Control - Neurologically involved: modified exercise program, Version #1, date 5-15-10

HIPAA Authorization(s):
- The UC IRB determined that HIPAA Authorization is not required when subjects are enrolled at UIC, as no PHI will be collected from medical records following enrollment. Additionally, any PHI collected from patients at Rush during the recruitment process must be approved by the Rush IRB.

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1. Your research protocol number (2007-0115) on any documents or correspondence with the IRB concerning your research protocol.

2. Review and comply with all requirements as stated in the enclosure.

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We wish you the best as you conduct your research. If you have any questions or need further help, please contact OPRS at (312) 996-1711 or me at (312) 355-1404. Please send any correspondence about this protocol to OPRS at 203 AOB, M/C 672.

Sincerely,

[Signature]

Sheriab R. Graham, IRS
IRB Coordinator, IRB #1
Office for the Protection of Research Subjects

Enclosures:

1. UIC Investigator Responsibilities, Protection of Human Research Subjects
2. Informed Consent Document(s):
   a) UIC Consent: Exercise and Motor Control - Neurologically Normal; Version #6, date 5-15-10
   b) UIC Consent: Exercise and Motor Control - Neurologically Involved; Version #7, date 5-15-2010
   c) Exercise and Motor Control - Neurologically involved; modified exercise program, Version #1, date 5-15-10
3. Recruiting Material(s):
   a) Phone Screening Script, Exercise and Motor Control; Version #1, 4-6-07
   b) Flyer: Volunteers Needed; Version #4, 5-15-2010

[Signature]
Charles B. Walker, Department of Kinesiology and Nutrition, M/C 517
OVC Administration, M/C 672
VITA

NAME: Fabian Jude David

EDUCATION: Bachelor of Science, Physical Therapy, Sri Ramachandra Medical College and Research Institute, Chennai, Tamilnadu, India, 1998

Post-Graduate Diploma, Special Education, Spastic Society of India, Chennai, Tamilnadu, India, 1999

Master of Science, Movement Science, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA, 2004

Doctor of Philosophy, Kinesiology, University of Illinois at Chicago, Chicago, Illinois, USA, 2012

HONORS: Outstanding Thesis Award, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA, 2004

Distinction in Anatomy, Sri Ramachandra Medical College and Research Institute, Chennai, Tamilnadu, India, 1999

PROFESSIONAL MEMBERSHIP: The Society for The Neural Control of Movement


VITA (continued)


VITA (continued)


