THE EFFECTS OF HIGH-SPEED, LOW-FORCE RECUMBENT CYCLING: AN INTERVENTION IN OLDER A DULTS AND PARKINSON'S DISEASE

by

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ABSTRACT

Decreased mobility substantially reduces independence and quality of life while contributing to increased rates of disability and health care costs. Exercise is a proven strategy to improve these qualities. Exercise is known to benefit every physiological system with the strongest literature support for cardiovascular health and strength gains. However, less is known about the potential to enhance mobility with exercises that target rapidly adapting central nervous system (CNS) factors. While the current exercise recommendations from federal agencies (CDC, NIH, and DHHS) are prudent, they neglect the potential benefits of high speed exercises that target the CNS correlates of muscular quickness. Results of this research are expected to inform improvements in exercise recommendations for older adults and people with movement disorders. Additionally, results are expected to fill a gap in the literature related to neural adaptations to high speed training in older adults and people with Parkinson's disease (PD).

The purpose of Aim 1 was to determine whether there exist age-related differences in the speed and control of rapid isometric force pulses in different muscles in young and older adults. It was hypothesized that older adults would have lesser rate of force development-scaling factors (RFD-SF) and more variability in the performance of rapid force production.

The purpose of Aim 2 was to determine the effects of a six week exercise intervention that uses high-speed, low-resistance stationary recumbent cycling in older adults. Participants completed pre- and post-exercise tests as well as 4 week follow-up to determine retention of changes. It was hypothesized that there would be improvements in the following measures: 1) Time to peak force and the RFD-SF during isometric knee extension; 2) Standardized measures of walking function; 3) Perceived function and quality of life. It was also hypothesized that improvements in the previous measures would be retained four weeks after training. To elucidate the neuromuscular mechanisms that occur with improved speed in older adults, it was hypothesized that this would be most strongly related to the rate of rise in the surface electromyogram (RER). We also aimed to determine if training the legs affects CNS mechanisms that transfer to the following in older adults: 1) Increased time to peak force and RFD-SF during isometric elbow extension; 2) Improved RER in elbow extensors; 3) Improved hand dexterity. It was also hypothesized that improvements in the previous measures would be retained four weeks after training.

The purpose of Aim 3 was to develop an improved method to selectively quantify paired motor unit discharge behavior underlying tremor. The method was then tested before and after three different treatments. It was hypothesized that interspike interval serial correlation with cluster analysis would allow us to quantify paired motor unit discharge behavior from isometric contractions in which motor unit discharge behavior is not solely bimodal.

Chapter 1

INTRODUCTION

From the year 2000 to 2012, the population of older adults increased by over five million which comprises ~13% of the U.S. population (U.S. Census, 2012). This number will continue to rise and it is projected that by 2050, 20% of the U.S. population will be aged 65 or older. Of the current ~40 million older adults, 19% have some form of disability that requires the use of special equipment (e.g. cane, wheelchair, special bed or telephone) and 33% do not engage in any physical activity (Behavioral Risk Factor Surveillance System, 2010).

A specific patient population that suffers from disability includes individuals with Parkinson's disease (PD). PD is a degenerative disorder of the central nervous system that inhibits the ability to generate smooth, controlled movements resulting in tremor; a rhythmic muscle contraction-relaxation in one or more body parts. These oscillations typically present in the hands and progress to other limbs (Wenzelburger R, Raethjen J, Löffler K, Stolze H, Illert M, 2000). It is caused by dopaminergic neuron death in the basal ganglia; an area of the brain that contributes to control of voluntary movements (Yehene, Meiran, & Soroker, 2008). The average age of those with PD is 60 years and is the most common neurodegenerative disease after Alzheimer's (de Lau & Breteler, 2006). While there is no cure for PD, exercise has been proven to ameliorate dysfunction caused by dysregulation of dopamine (Ridgel, Vitek, & Alberts, 2009); thus, reducing the

prevalence of tremor. Together, impaired mobility in older adults and people with PD represents a substantial contribution to health care costs.

The aims of this study were to improve and expand upon current scientific knowledge relating to the effects of exercise interventions on movement disability. Much is known about how to elicit adaptations to the central nervous system (CNS) correlates of strength and power. In addition, evidence exists that motor training can induce structural and functional plasticity in the brain including the basal ganglia (Conner, Culberson, Packowski, Chiba, & Tuszynski, 2003) and motor cortex (Adkins, Boychuk, Remple, & Kleim, 2006). In the context of mobility, less is known about how high speed exercise can improve the CNS correlates of quickness, especially at submaximal force levels. Utilizing high-speed, low-resistance cycling, the CNS can be targeted with the potential to improve functional ability. Results of the following studies highlight the need to improve muscular quickness in older adults and support speed-based exercise as a means to improve muscular quickness.

Poor quality of movement (e.g. slowness or poor control) has implications for independent living, mobility, and quality of life (Taylor et al., 2004). If we learn that quickness can be improved without requiring high-force muscle contractions, this knowledge would be an asset for developing interventions to enhance mobility in older adults and potentially the frail elderly. In addition, testing the effects of an acute bout of exercise on the motor unit correlates of tremor in PD provides information about the mechanistic basis of tremor and an evidence base supporting a means of non-pharmacological interventions.

Age Related Slowing of Movement

Falls and related injuries are among the most common and severe medical problems reported in the elderly (Hayes et al., 1996). While weakness has a moderate relationship with falls, the ability to produce submaximal forces very quickly may be more important. A strength training study in elderly adults showed that the ability to prevent falls declines more quickly with age and is more related to functional performance than maximal muscle strength (Suetta et al., 2004). An inverted pendulum model of falling showed that the ability to recover from a trip is determined by response time which includes the time for both sensory detection and the motor response (van den Bogert, Pavol, & Grabiner, 2002). Older adults have exhibited delayed muscular activation of the step leg in response a perturbation when compared to young (Thelen et al., 2000). Such slowing is also visible in measures of finger tapping times (Cousins, Corrow, Finn, & Salamone, 1998).

Not only is quickness relevant for fall prevention, it is also a likely determinant of success in many functional tasks that are not always correlated to measures of strength or peak power (Jaric, Radosavljevic-Jaric, & Johansson, 2002). Examples of such tasks affected by slowed movements may include movement initiation and catching a falling object (Hausdorff, Yogev, Springer, Simon, & Giladi, 2005), safely crossing the street (Langlois et al., 1997), typing and double-clicking a computer mouse (Bean, 2003). Optimal function translates to improved quality of life, independent living and decreased health care expenditure (Taylor et al., 2004).

Studies depicting age related slowing of movement during rapid isometric contractions (Macaluso et al., 2003; Klass, Baudry, & Duchateau, 2008; Bellumori, Jaric, & Knight, 2013) highlight the necessity of developing exercise interventions to improve this quality.

Improving Quickness

Physical quickness is an important movement quality in the contexts of aging, pathology and rehabilitation. Under the instructions to produce isometric muscular force pulses most rapidly (Wierzbicka, Wiegner, Logigian, & Young, 1991) and across a range of submaximal amplitudes, there is a positive linear relationship between the peak force (PF) of a pulse and the corresponding rate of force development (RFD). Such scaling results in relative invariance in the time required to achieve peak force regardless of the strength of the muscular contraction. Among contextually varied publications related to the scaling of RFD with respect to PF (Gordon & Ghez, 1984, 1987; Klass, Baudry, & Duchateau, 2008), the early paper by Freund & Budingen (1978) provides the most comprehensive and relevant background for this proposal.

The ability to generate force rapidly (RFD) in the knee extensors was shown to respond positively to sensorimotor training (Gruber & Gollhofer, 2004). With high ecological relevance to falls, this sensorimotor training included postural stabilization tasks consisting of exercises on wobbling boards, spinning tops, soft mats, and two-dimensional free moving platforms. Maximum RFD increased by 33% after training. This gain in RFD was accompanied by increases in vastus medialis surface EMG within

the first 100 ms of activation, which is a similar measure to the RER in aims 2 and 3. While promising, this training may be inappropriate for those who are frail or have impaired motor control.

Rapid force production is important for joint stabilization, and enhanced neuromuscular activation is an essential element to actively stiffen complexes within a short period of time (Gruber & Gollhofer, 2004). Increases in the ability to generate force have been attributed to improved neural drive to muscles. Consistent with the enhanced EMG, Gruber and Gollhofer (2004) cited increases in MU firing rate and earlier recruitment (Van Cutsem, Duchateau, & Hainaut, 1998). RFD is highly related to MU discharge rate (Nelson, 1996; Van Cutsem et al., 1998), changes in the recruitment of MUs (Kukulka & Clamann, 1981), or a combination of the two (Duchateau & Hainaut, 2003).

Resistance training increases RFD in young adults with corresponding increases in surface EMG, during the initial 100 ms of muscle activation (Aagaard, Simonsen, Andersen, Magnusson, & Dyhre-Poulsen, 2002; Van Cutsem et al., 1998). Barry et al. (2005) sought to determine if older adults also exhibit these changes during maximal rapid contractions of the elbow flexors. Results confirmed that four weeks of progressive resistance training significantly increases peak RFD (28.6% gain) and EMG values (16.8% gain) throughout the initial 100 ms of muscle activation. The present aims take a similar approach to testing a novel exercise intervention yet with more comprehensive examination of central and functional adaptations.

Van Cutsem et al. (1998) analyzed the changes in single MU behavior, in the tibialis anterior, as it contributes to increases in RFD after dynamic training. Subjects were trained 5 days a week for 12 weeks. Each training session consisted of ten sets of ten fast dorsiflexions against a load of 30-40% of the individual's maximal muscle strength. MU discharge rate increased significantly with training at submaximal force levels (30-40% MVC). That this study used low force levels for training provides support that maximal effort is not necessary to elicit strong neural adaptations. An increase in the percentage of 'doublet' firings (5.2 to 32.7%) was also observed. A doublet occurs when a MU fires twice in rapid succession, with brief (2-5 ms) interspike intervals. Doublets play a primary role in the ability to generate rapid force increases during movement initiation. It was concluded that with submaximal dynamic training, additional doublets and increased maximal firing rates contribute to RFD increases in voluntary muscle contraction. The present exercise intervention also used low force exercises but was based on stationary recumbent bicycles which are more accessible to older adults than isokinetic dynamometers.

Much has been learned about the neural basis of strength and RFD from exercise training studies and comparisons of young and older adults. A significant contribution to this work would be to develop and test exercise training methods that are appropriate for people with existing mobility limitations. The present intervention avoids high musculoskeletal loads and utilized seated cycling to reduce fall risk.

Neural & Muscular Contributions to Quickness

Initial motor unit firing rates during rapid muscle contractions are much higher than those observed during constant force and maximal effort voluntary contractions. For example, firing rates of 25-35 pulses per second during sustained contractions were seen in the FDI; when contractions were performed as fast as possible, firing rates increased to 80-100 pulses per second (Tanji & Kato, 1973).

Klass et al. (2008) compared MU discharge frequencies and RFD between young and older adults during rapid, submaximal, isometric contractions. Force exerted by the ankle dorsiflexors was evaluated and surface and intramuscular EMG were obtained from the tibialis anterior. At peak RFD during fast contractions, older adults exhibited a lower maximal RFD and integrated EMG (percent of total EMG burst) than the younger adults by 48% and 16.5%, respectively. During the contractions, older adults also displayed lower MU discharge rates and fewer double discharges. It was concluded that the age-related declines in neural activity and muscle contractile properties impaired the performance of rapid isometric contractions by older adults. Similar findings of less double discharge were also observed in older adults who performed ramp contractions to 50% MVC at rates of 10, 20, and 30% MVC/s (Christie & Kamen, 2006).

Muscle fiber type is one determinant of the amount and quickness of force that can be generated by muscle (Andersen & Aagaard, 2006). When classified by contractile properties, there are two general types of muscle fibers; type I and type II. Type I muscle fibers can be described as slow oxidative with relatively high endurance whereas type II are more involved with rapid, forceful muscle contractions. Typically, there has been a

greater interest in type II fibers when studying rapid force production and age-related sarcopenia (Dirks & Leeuwenburgh, 2002). A disproportionate atrophy of type II fibers, as compared with type I, is seen in older adults. Neurological changes are believed to be a major contributor to this sarcopenia (Dirks & Leeuwenburgh, 2002) including the decline in excitable MUs (Vandervoort, 2002). In age related remodeling of the nervous system, literature suggests that the death of larger motor neurons precedes the death and loss of fast twitch muscle fibers. Fortunately, it has been shown that higher rates of muscular contraction result in greater recruitment of fast-twitch MUs (Farina, Macaluso, Ferguson, & De Vito, 2004). If high-speed exercise excites the larger neurons that are affiliated with the fast twitch fibers, these neurons might be preserved.

Central Adaptation with Exercise

In creating exercise interventions that aim to improve function through CNS mechanisms, one aim was to determine whether training one set of extremities can elicit improvements in other extremities and functional tasks. It has been shown in Parkinsonian mice, that the rate of forced exercise is a primary contributor to global improvements in function (Tillerson, Caudle, Reveron, & Miller, 2003). Tandem cycling was utilized as a model to determine if this principle also applies to humans in which only the legs were trained. After 8 weeks of cycling, clinical measures of bradykinesia and rigidity improved 35% along with bimanual dexterity. These improvements were retained four weeks following exercise training and were attributed to alterations in feedforward processes with exercise suggesting an adaptation in central mechanisms

(Ridgel et al., 2009). The authors note that although improvements were evident and retained, the exact mechanism responsible for changes in central function remain unknown.

In healthy adults, voluntary exercise in both the upper (Lotze, Braun, Birbaumer, Anders, & Cohen, 2003) or lower (Perez, Lungholt, Nyborg, & Nielsen, 2004) extremities has been shown to increase motor cortical activation. This may be due to an increase in afferent feedback which contributes to the increased cortical activation (Ridgel et al., 2009). In the present work, it is postulated that the recruitment of fast-twitch MUs, in conjunction with increased motor cortical activation, may contribute to a central adaptation with exercise that results in improved central nervous drive.

Improvements following high intensity exercise may also be attributed to neuroplasticity, reduced dopamine loss, and increased brain derived neurotrophic factor. Activity dependent scaling of GABAergic synapse strength is regulated by brain derived neurotrophic factor which is enhanced with exercise, possibly due to increased blood flow to the brain (Fisher et al., 2008). This provides promising evidence of central adaptations with exercise. However, one limitation of this study was that the protocol for assessing function matched that of the training intervention and results may be attributable to a learning or practice effect (Ridgel et al., 2009). In the proposed study, we address this limitation with our design in which we study the central effects of high-speed training for the legs on the symptoms of quickness in the arms and tremor in the hands.

"To determine if exercise alters central motor processes, motor assessments must be unique from the training protocol to minimize any improvements as a result of

practice. If exercise does lead to changes in motor control processes, then improvements in the motor performance of the non-exercised effectors would be expected (e.g. improved upper limb function following lower extremity exercise; Ridgel et al., 2009)." For this exact reason, we tested upper extremity neuromuscular function and hand dexterity after exercise in the legs.

Tremor in Parkison's disease

A quality aspect of mobility is the smoothness with which muscular contractions or posture can be maintained. This is impaired in people with PD through the manifestaion of muscle tremors. The presence and severity of tremor varies. The amplitude and frequency of tremor in isometric contractions is known to be affected by anxiety, fatigue, pharmacological interventions and deep brain stimulation. Using methods similar to our measure of quickness control in older adults, Wierzbicka et al. (1991) demonstrated poor control of rapid exbow extension contractions when subjects were instructed to produce force as quickly as possible. EMG showed an inability for people with PD to deliver single discrete bursts of excitation to the muscle (EMG bursts). The multiphasic EMG bursts resulted in disjointed muscle contractions. Ridgel et al. (2009) showed that tandem cycling resulted in improved hand dexterity, however, the specific neural adaptations remain unclear.

Elek et al. (1991) examined the relationship between characteristics of paired MU discharge and tremor amplitude in pathological and voluntary tremor. The mean inter-spike intervals alternated between 10 ms and 90 ms in both conditions along with strong

evidence of MU synchrony. The conclusion was that paired discharge was not necessarily due to a MU pathology, but a response to impaired input in which the motor neurons produce paired pulses in response to abnormally strong excitation (Bawa & Calancie, 1983; Elek et al., 1991).

While the symptoms of Parkinson's disease originate in the basal ganglia with dopamine dysregulation, discharge behavior of alpha motor neurons reveals the peripheral manifestation of PD. Paired MU discharge causes excessive nonlinear summation of twitch forces which results in muscular force tremor (Dengler, Wolf, Schubert, & Struppler, 1986; Elek et al., 1991; Taylor & Stephens, 1976). This same type of discharge behavior is used for rapid force production (Van Cutsem et al., 1998). There is sparse literature on this abnormal discharge behavior in tremor with even less evidence on the effects of exercise on tremor. However, anecdotal evidence supports the potential for exercise to reduce tremor which warrants further investigation. By stimulating the motor cortical areas of the brain with high speed, rhythmic movements, this may elicit adaptations in the CNS to deliver MU action potentials in a more normal fashion.

Summary

Current exercise recommendations for older adults aim to improve balance, flexibility, strength and endurance. Older adults suffer from slowed movements and nowhere do recommendations suggest an activity that will enhance this quality. Non-voluntary exercise has been shown to elicit global improvements in function and quality of life in people with PD (Ridgel et al., 2009). However, voluntary exercise may be more

ecologically relevant in that once the exercise/activity is learned, individuals can continue this independently to maintain improvments from the intervention. Walking studies have been utilized to elicit such improvements but may not be ideal strategies for frail elderly or certain patient populations who struggle with walking for extended periods of time (e.g. PD, stroke, knee replacements). Therefore, the presented cycling intervention may prove more applicable to individuals of all functional abilities. Relative to the existing literature, the present experiments are more comprehensive, and the results contain detailed analyses of functional, neural, and central adaptation mechanisms in older adults along with MU paired discharge in people with PD.

Specific Aims

Slowness of movment has implications for mobility and independent living in older adults. In a comprehensive review paper, Sayers (2008) highlighted the importance of high velocity power training that utilizes lower resistances to improve slowness because these movements are more related to acitivities of daily living than maximal effort power training. High velocity power training at 20% of maximal strength elicited the highest improvement in balance in older adults compared with training at either 50% or 80% of max (Orr et al., 2006). High-speed, low-resistance training has been shown to improve measures of function, pain and disability in people with knee osteoarthritis (Sayers, Gibson, & Cook, 2012). Reducing force output and increasing contraction velocity may improve the oxygen partial pressure and improve blood flow and diffusion within the knee joint and contribute to positive outcomes. Sayers noted that future studies should address the effects of this type of training in older adults and certain patient populations. The presented studies are consistent with this call to action.

1. To determine whether there exist age-related differences in the speed and control of rapid isometric force pulses in different muscles between young and older adults.

H1.1: Older adults will have lesser rate of force development-scaling factors (RFD-SF)

H1.2: Older adults will have more variability in rapid force production (R^2).

2. To determine whether a high- speed, low-resistance exercise intervention can improve the speed of muscular force production, function and quality of life in older adults.

H2.1: Force and surface electromyography (EMG) measures during rapid isometric contractions during knee extension will improve after training.

H2.2: Walking function will improve after training (Timed Up & Go).

H2.3: Training the legs will transfer to improvements in measures of upper extremity force, EMG, and had dexterity (9 Hole Peg Test).

H2.4: Perceived function and quality of life will improve after training.

Tremor is defined as involuntary, rhythmic oscillatory muscle contractions in one or more body parts and is one of the primary symptoms in Parkinson's disease (PD). It results from paired discharge of motor units in which there is a short interspike interval (ISI) followed by a long ISI. In a recent project investigating the acute effects of speed-based exercise sessions on paired discharge behavior (unpublished preliminary studies, Appendix A), the paired discharge behavior varied considerably in its severity or it waxed and waned throughout prolonged (72-90 s) recording of isometric force. Due to the large amount of variability in the presentation of tremor in people with PD, we sought to develop and test a methodological approach for analysis of paired motor unit discharge behavior in tremor. The methodological challenge to overcome is that when paired discharge behavior is inconsistent or less severe, ISI distributional statistics that assume

bimodal behavior (ISI-short, ISI-long) fail to isolate ISIs of paired discharge from those that might represent non-tremor related discharge.

3. To develop a method to selectively quantify paired motor unit discharge behavior underlying tremor.

H3.1: ISI serial correlation with cluster analysis will allow us to quantify paired motor unit discharge behavior from isometric contractions in which motor unit discharge behavior is not solely bimodal.

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Chapter 2

AGE RELATED DECLINE IN THE RATE OF FORCE DEVELOPMENT-SCALING FACTOR (RFD-SF)

Abstract

Physical quickness is less in older adults with implications for fall prevention, movement initiation and activities of daily living. The purpose was to compare control of rapid contractions in young and older adults within two diverse muscle groups; powerful elbow extensors (EE) and dexterous index finger abductors (IFA). Most-rapid force pulses to a variety of levels were recorded and the relationship between peak force and rate of force development (RFD) were analyzed with linear regression. The resulting slope represents the dependent variable of interest, the RFD-scaling factor (RFD-SF). RFD-SF of EE and IFA strongly correlated both overall ($r=.87$, $p<.01$) and separately in young ($r=.60$, $p<.05$) and older ($r= .77$, $p<.01$) adults. RFD-SF values were different between muscle groups ($F_{1,28}=19.1$, $p<.001$) and also less in elderly ($F_{1,28}=32.6$, $p<.001$). We conclude that RFD-SF provides a sensitive assessment of muscle quickness that can be utilized to evaluate neuromuscular function in aging humans.

Introduction

Approximately 13% of the United States population is comprised of people over the age of 65 (U.S. Census, 2010). It is projected that this number will increase to 20% by 2050. The ability to generate rapid muscle contractions declines with age (Klass, Baudry, & Duchateau, 2008). This has implications on falls, independent living and quality of life (Rowe & Kahn, 1998; Spiriduso & Cronin, 2001), and may be substantially affected by physical activity levels in this population (Spiriduso & Cronin, 2001).

Falls and related injuries are among the most common and severe medical problems reported in older adults (Hayes et al., 1996). While much of the response to a perturbation is determined in the lower extremity, the whole body center of mass control and upper extremity responses to reach for support or prepare for collision are also very important (Burkhart & Andrews, 2013). In addition, upper extremity movement is often the first action utilized to cease forward motion in response to a perturbation (Troy & Grabiner, 2007). While weakness is a moderate predictor of falls (Suetta et al., 2004), the ability to generate submaximal forces quickly may be an important determinant of injury prevention. For example, the ability to prevent falls declines rapidly with age and is more related to functional performance (Bassey et al., 1992) than maximal muscle strength (Suetta et al., 2004).

The ability to recover from a perturbation is well predicted by response time which includes the time for both sensory detection and the motor response (van den Bogert, Pavol, & Grabiner, 2002). A delayed response time will allow greater displacement of the mass from the vertical and therefore require greater torque for its

correction. Conversely, earlier responses can return the mass to its stable position with less forceful contractions. Empirically, older adults have exhibited delayed muscular activation of the step leg in response a perturbation when compared to young (Thelen et al., 2000).

Not only is the quickness of submaximal responses relevant for fall prevention, it is also a likely determinant of success in many functional tasks that relate more to muscle power than strength alone (Bean et al., 2002; Sayers, 2008). Although falls represent a clear public health concern with quantifiable medical costs (Hayes et al., 1996), poor quality of movement (e.g. slowness, weakness or poor control) has broader implications for independent living, quality of life, and overall healthy aging (Rowe & Kahn, 1998; Spiriduso & Cronin, 2001). The ability to assess quickness in older adults separately from maximal strength or power is an asset for the development of interventions to prevent injury and promote optimal function.

In a series of force pulses performed across a range of submaximal amplitudes, there is a strong linear relationship between the peak force (PF) achieved and the same pulse's peak rate of force development (RFD; Freund & Büdingen, 1978). The slope of this relationship, which we termed the RFD scaling factor (RFD-SF, Bellumori, Jaric, & Knight, 2011) quantifies the extent to which RFD scales with contraction amplitude. In healthy adults, a greater RFD-SF provides relative invariance in the time required to reach PF regardless of contraction amplitude. With a low scaling factor, the time required to reach peak force increases with force amplitude. The RFD-SF is known to be less in the elderly when compared with young adults (Klass et al., 2008) and can be increased

with power training in the young (van Cutsem et al., 1998). In people with Parkinson's disease, the RFD-SF is considerably less in more highly affected individuals (Wierzbicka, Wiegner, Logigian, & Young, 1991). This supports the construct validity of the RFD-SF measure considering the effects of bradykinesia on movement initiation. Theoretically, the remarkable linearity of the PF-RFD relationship allows the RFD-SF measure to be obtained without requiring more than moderate force muscular contractions. It is also noteworthy that in its computation, the RFD-SF has often been normalized (units are $N \cdot s^{-1}$ / N), allowing easy comparisons between muscle groups and subjects, independent of strength or size (Mirkov, Nedeljkovic, Milanovic, Jaric, 2004).

The first aim was to compare the control of rapid submaximal force production in young and older adults as using the regression-based RFD-SF protocol. This was achieved by calculating RFD relative to force production. It was hypothesized that young adults would have higher RFD-SF values and that they would demonstrate better ability to consistently produce maximal RFD across submaximal force levels (based on R^2). The second aim was to test the concept that the RFD-SF is a general characteristic of an individual rather than an effector-specific one. Accordingly, it was hypothesized that the RFD-SF values obtained from the powerful elbow extensors would be correlated with RFD-SF values from the dexterous index finger abductors. Information obtained from this study will guide the development of exercise interventions that target the rapidly adapting nervous system, specifically regarding our dependent measures, in an attempt to prevent injury and enhance mobility and quality of life in older adults.

Methods

In order to assess quickness across the continuum of force levels, we used methods similar to those used by others who have studied control mechanisms (Freund & Büdingen, 1978; van Cutsem & Duchateau, 2005; Andersen, Boltermann, Jørgensen, Sjøgaard, 2008), aging (Klass et al., 2008) and clinical topics (Wierzbicka et al., 1991). Using recordings of most-rapid isometric force pulses performed across a full range of amplitudes, linear regression was applied to the relationship between RFD and PF. The regression parameters (slope and R^2) were the dependent measures of interest, with particular focus on slope (RFD-SF) and R^2 as the indicators of quickness and performance consistency, respectively. Although included in the present analysis, the y-intercept is typically small relative to the full range of RFD values and receives little attention in this paper and prior literature (Wierzbicka et al., 1991; van Cutsem & Duchateau, 2005; Klass et al., 2008).

Data were obtained from both elbow extension (EE) and index finger abduction (IFA). EE is a primary action in the upper extremity utilized frequently during daily activity and also relevant to preventing a fall during rapid grasping of support. IFA was chosen to represent a small and dexterous muscle group. The test-retest reliability for this protocol has been determined in young adults, in three muscle groups (RFD-SF ICC $\geq$ 0.83, R^2 ICC $\geq$ 0.77) (Bellumori & et al., 2011).

Subjects

Subjects included 15 young and 15 older healthy adults (Table 2.1), of varied physical dimensions and activity levels ranging from sedentary to highly active. The following characteristics were recorded: height, body mass, and hand dominance. Exclusion criteria included injury to the left arm or hand within the past 6 months that required medical treatment, low back pain, uncontrolled hypertension, arthritis, or osteoporosis. To reduce bias against those older adults who lack the ability to travel to the laboratory, testing was conducted at a central location within a local retirement community. This group of individuals volunteered to participate following a presentation of the proposed study. All participants signed an institutionally approved document of informed consent.

Table 2.1: Subject characteristics ± (SD).

Age	Gender	N	Age (years)	Height (cm)	Mass (kg)
Young	Male	7	23.1 (1.6)	179 (5.9)	86 (17.7)
	Female	8	22.8 (3.6)	165 (6.0)	62 (7.0)
Older	Male	6	83.5 (5.8)*	179 (7.4)	74 (13.9)
	Female	9	80.2 (6.0)*	161 (7.5)	65 (14.3)

* different from young adults ($p<.05$)

Procedures

Testing included the recording of isometric force pulses from the left (non-dominant) limbs during isometric EE and IFA tasks. All participants were right hand dominant and the non-dominant limb was used for testing purposes. Handedness was determined as the subjects' preferred writing hand. Prior to testing in each muscle group, three 3 second isometric maximal voluntary contractions (MVC) were completed with 60

seconds rest between each trial. MVC was defined as the highest value of the three consecutive trials and was used to specify tasks as a relative percentage of maximal force (%MVC). Although rare, if large differences were observed in MVC values (>10%), trials were repeated until consistent.

The RFD-SF Protocol

Subjects were instructed to produce each isometric force pulse as quickly as possible and then relax instantly. They were also instructed not to target force levels because targeting slows rate of force production (Gordon & Ghez, 1987). Subjects were encouraged to practice until they felt comfortable with the task and could perform force pulses as instructed. They then completed five trials consisting of five brief pulses to each of five approximate amplitudes (20, 40, 60, 80, 100% MVC) with 60 seconds rest between trials. To minimize an order effect, the five pulses to each amplitude were performed in blocks in a balanced order. Visual feedback of force was provided to the subjects as a vertical bar graph, on a computer screen placed near eye level. There were approximately two seconds of rest between consecutive pulses and timing was controlled by verbal "go" cues from the experimenter. Testing was completed in EE and IFA in less than one hour.

Isometric EE forces were recorded with the subjects in a standing position and while holding an instrumented pole (SM-50, Interface, Scottsdale, AZ, USA, (Bellumori et al., 2011). Subjects stood with their shoulder in a neutral position and elbow flexed at

90º. Pulses were performed while holding the pole and generating an isometric force with forearm in the downward direction toward the floor.

IFA forces were obtained with subjects seated comfortably in a standard height office chair with the palmar surface of their left hand resting on the force measuring device at standard table height (Bellumori et al., 2011). Isometric IFA forces were recorded from a strain gauge force transducer (MB-10, Interface, Scottsdale, AZ, USA). The index finger was oriented perpendicular to the measurement axis of the force transducer and held against it with a small segment of hook and loop fastener. A block of wood held the thumb at approximately 80º with respect to the index finger.

Data Acquisition

A Grass Instruments Model 15LT (West Warwick, RI, USA) system was used to amplify and filter (low pass cutoff at 30 Hz) signals from both force transducers. Analog signals were digitized at 200 Hz using a 16-bit acquisition board (PowerDaq Series, United Electronics Industries, Walpole, MA, USA). Data acquisition and visual display of force were controlled using Dasylab software (Measurement Computing Corporation, Norton, MA, USA).

Data Reduction

Data were processed by a single investigator in custom software (MATLAB, MathWorks Inc., Natick, MA) to obtain peak force and peak RFD measures from each pulse in the force-time curves. The rate measure was taken from the first derivative of the

force-time curve computed over overlapping 0.1 s intervals (Andersen et al., 2008). Five pulses per each of five trials (i.e., to the force levels 20, 40, 60, 80, 100% MVC), resulted in 125 measurements for both muscles. For each subject and the muscle group, linear regression equations were computed for the 125 data points to describe the PF-RFD relationship. While all regression variables were calculated and reported in results, the slope (RFD-SF) and R^2 of the regression equation were the primary dependent measures of interest in the analysis of rapid force production. A methodological distinction from some relevant literature is that the regression parameters are calculated as dependent measures representing individuals, rather than to summarize aggregate data (Van Cutsem, Duchateau, & Hainaut, 1998; Klass et al, 2008).

Statistical Analysis

R statistical software (www.r-project.org) was used for analysis. A two-factor analysis of variance (ANOVA) with one between-subjects factor (age group, 2-levels) and one within-subjects factor (muscle group, 2-levels) was used to test differences between age groups and muscle groups. Before the comparisons, r was normalized using the Fischer z-transform. Pearson's product moment correlation coefficients (r) were calculated to quantify associations between the two muscles and relationships between PF-RFD parameters and potential covariates (e.g. normalized strength, body mass).

Results

ANOVA indicated significant interactions for strength ($F_{1,28}$=275.6, p<.0001) and maximum RFD ($F_{1,28}$=20.2, p<.0001), such that MVCs were 39% less in the elbow extensors of older adults (p<.001) and 27% less in the index finger abductors of older adults PF (p=.002). Older adults had 48% less RFD (p<.001) in the elbow extensors and 49% less RFD (p<.001) in the index finger abductors when compared with the young group (Table 2.2).

Table 2.2: Mean ± (SD) regression parameters, maximal voluntary contraction (MVC), and peak rate of force development (RFD) in each age and muscle group.

Muscle	Age	RFD-SF	R^2	*Y*-intercept	MVC (N)	RTD (Nm/s)
EE	Young	8.9 (.7)	.97 (.05)	44.4 (25.7)	102.9 (27.3)	1041 (320)
	Older	6.4 (1.8)*	.80 (.10)*	74.3 (44.1)	63.2 (21.0)*	539 (217)*
IFA	Young	8.2 (.8)	.97 (.03)	32.3 (23.7)	26.5 (7.6)	273 (83)
	Older	5.5 (1.7)*	.80 (.10)*	63.5 (42.0)	19.3 (5.6)*	140 (55)*

* different from young adults (p<.05)

ANOVA indicated no interactions in any PF-RFD variable (slope: $F_{1,28}$=.21, p=.65; R^2: $F_{1,28}$=.08, p=.78; y-intercept: $F_{1,28}$=.01, p=.93). There were significant differences between age groups for all regression parameters ($F_{1,28}$>8.2, p<.01) suggesting that older adults exhibited less scaling of RFD with PF and less consistency in producing maximal force across the full continuum of forces. There were differences between muscles in RFD-SF ($F_{1,28}$=19.1, p<.001) and R^2 ($F_{1,28}$=4.6, p=.04) and y-intercept did not differ between groups ($F_{1,28}$=2.6, p=.12).

RFD-SF of EE and IFA were strongly correlated overall (r=.87, p<.01) and moderately so in separate analysis of young (r=.6, p<.05) and older (r= .77, p<.01) adults (Figure 2.1). It appears that a more heterogeneous sample supported the hypothesis that the RFD-SF of one muscle group could be utilized to describe an individual's neuromuscular function. Strong correlations between RFD-SF and MVC were not evident (young: IFA r=.16, EE r=.07; old: IFA r=-.21, EE r=.31; p>.05). When age groups were pooled together, there was a strong relationship between RFD-SF and peak RFD in both muscles (IFA r=.71, EE r=.74, p<.05) with a moderate relationship when separated by age group (young: IFA r=.45, EE r=.34; old: IFA r=.48, EE r=.77).

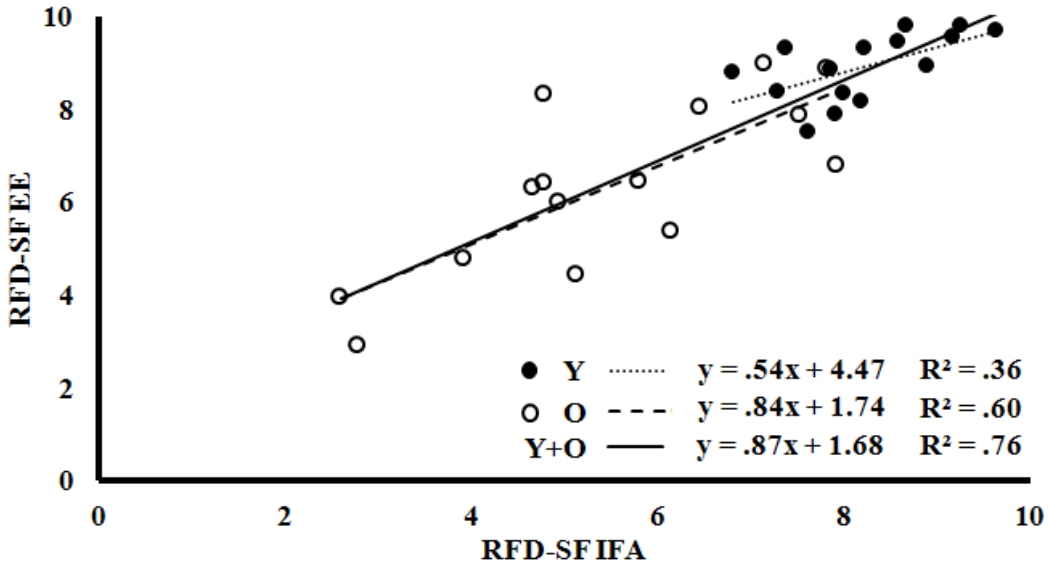

Figure 2.1: The relationship between individual RFD-SF obtained from elbow extensors (EE) and index finger abductors (IFA). The regression lines and corresponding equations are presented for young adults (Y: *R* = .60, p<.05), older adults (O: *R* = .77, p<.01), and all subjects (Y+O: *R* = .87, p<.01).

Discussion

The results obtained from this study supported the hypotheses related with our first aim - older adults had lower RFD-SF values than young adults and exhibited lower R^2 values. Together these indicate less scaling of RFD with PF as well as less consistent production of peak RFD across a continuum of force levels. Regarding our second aim, the moderate-strong correlations of RFD-SF between two functionally diverse muscle groups suggest that RFD-SF quantifies a general characteristic of an individual.

Aging is known to alter both muscular and neural determinants of rapid movements (Larsson, Grimby, & Karlsson, 1979). Not only do muscle mass and strength decrease with age, but contraction speed also slows. This is most likely due to the atrophy of type II fibers (Lanza, Towse, Caldwell, Wigmore, & Kent-Braun, 2003), decreased muscle fiber number and size (Brown, 1987), fewer motor units (Brown, 1973), and changes in muscle histochemistry (Lexell, Downham, & Sjõström, 1986). Much of these changes are reflected by a decrease in muscle cross-sectional area in elderly (Kent-Braun & Ng, 1999). Age-related declines in neural input to muscle include less motor unit double discharge (Christie & Kamen, 2006; Klass et al., 2008), lower maximal firing rates (Connelley, Rice, Roos, & Vandervoort, 1999; Kamen & Knight, 2004) and slower neuronal conduction times (Critchley, 1956; Bornstein, 1985; Bennett & Castiello, 1994; Thelen et al., 2000). Overall, there is a biased decline in factors associated with faster movements.

Consistent with known strength differences (Izquierdo, Aguado, Gonzalez, López, & Häkkinen, 1999; Barry, Warman, & Carson, 2005; Klass et al., 2008), the young adults

were 39% stronger in EE and 27% stronger in IFA than older adults. Klass et al. (2008) reported a 28% difference in strength between young and older adults during dorsiflexion. Young adults also produced approximately 49% greater maximal RFD than older adults in both muscles. Klass et al. (2008) reported a 48% difference in RFD between young and older adults.

In a related study involving ankle dorsiflexion, Klass et al. (2008) observed age related differences in regression parameters from the PF-RFD relationship that were obtained from aggregate data in samples of young and older adults, rather than from individuals. Agreement between the former and the present findings shows that either method is sensitive to the effects of aging. In the former study, the RFD-SF (regression slope) values from ankle dorsiflexion in older adults (6.0) were comparable to our results for EE (6.4) and IFA (5.5). Klass et al. (2008) also demonstrated that motor unit firing rates and doublet discharge are neural mechanisms that parallel these age-related differences in quickness.

A limitation of this study is that RFD-SF measures were not obtained from the lower limbs in older adults due practical constraints on field testing. Obtaining lower limb measurements would have strengthened our hypothesis that RFD-SF in one muscle group could represent a whole body measurement and should be added to future studies. However, the observed values and magnitude of age group differences in RFD-SF and R^2 were comparable between the upper extremity assessed in the current study and the lower extremity in the Klass et al. (2008) study. Such a comparison suggests that this aging effect could be generalized to the whole body, rather than being muscle-specific.

In the absence of data on neuromuscular activation (e.g. electromyography or motor unit recordings), we cannot identify the relative contributions to this age group difference from muscular or neural factors. Furthermore, even if such measures point to neural factors, such as the reduced motor unit firing rates reported by Klass et al. (2008), the question that follows is the extent to which neural slowing is due to changes in descending drive from the brain to the motor neuron pool and/or due to spinal level mechanisms and intrinsic motor neuron properties. The answers to such questions will guide the development of interventions such that they either target anatomically specific substrates for regional improvements in function or higher level central nervous system substrates for whole body improvements.

In the present sample, RFD-SFs for older adults were 28% less during EE and 33% less during IFA than young indicating that the well-known age-related changes in maximal RFD are indicative of altered control of quickness across the full range of force levels.

The R^2 values provided a measure of consistency in performance such that individuals who could reliably produce most rapid pulses had the greatest R^2. Supporting our hypotheses, young adults demonstrated 18% better performance (Table 2.2). The abundance of pulses used in individual regression plots allowed us to observe an interesting phenomenon in the PF-RFD plots. Specifically, variability in peak RFD values appeared to be constrained against an upper limit (Figure 2.2 – Note: This line does not represent the RFD-SF parameter). These two particular subjects' data were chosen to represent this phenomenon because the greater variability in pulses (lower R^2)

allows clearer depiction of the upper limit. We posit that this may be a constraint imposed by the upper limits of muscle fiber shortening velocity and muscle mechanical properties and that variation in neural input is primarily responsible for deviations below this line.

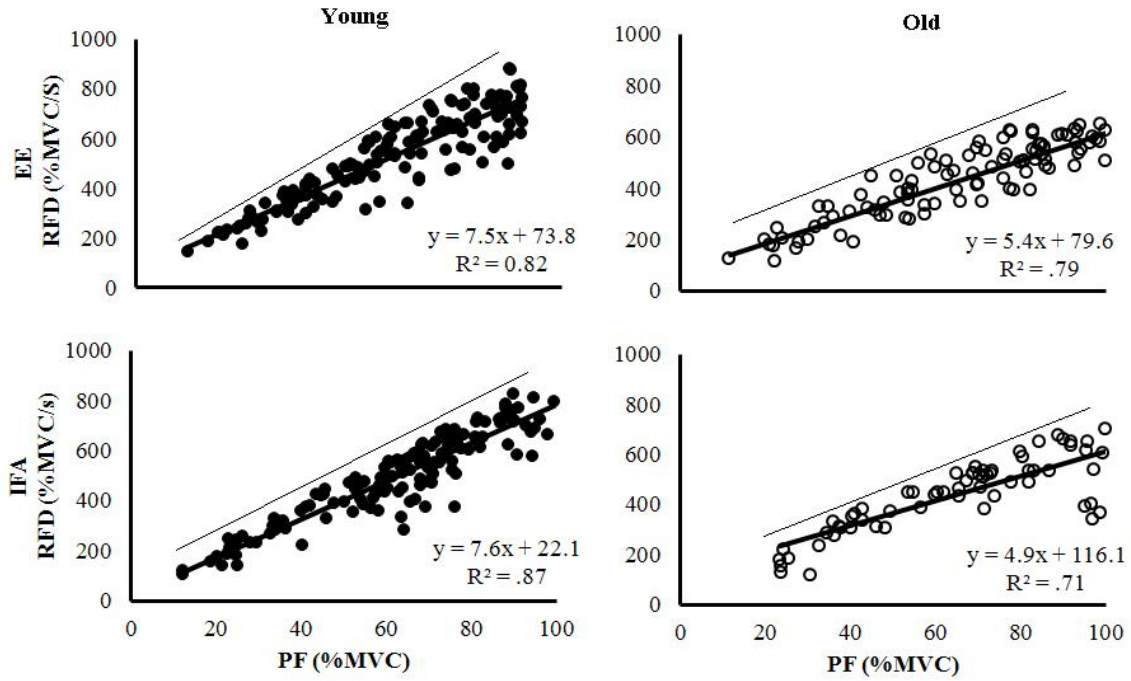

Figure 2.2: The PF-RFD relationship obtained from the elbow extensor (EE) and index finger abductors (IFA) of two representative subjects (young and older adult). The slope of the regression lines depicts the obtained RFD-SF. The thin line above data points represents the upper limit to performance, possibly due to limitations in muscle fiber shortening velocity and muscle mechanical properties.

Compared to the muscle-muscle correlations between RFD-SFs previously reported for young subjects (r=.6; Bellumori et al., 2011) the relationship between EE and IFA in this more heterogeneous sample of young and elderly (r=.87) more clearly reveals the nature of the RFD-SF as a variable that describes individuals (Figure 2.1).

This provides further support that it may be possible to assess a single muscle group in order to quantify a person's quickness as it relates to functional ability, neuromuscular health, and the effects of interventions. This measurement could be developed into a routine test for both clinicians and physiologists to monitor and track and individual's neuromuscular health over time.

This study demonstrates a clear decline in neuromuscular function with age. Fortunately, older adults are known to be highly responsive to strength and power training interventions that positively affect RFD (Häkkinen et al., 1998; Barry et al., 2005). However, the extent to which the known improvements in maximal RFD in the elderly might extend to quickness at submaximal force levels has yet to be determined. Although the observed increases in the 2005 study (Barry et al.) were attributed to a motor learning mechanism (Barry & Carson, 2004) it does not diminish the importance that this parameter can be improved in older adults. Additionally, maximal strength contractions may not be ideal for the frail elderly or certain patient populations. This highlights the importance of interventions to improve muscular quickness that do not require maximal effort.

Conclusion

Based on these results, the rate of force development scaling factor (RFD-SF) is sensitive to age-related slowing and individual subject differences. It also correlates across diverse muscle groups making it generalizable to an individual's entire neuromuscular system. Although many of the neural and muscular determinants of the

RFD-SF may be common to strength and power, this research paradigm assesses the quickness of submaximal force contractions which are highly relevant to activities of daily living. This paradigm may have high utility in a variety of topics. The assessment may be more amenable to the frail elderly than high force tests of strength and power. The ability to rapidly stiffen joint complexes to avoid injury is a topic of high interest (Gruber & Gollohofer, 2004) and rapid upper extremity movements are relevant to fall outcomes (Kim & Ashton-Miller, 2003). Not only is the control of quick movements relevant to the elderly, but it has clinical application to individuals with any neurological disorders that involves slowing, including, but not limited to, stroke and Parkinson's disease (Wierzbicka, et al., 1991). The reported results identify specific age related differences in neuromuscular control that can be targeted in exercise interventions. Future studies should target some important topics. First would be to clarify the link between improved RFD-SF and enhanced mobility and identify which standard functional assessments are most related to the RFD-SF. It is also pertinent to determine whether the improvements occur due to central or peripheral mechanisms and whether training one set of extremities can elicit a whole body improvement.

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Chapter 3

EFFECTS OF HIGH-SPEED, LOW-RESISTANCE RECUMBENT CYCLING ON FUNCTION AND NEUROMUSCULAR QUICKNESS IN OLDER ADULTS

Abstract

Although slow movement is obvious among older adults, little research supports the safe practice of speed-based exercise in this population. The purpose was to determine the effects of a 6 week speed-based exercise program in older adults. Stationary recumbent cycling was selected to minimize fall risk. Minimal resistance reduced musculoskeletal loads and cardiovascular demand. Two weekly 30 minute exercise sessions consisted of interval training in which subjects pedaled at preferred cadence and with 10, 20 s fast cadence intervals. Participants (n=14, 73(7.6) years) completed pre- and post-exercise tests, and a 4 week retention test. No significant changes were observed in a subset of participants (n=7) who served as time-controls. After training, there were improvements in time to peak force, rate of force development-scaling factor (RFD-SF), and rate of electromyography rise (RER) during isometric knee extension and functional tests ($p<.05$). Improvements were maintained 4 weeks after the intervention. A central mechanism was implicated because the lower extremity exercise elicited improvements in the untrained upper extremities (elbow extension time to peak force, RFD-SF, and 9-Hole Peg Test, $p<.05$). These results support a speed work strategy

which complements current exercise recommendations for older adults and potentially people with movement limitations while supporting rapid neural adaptations to high-speed training in older adults.

Introduction

In older adults, slowness of movement has implications for postural stability, fall prevention, and activities of daily living (Kim & Ashton-Miller, 2003; Klass, Baudry & Duchateau, 2008; Miszko, Cress, Slade, Covey, Agrawal & Doerr, 2003). Current exercise recommendations for older adults predominantly aim to improve balance, flexibility, strength, and endurance (Chodzko-Zajko et al., 2009). While these recommendations from federal agencies (e.g. Centers for Disease Control and Prevention, National Institutes on Aging) are prudent and well-evidenced, they neglect the important contribution of movement velocity to power and function. Reduced muscle power has a greater impact on functional declines than muscle strength alone (Bean et al., 2002; Cuoco et al., 2004; Foldvari et al, 2000; Skelton et al., 1994; Suzuki, Bean & Fielding, 2001). Because muscle power is lost earlier and at a faster rate than muscle strength in aging adults (Metter et al., 1997), interventions to preserve or improve movement velocity are warranted. Improvements in balance and strength implicitly involve neural and muscular contributors to speed; however, we believe that a direct focus on speed-based exercises (speed work) can elicit meaningful functional benefits through exercise modalities that are amenable to many older adults. Furthermore, in the development of comprehensive, progressive programs to improve physical independence in older adults

one should consider the value of a strategy that, first, “reawakens” the nervous system as a precursor to subsequent emphasis on strength, endurance, and more challenging balance activities.

Together with muscle fiber type (Larsson, Li, Frontera, 1997), rates of muscular force development and movement speed are determined by the rate at which the nervous system activates muscle tissue (Freund, 1978). The rapid isometric force pulse model (Freund, 1978; Bellumori, Jaric & Knight, 2011; Bellumori, Jaric & Knight, 2013) has been informative in this context, demonstrating the relationship between initial motor unit firing rates and rate of EMG rise (van Cutsem et al., 1998), the reduction of both measures in older adults (Klass), and the trainability of these neural factors in the young (van Cutsem et al., 1998). Making the important link between these measures of neuromuscular activation and an important speed-based activity of daily living, Clark et al., (2013) demonstrated that the rate of EMG rise in the triceps surae was 38% lower in well-functioning older adults who exhibited slower maximal walking speeds. It is known that such neural factors adapt very quickly to exercise stimuli (Moritani & Devries, 1979; Enoka, 1988), even in older adults (Kamen & Knight, 2004).

Power and functional performance can be improved through high-velocity resistance training in older adults (Miszko et al., 2003; Sayers, Guralnik, Thombs, & Fielding, 2005). Considering alternate exercise modalities, high-speed cycling has also demonstrated good efficacy (Macaluso, Young, Gibb, Rowe & De Vito, 2003). For the frail elderly and certain patient populations, avoiding high musculoskeletal loads may be beneficial to minimize muscle soreness and potential risk of injury. The importance of

high-speed power training that utilizes low resistance has been highlighted because these movements are more related to activities of daily living than maximal effort power training (Sayers, 2008). A growing body of evidence supports the use of high-speed exercises to enhance power (Fielding, LeBrasseur, Cuoco, Bean, Mizer & Fiatarone-Singh, 2002; Marsh, Miller, Rejeski, Hutton & Kritchevsky, 2009; Miszko et al., 2003). In addition to neural and muscular adaptations, there is also evidence that enhanced mobility occurs together with (or partially through) improved in self-efficacy (Yeung et al., 2014).

The aim was to evaluate the effects of a high-speed, low-resistance recumbent cycling intervention on perceived health status, physical function, and neuromuscular quickness in older adults. Whereas previous studies aimed to achieve high power output through a combination of high speed pedaling and variable resistance (Macaluso et al., 2003; Sayers, Guralnik, Thombs, & Fielding, 2005), the novelty of our program is that individuals are able to attain high speeds against minimal resistance. Exercise was performed on a stationary recumbent bicycle with no added resistance except that which was provided by the fly wheel. A recumbent bicycle was chosen over an upright bicycle to reduce potential risk of falling and ease of mounting. The present intervention included two exercise sessions per week for 6 weeks (12 total exercise sessions). We utilized an interval training approach in which participants completed ten repetitions of pedaling for 20 seconds at a fast rate followed by one minute of pedaling at a comfortable rate. There was a 5 minute warm up and cool down period at the participant's preferred pedaling cadence. The use of little resistance is intended to minimize muscle soreness and

discomfort while allowing individuals to attain high speeds on the bicycle. Thus, it is possible to target primarily neural factors of muscular quickness while minimizing outcomes that could otherwise be due to strength gains.

We hypothesized that there would be improvements in (and retention of) perceived health and functional status, whole body mobility, and neuromuscular quickness and its control. Exploring the possibility of central adaptations, we also tested the hypothesis of improved neuromuscular quickness and function in the untrained upper extremity.

Methods

Participants and Recruitment

Participants included 14 older adults (mean (SD) age: 73 (7.6), height: 163.1 (9.3) cm, mass: 76.8 (12.1) kg) as determined a priori using G*Power ($\alpha = 0.05$, $\beta = 0.8$) and were recruited via newsletter announcement from a local senior center. All participants were right hand dominant and the left side was used for all assessments during testing. Exclusion criteria included injury to the lower or upper extremity within the past 6 months that required medical treatment, low back pain, or uncontrolled hypertension. All participants signed an institutionally approved informed consent and provided physician's clearance if they answered yes to one or more questions in the Physical Activity Readiness Questionnaire. All participants were tested and supervised during exercise by the same experimenter to eliminate a potential source of variance.

Testing & Exercise Program Schedule

See Table 3.1 for structure of the testing and exercise program. Half of the participants served as a time control (N=7) by participating in two baseline tests that occurred on the same timescale of observation with respect to the exercise intervention (weeks 1 and 6). During the time control phase, these individuals were instructed to continue their normal daily activities. After the time control period, seven more participants joined for the exercise portion of the study. Fourteen older adults participated in the six week exercise intervention with baseline, post-intervention, and four week follow-up tests.

Table 3.1: Testing and exercise schedule (by week). All participants received the exercise treatment while the time control group had two baseline tests separated by 6 weeks. Testing occurred within the first and last week of the time control phase (N=7) and within the first and last week of starting and finishing the exercise intervention (N=14).

	Week 1		**Week 6**		**Week 12**	**Week 16**
Testing Schedule	Baseline 1	Time Control (N=7)	Baseline 2	Intervention (N=14)	Post	Follow-Up

The inclusion of the time control group was intended to elucidate potential improvements in dependent measures due to the mere exposure to the laboratory tests and is an informed paradigm based on the long known phenomenon termed quick jumps in strength (Schenck & Forward, 1965).

Laboratory Tests

Questionnaires: Participants completed standard questionnaires related to physical function, disability, and quality of life. The Activities-specific Balance Confidence (ABC) Scale includes 16 items and asks a person to rate their level of confidence that they will not lose their balance doing different activities on a scale from 0% (not confident) to 100% (completely confident; Powell & Myers, 1995). ABC was also shown to be an effective tool in predicting future falls (Mak & Pang, 2009). The Short Form-36 Health Survey (SF-36) is a 36 question survey to assess a person's perceived health status related to physical, social, mental and emotional health (Ware & Sherbourne, 1992).

Functional tests: Participants were instructed to perform functional tests "as fast and as safe as possible". After practicing the tasks, participants performed three timed trials of the each test with the best time being used for data analysis. The Timed Up and Go Test (TUG) is used to assess overall functional mobility with strength, speed, and balance components. It measures the time taken by an individual to stand up from a standard arm chair (seat height 46 cm, arm height 65 cm), walk a distance of 3 meters, turn, walk back to the chair, and sit down (Podsiadlo & Richardson, 1991). The 9-Hole Peg Test is a quantitative test of upper extremity function. The participant is seated at a table with a small, shallow container holding nine pegs and a wooden block containing nine empty holes. On a start command, the participant picks up the pegs one at a time, puts them in the 9 holes, and, once they are in the holes, removes them again as quickly as possible one at a time, replacing them into the shallow container. The total time to

complete the task is recorded (Earhart, Cavanaugh, Ellis, Ford, Foreman & Dibble, 2011). Both tests are standardized assessments of physical function.

Strength tests: Isometric maximal voluntary contractions (MVC) were measured in both the lower (knee extension) and upper extremity (elbow extension). MVC was defined as the greatest value of the three maximal contractions with at least 60 seconds of rest between attempts. This was used to provide visual biofeedback of force as a percentage of maximal force (%MVC). All force measurements were taken from the left side.

Isometric knee extension forces were obtained with participants seated in a comfortable chair and their distal leg affixed to a strain gauge force transducer (SM-250, Interface Inc., Scottsdale, AZ, USA). Participants were seated in an upright position with back support, and both the hip and knee flexed at ~70°. A force transducer was coupled to the bench using a ball joint to allow some freedom of knee extension direction without imparting off-axis forces on the transducer. The transducer was coupled to the distal leg with a 9.7 cm wide rigid plastic cuff made from a bisected piece of polyvinyl chloride pipe. With a small segment of cloth surrounding the leg, the cuff was secured by 5 cm wide hook and loop fastener. These materials were selected to minimize the effect of material compression on measures related to movement initiation (Corcos, Gottlieb, Latash, Almeida, & Agarwal, 1992).

Isometric elbow extension forces were recorded with the participants seated in the same knee extension testing chair while holding an instrumented wooden pole (SM-50, Interface Inc., Scottsdale, AZ, USA). The shoulder was in a neutral position and elbow

flexed at 90º. Participants grasped and pushed down on a pole resembling a walking stick. Due to the time needed for experiment setup, participants were seated throughout testing to prevent fatigue. Prior research in our laboratory has shown these methods to have good day-day reliability (Intra-Class Correlation > 0.8; Bellumori et al, 2011).

Quickness testing: Time to peak force, RFD-SF, and R^2 values were obtained using the same equipment and setup used for strength tests through similar methods used by others (Freund & Budingen, 1978; Klass et al., 2008; Wierzbicka et al., 1991). Knee extension pulses were performed isometrically to mimic a rapid forward kick. Elbow extension pulses were performed isometrically (while holding the device like a ski pole) by rapidly pushing the pole downward against the floor.

Instructions were to produce each pulse as quickly as possible and then relax instantly. After viewing a demonstration by the experimenter, participants practiced until they felt comfortable with the task and could perform force pulses as instructed. Pulses were produced in randomized sets of 20 (to varying levels between 20-80% MVC) with at least 2 minutes of rest between sets. A total of 5 sets were performed to obtain 100 force pulses. 75 or more pulses are necessary to obtain a reliable RFD-SF (Bellumori et al., 2011). Timing to perform force pulses was controlled by a metronome set at 30 beats per minute. Visual feedback of force was provided to the participants as a vertical bar graph on a computer screen placed at eye level.

From the numerous force pulses, time to peak force was calculated as the time from onset of force to the peak or the force pulse. Peak RFD was calculated as the derivative of the force pulse over over-lapping 0.1 s intervals. Linear regression was used

to quantify the relationship between the peak force and corresponding peak RFD along with obtaining R^2 values (Figure 2.1). The slope of the regression line obtained from the peak force and peak RFD provides the RFD-SF (Bellumori et al., 2011). R^2 represents consistency of performance during rapid isometric force pulses (Bellumori et al., 2011).

The knee and elbow extensors were chosen for their functional relevance to activities of daily living and prevalence in mechanistic and rehabilitation research. Knee extension is relevant in walking and sit-to-stand tasks. Elbow extension is a primary action in the upper extremity utilized frequently for reaching and support tasks.

Muscle electrical activity: As a non-invasive surrogate of initial motor unit firing rates (Corcos, Gottleib & Agarwal, 1989), rate of rise of the surface electromyogram (RER – see Data Reduction for calculation) was used to examine rate of neuromuscular activation (Clark et al., 2011). RER recordings were obtained from the left vastus lateralis and triceps brachii muscles during both strength and quickness testing. After cleansing the skin with ethyl alcohol, disposable adhesive surface electrodes were placed on the skin over the muscle of interest. Bioamplifiers were used to amplify and filter the signals as needed (Grass-Telefactor, Warwick, RI).

Exercise Intervention

The exercise sessions were held in a local senior center fitness center. Participants trained for six weeks under the supervision of the experimenter (2 days per week = 12 total sessions). A six week time period was chosen because neural adaptations are expected to occur in this period of time while muscular adaptations are minimal

(Moritani & deVries, 1979). Exercise was performed on a stationary recumbent bicycle (Life Fitness, Platinum Club Series Recumbent Lifecycle) with no added resistance (Level 1). During the first session, participants were instructed to pedal at a comfortable cadence as if they were watching television and leisurely pedaling at the same time. This was determined to be their preferred pedaling cadence and values ranged from 40-80 revolutions per minute (RPM) between participants. These cadences correspond to 25-50 watts of power output on the specific bicycle used. Fast cycling was initially defined as 20% faster than preferred pedaling cadence. Each exercise session began with a 5 minute warm up at preferred pedaling cadence. Then participants alternated between periods of fast and slow pedaling. This included 10 intervals of fast pedaling for 20 seconds followed by 60 seconds of slow pedaling at preferred cadence. Longer recovery was given, if needed. The session concluded with a 5 minute cool down at preferred pedaling cadence. Each session lasted approximately 25 minutes. As participants progressed through training, their fast cycling pace was increased based on ability in sensible, individually determined increments. Heart rate was monitored throughout exercise. When necessary, speed of cycling was adjusted to keep exercising heart rates below 70% of age predicted maximum determined with the Karvonen method (Karvonen, Kentala & Mustala, 1957).

Data Acquisition

A Grass Instruments Model 15LT (West Warwick, RI, USA) bioamplifier system was used to amplify and filter (low pass cutoff at 30 Hz, -6 dB) signals from each of the

force transducers. Analog signals were digitized at 2 kHz using a 16-bit acquisition board (PowerDaq Series, United Electronics Industries, Walpole, MA, USA). Data acquisition and the visual display of force was controlled using Dasylab software (Measurement Computing Corporation, Norton, MA, USA).

Data Reduction

Force data were processed by a single investigator using National Instruments Labview software (2012) to obtain time to peak force as well as corresponding peak force and peak RFD measures from each pulse. Time to peak force was calculated as the time from force onset to the maximum of individual force pulses. The RFD time series was computed from the force recording using the finite difference method over overlapping 0.1 s intervals (Winter, 1990). RFD-SF and R^2 values were obtained from linear regression of peak force and peak RFD. Time to peak force was calculated as the amount of time between force onset and peak force.

RER of each force pulse was also obtained with National Instruments Labview software (2012). Surface EMG bursts were full wave rectified, low-pass filtered at 20 Hz and normalized to MVC. The first derivative of the linear envelope between activation onset and peak EMG was recorded as the RER (Clark, et al., 2011; Chou, Palmer, Binder-Macleod & Knight, 2013).

Statistical Analysis

All statistical tests were performed using SPSS (version 22, IBM SPSS Statistics, Armonk, NY). Due to a low sample size within the time control group (N=7), we used Wilcoxon signed-rank tests (nonparametric equivalent of paired sample t-test) to make comparisons between baseline 1 and baseline 2 tests. Paired sample t-tests were used to compare preferred and fast pedaling cadence separately, as measured at the first and the last training sessions. One-way repeated measures ANOVA with three levels representing measurement sessions (baseline 2, post-intervention and follow-up) were used separately for each variable (N=14). The data were Greenhouse-Geisser corrected if the assumption of sphericity was violated and post-hoc tests with Bonferroni corrections were applied for multiple comparisons. Alpha level was set at 0.05.

Results

Time Control

Table 3.2 presents measurements taken at baseline 1 and baseline 2; before and after completion of the time control period of six weeks (N=7). Results revealed no significant changes in any of the selected dependent variables indicating that there was no effect exposure to lab measurements.

Intervention

Statistical analysis included all trained participants (N=14, see Table 3.3 for mean (SD)). Preferred pedaling cadence ranged from 40–80 RPM between individuals (mean (SD): 57.5 (12.2) RPM, 36.6 (10.3) watts) and was similar between the first and last

session (t= -.236, p>.05). Fast pedaling cadence was 77.4 (21.6) RPM (49.2 (13.9) watts) on day one and increased 36% to 105.1 (30.1) RPM (62.6 (11.9) watts) on day twelve of training (t= -7.13, p<.001).

There was no effect of session for either perceived health status (Short Form-36: $F_{(2,26)}$=3.54, p>.05) or the activities of balance questionnaire scores ($F_{(1.15,15)}$=0.376, p>.05).

There was a significant main effect of test session for both the TUG ($F_{(1.09,14.1)}$=38.23, p<.001) and the 9-Hole Peg Test ($F_{(1.3,16.9)}$=11.7, p<.001). Pairwise comparisons indicated that functional tests improved with the intervention and remained improved in the follow-up session as compared to those measured at baseline 2. Measurements at follow-up were not different from those after the intervention (p>.05).

Time to peak force was different among sessions (knee extension; $F_{(2,26)}$=10.01, p<.01; elbow extension; $F_{(2,26)}$=9.81, p<.01). Contraction times decreased 13% in knee extension (p<.01) and 11% in elbow extension (p<.01) after the completion of exercise intervention, and remained similar to the post-intervention session when tested at follow-up (p>.05). It is noteworthy that these improvements occurred in the absence of strength gains (as assessed by MVC) in either knee ($F_{(1.4,18.2)}$=4.11, p>.05) or elbow extension ($F_{(2,26)}$=.786, p>.05).

RFD-SF differed among sessions for the knee extensors ($F_{(2,26}$=7.08$_{)}$, p<0.1) and elbow extensors ($F_{(2,26)}$=8.63, p<0.01). Individual comparisons revealed that the RFD-SF of knee extensors significantly improved by 31% after the exercise intervention (p<.01). Supporting the hypothesis that training the legs would transfer to improvements in the

upper extremities, RFD-SF of elbow extensors also significantly increased after exercise intervention by 38% ($p<.01$). At follow-up, RFD-SF values of both knee and elbow extensors trended back toward baseline 2 but were not significantly different from measures taken at the end of the 6 week exercise program ($p>.05$).

R^2, a quality measure of one's variability in performing rapid force pulses, differed among sessions for the knee extensors ($F_{(2,26)}=13.3$, $p<.01$) and elbow extensors ($F_{(2,26)}=5.77$, $p<.01$). Individual comparisons revealed improvements in the knee extensors after the intervention ($p<.01$) and remained improved at follow-up ($p>.01$). For the elbow extensors, only the follow-up test was significantly different from baseline 2 ($p<.01$).

RER differed among sessions for both knee extension ($F_{(2,26)}=5.11$, $p<.05$) and elbow extension ($F_{(2,26)}=6.52$, $p<.01$) indicating an improvement by 40% and 85% in the post-intervention session in the legs and arms, respectively. Both of these variables measured in the follow-up session were similar to those measured in baseline 2 and post-intervention sessions ($p>.05$).

Table 3.2: Means(SD) for the time control group (N=7) when tested on two occasions before starting the exercise program (KE: knee extension; EE: elbow extension).

	Muscle	Baseline 1	Baseline 2	Z	P value
Timed Up and Go (s)		7.86(2.21)	7.42(1.99)	-1.18	.24
9-Hole Peg Test (s)		31.97(8.39)	30.72(7.23)	-.11	.92
RFD-SF (s^{-1})	**KE**	4.91(3.02)	5.83(2.29)	-1.01	.31
	EE	5.64(2.94)	6.4(3.95)	-1.52	.13
R^2	**KE**	.55(.23)	.67(.15)	-1.80	.07
	EE	.61(.19)	.68(.19)	-.32	.75
Time to Peak Force (s)	**KE**	.34(.12)	.30(.12)	-1.19	.23
	EE	.28(.10)	.33(.14)	-1.89	.06
Maximal Voluntary Contraction (N)	**KE**	259.2(93.7)	262.0(99.8)	-1.35	.18
	EE	85.6(13.1)	89.3(17.9)	-1.31	.16

Table 3.3: Means(SD) for dependent measures (N=14; ABC Scale: Activities Specific Balance Confidence Scale, RFD-SF: rate of force development-scaling factor, KE: knee extension; EE: elbow extension; RER: rate of electromyography rise).

	Muscle	Baseline 2	Post	Follow-Up
Timed Up and Go (s)		9.3(3.1)	7.0(2.1) [a**]	6.8(2.0) [b**]
9-Hole Peg Test Left (s)		32.0(8.4)	26.8(6.6) [a**]	26.3(5.1) [b*]
Short Form-36		78.8(10.6)	83.7(11.2)	84.5(10.1)
ABC Scale		87.9(12.3)	92.9(5.9)	91.7(6.7)
RFD-SF (s^{-1})	**KE**	4.9(3.0)	6.4(2.6) [a**]	6.0(2.4)
	EE	5.6(3.0)	7.7(3.6) [a**]	6.5(2.9)
R^2	**KE**	.55(.23)	.72(.16) [a**]	.73(.17) [b**]
	EE	.61(.19)	.69(.19)	.76(.18) [b*]
Time to Peak Force (s)	**KE**	.31(.13)	.27(.11) [a*]	.23(.12) [b**]
	EE	.26(.13)	.23(.09) [a**]	.21(.10) [b**]
Peak RER (%MVC/s)	**KE**	735(607)	1025(745) [a*]	889(419)
	EE	585(435)	1080(746) [a*]	846(550)
Maximal Voluntary Contraction (N)	**KE**	260.3(87.1)	271.4(94.1)	275.4(101.4)
	EE	89.9(18.4)	96.0(23.7)	94.3(22.4)

[a] Differences between baseline 2 and post intervention
[b] Differences between baseline 2 and follow-up
[*] $p<.05$
[**] $p<.01$

Discussion

The current study was designed to explore the effects of a speed based exercise intervention program on the measures of perceived health status, physical function, and neuromuscular quickness in healthy older adults. Overall, our results mainly supported our hypothesis indicating that a high-speed, low-resistance exercise intervention improves physical function and neuromuscular quickness and that these improvements would last four weeks after the intervention. Moreover, results indicated that the improvements in the rate of muscle contraction could explain the improved neuromuscular function and control of rapid force production. Finally, the improvements seen in the upper extremity function and neuromuscular quickness indicate central adaptations to speed based exercise training.

Physical Quickness

Physical quickness is an important movement quality in the contexts of aging, pathology and rehabilitation. Under the instructions to produce isometric muscular force pulses most rapidly (Wierzbicka, Wiegner, Logigian, & Young, 1991) and across a range of submaximal amplitudes, there is a positive linear relationship between the peak force of a pulse and the corresponding peak rate of force development (RFD). The slope of regression quantifies how well an individual is able to scale RFD with contraction amplitude and is termed, the RFD-SF (Bellumori et al., 2011). R^2 of regression represents the amount of variability in rapid force production across force levels. In healthy young adults, a greater RFD-SF results in relative invariance (high R^2 values) in the time

required to achieve peak force (time to peak force) regardless of the strength of the muscular contraction (Freund & Büdingen, 1978). The RFD-SF is known to be less in older adults when compared with young (Klass et al., 2008). Among contextually varied publications related to the scaling of RFD with respect to peak force (Gordon & Ghez, 1984, 1987; Klass, Baudry, & Duchateau, 2008), the early paper by Freund & Büdingen (1978) provides the most comprehensive background for the RFD-SF measure as it relates with time to peak force. The rate of electromyography rise (RER) provides specific information about the rate of neural stimulation during rapid force production and contributes to RFD-SF (van Cutsem et al., 1998; Chou et al., 2013).

High-Speed Low-Resistance Cycling

There was 100% compliance from participants in this study. There was no mention of muscle strain or discomfort during or after exercise sessions. Due to the interval nature of the exercise, a total of 3.33 minutes of high-speed cycling was completed during each exercise session. The rest of the session was completed at preferred pedaling cadence. It is notable that the short amount of time that high effort was required resulted in positive effects from this program. Furthermore, due to the nature of seated exercise and low requirement for postural support, this mode lends itself to a greater total number of movement repetitions (revolutions) and less postural demand than other training modalities such as walking.

In two review papers (Sayers, 2002; Macaluso, et al., 2003), authors highlight the utility of exercise programs that target power rather than strength alone. Muscle power

has been shown to correlate with functional tasks (Skelton, Greig, Davies, & Young, 1994). Previous studies have shown improvements in function and muscle power with resistance training. These programs ranged from 10-16 weeks with three exercise sessions per week (see Macaluso & De Vito, 2004 for summary). A novel aspect of the present exercise program is that significant results were obtained after only 6 weeks (2 sessions per week = 12 sessions). Similar to Macaluso et al. (2004), we employed the use of high-speed intervals in our cycling program. The notable difference is that our program utilized the lowest resistance setting to minimize muscular and joint loading while allowing participants to achieve high RPMs. The intent was to minimize discomfort and injury risk in an older population. Participants noted that the exercise was relatively easy due to the low resistance. Additionally, because it lasted only 25 minutes 2 days per week, it fits in well with a more comprehensive exercise program that includes stretching, strengthening, and cardiovascular activities.

Function and Age Related Slowing of Movement

Although scores on the SF-36 and ABC trended toward improvements after our cycling intervention changes were not significant. A limitation of the study was a small number of participants and these measurements may prove significant with a larger sample size. Such improvements would support the notion that exercise affects mental well-being and could translate to improved quality of life, independent living, and decreased health care expenditure (Taylor et al., 2004).

Functional measures that relate to mobility and hand dexterity improved with high-speed, low-resistance exercise. Neuromuscular quickness is a likely determinant of success in many functional tasks that are not always correlated to measures of strength (Jaric, Radosavljevic-Jaric, & Johansson, 2002). Examples of such tasks affected by slowed movements include movement initiation and catching a falling object (Hausdorff, Yogev, Springer, Simon, & Giladi, 2005), safely crossing the street (Langlois et al., 1997), typing and double-clicking a computer mouse (Bean, 2003).

Previous studies have highlighted the importance of muscular quickness for fall prevention (van den Bogert, Pavol, & Grabiner, 2002). While weakness has a moderate relationship with falls, the ability to produce submaximal forces very quickly may be more important. The ability to prevent falls declines with age and is more related to functional performance than maximal muscle strength (Suetta et al., 2004). The present study showed improvements in the TUG which is a standardized test that incorporates functional components of strength, walking speed, and balance. Because impairments in these three components relate to risk of falling, it may be prudent for clinicians to consider high-speed interventions for at risk older adults.

Improvements in Rapid Force Production

The time to peak force and RFD-SF are reliable measures of how neuromuscular quickness is controlled and are informative measures that can detect impairments in neuromuscular function (Wierzbicka et al., 1991; Bellumori et al., 2011, 2013). These values decrease with aging (Klass et al., 2008; Bellumori et al., 2013) and are determined

by specific patterns of motor unit discharge (Van Cutsem et al., 1998). In an aging study, older adults exhibited 28% and 33% lower RFD-SF than younger adults in elbow extension and index finger abduction, respectively (Bellumori et al., 2013). Because aging physiology typically has a negative effect on motor function, these results demonstrate the importance of preventing declines of the time to peak force and RFD-SF in older adults. After six weeks of high-speed low-resistance cycling, time to peak force and RFD-SF increased significantly in knee extensors and elbow extensors, two muscle groups that are ecologically relevant to many activities of daily living. Figure 3.1 depicts the shift in the relationship between peak force and peak RFD for one individual with training. RFD-SF increased along with R^2 values and peak RFDs across force levels. R^2 values represent the level of variability in force output across a range of amplitudes.

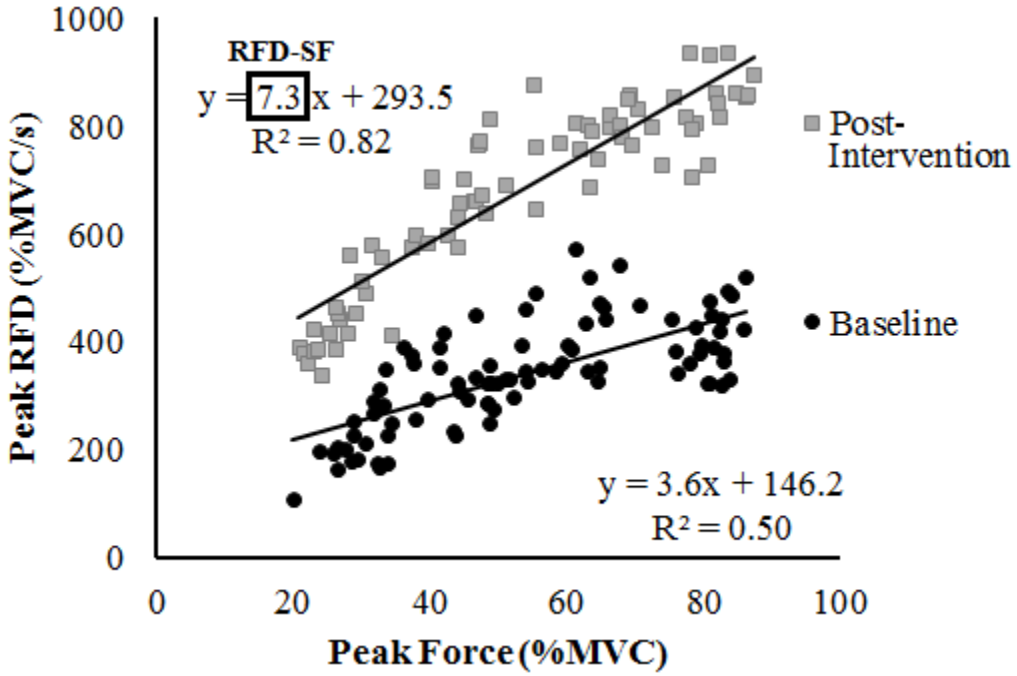

Figure 3.1: An example of one individual's improvement in the rate of force development-scaling factor (RFD-SF) after 6 weeks of exercise.

In a dataset that includes both young and older adults, a strong correlation exists (r = .87) between the RFD-SF of elbow extensors and index finger abductors (Bellumori et al., 2013). This suggests that the RFD-SF describes a general neuromuscular characteristic of an individual, rather than providing information that is only joint specific. Because RFD-SF is mathematically independent of strength and muscle size, this also suggests that the determinants of quickness include a neural factor along with the known contributions from muscle fiber type. In support of this, our results showed that training the legs (and its central controller) resulted in a transfer to improvements in the untrained arms. While we did not directly measure brain function, we speculate that

improvements may have occurred because these rapid movements are controlled by common central nervous system structures that control both the legs and arms (Alberts et al., 2011).

Neural Improvements

Rate of electromyography rise during rapid force production improved in the knee and elbow extensors after six weeks of exercise. Rapid force production is important for joint stabilization during walking and enhanced neuromuscular activation is an essential element to actively stiffen joints within a short period of time (Gruber & Gollhofer, 2004). Increases in the ability to generate force have been attributed to improved neural drive to muscles. Consistent with the enhanced RER, Gruber and Gollhofer (2004) cited increases in motor unit firing rate and earlier recruitment (Van Cutsem et al., 1998). RFD is highly related to motor unit discharge rate (Nelson, 1996; Van Cutsem et al., 1998), changes in the recruitment of motor units (Kukulka & Clamann, 1981), or a combination of the two (Duchateau & Hainaut, 2003). These neural factors are likely to be the primary contributors to the increases seen in time to peak force and RER (Chou et al., 2013).

The ability to generate force most rapidly in the knee extensors has been shown to respond positively to sensorimotor training (Gruber & Gollhofer, 2004). With high ecological relevance to falls, Gruber & Gollhofer's sensorimotor training included postural stabilization tasks consisting of exercises on wobbling boards, spinning tops, soft mats, and two-dimensional free moving platforms. Increases in vastus medialis surface EMG within the first 100ms of activation were observed, which is a similar measure to

the RER in our study. While promising, the previously mentioned balance training may be inappropriate for those who have impaired motor control. In the current study, RER increased by 40% in the legs and 85% in the arms supporting our speed based training as a viable alternate intervention to target neural adaptations to exercise.

Transfer Effect of Exercise

In creating exercise interventions that benefit whole body function, one aim was to determine whether training one set of extremities can elicit improvements in other extremities and functional tasks. In healthy adults, voluntary exercise in both the upper (Lotze, Braun, Birbaumer, Anders, & Cohen, 2003) or lower (Perez, Lungholt, Nyborg, & Nielsen, 2004) extremities has been shown to increase motor cortical activation while involuntary exercise does not. In the present work there were improvements in functional measures, time to peak force, RFD-SF, and RER in both the trained legs and untrained arms. Based on previous studies (Lotze et al., 2003; Perez et al., 2004), it may be possible that increased activation of the motor cortex and basal ganglia elicited general improvements in central nervous drive. However, future studies should aim to elucidate the specific areas of the brain that are targeted with high-speed exercise.

Improvements following high intensity exercise may also be attributed to neuroplasticity. Activity dependent scaling of GABAergic synapse strength is regulated by brain derived neurotrophic factor which is enhanced with exercise, possibly due to increased blood flow to the brain (Fisher et al., 2008). This is promising evidence of central adaptations with exercise. If exercise alters central motor processes, it could be

expected that training one set of limbs would transfer to non-exercised limbs (Ridgel et al., 2009). In the present study, we studied the central effects of high-speed training for the legs on improved manual dexterity and quickness in the arms. Upper extremity function and hand dexterity improved in older adults with promising results that high-speed low-resistance cycling has a significantly positive impact on overall physical function.

Conclusion

Despite variability between subjects, our high-speed, low-resistance cycling program elicited improvements in the ability to produce rapid isometric muscle contractions across a full range of forces. Such contractions are especially relevant to older adults and individuals with neural impairments in activities of daily living including fall prevention, typing, catching an object before it falls, and crossing the street quickly. This exercise resulted in improvements in the TUG which is a standardized measure of overall functional mobility. Improvements in the RFD-SF and RER in elbow extensors as well as the 9-Hole Peg Test suggest that training one set of muscles may induce adaptations in the central nervous system. Interestingly, RFD-SF trended back toward baseline four weeks post-exercise ($p>.05$) while functional measures remained relatively constant. Retention of functional improvements may be suggestive of enhanced self-efficacy in these tasks. In addition, decreases in RFD-SF highlight the importance of remaining active to maintain neuromuscular function. Future studies should elucidate other functional tests that can be enhanced with this exercise program and determine if

positive results from this specific exercise program extend to clinical populations known with decreased speed of movement (e.g. Parkinson's disease).

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Chapter 4

CLUSTER ANALYSIS TO ISOLATE AND QUANTIFY PAIRED MOTOR UNIT DISCHARGE BEHAVIOR IN PEOPLE WITH PARKINSON'S DISEASE

Introduction

Tremor is defined as involuntary, rhythmic oscillatory muscle contractions in one or more body parts and is one of the primary symptoms in Parkinson's disease (PD). Although there are medications for reducing tremor and other PD symptoms, they not only lose effectiveness as the disease progresses, but also have severe side effects (e.g. dyskinesia, insomnia, increases in high risk behaviors, etc.). Drug-related side effects, along with PD related symptoms, further diminish the quality of life of a PD patient. Therefore, there is a need for a non-drug treatment that could be either a supplement or an alternative to the traditional medical and pharmaceutical approach toward PD.

A contributor to mobility is the smoothness with which muscular contractions or posture can be maintained. This is impaired in people with PD through the manifestaion of muscle tremors which occur at a frequency between 4 and 6Hz (Jankovic, 2008). The presence and severity of tremor varies greatly between and within individuals. The amplitude and frequency of tremor in isometric contractions is known to be affected by anxiety, fatigue, pharmacological interventions and deep brain stimulation. Elek et al. (1991) examined the relationship between characteristics of paired motor unit (MU) discharge and tremor amplitude in pathological and voluntary tremor. Paired MU

discharge refers to two rapid MU firings (short inter-spike interval; ISI) followed by a longer ISI. The mean ISIs alternated between 10ms and 90ms in both ISI durations. The atypically short ISI durations in paired discharge behavior cause the unwanted fluctuations in force and the ISI duration is inversely correlated with tremor magnitude. Howewever, it should be understood that paired discharge was not necessarily due to a pathology at the level of the MU, but a response to disordered input in which the motor neurons produce paired pulses in response to abnormally strong excitation (Bawa & Calancie, 1983; Elek et al., 1991). More recently, using funtional magnetic resonance imaging (fMRI), Helmich et al. (2011) suggested that the basal ganglia triggers a cerebellar circuit that results in the production of tremor.

While the symptoms of PD originate in the basal ganglia with dopamine dysregulation, discharge behavior of alpha motor neurons reveals the peripheral manifestation of PD. Paired MU discharge causes excessive nonlinear summation of twitch forces which results in muscular force tremor (Dengler, Wolf, Schubert, & Struppler, 1986; Elek et al., 1991; Taylor & Stephens, 1976). To supplement PD medications, speed training has recently become a valuable intervention strategy for people with PD (Ridgel, Vitek, & Alberts, 2009). Individuals who completed incremental speed-dependent training showed improvements in mobility after a single intervention (Pohl et al., 2003; Herman et al., 2007; Cakit, Saracoglu, Genc, Erdem, & Inan, 2007). Tremor, manual dexterity, and motor function improved in a study involving people with PD pedaling on a tandem bike with an assistant pedaling in front to augment the pedaling rate however, the specific neural adaptations remain unclear (Ridgel et al, 2009). There is

sparse literature on the abnormal discharge behavior in PD tremor with even less evidence on how exercise may effect the MU discharge behavior.

In a recent project investigating the acute effects of speed-based exercise sessions on paired discharge behavior (unpublished preliminary studies, Appendix A), the paired discharge behavior varied considerably in its severity or it waxed and waned throughout prolonged (72-90s) recording of isometric force. Due to the large amount of variability in the presentation of tremor in people with PD, the purpose of the present study was to develop and test a methodological approach for analysis of paired motor unit discharge behavior in tremor. The methodological challenge to overcome is that when paired discharge behavior is inconsistent or less severe, ISI distributional statistics that assume bimodal behavior (ISI-short, ISI-long) fail to isolate ISIs of paired discharge from those that might represent non-tremor related discharge.

After developing the method with the guidance of 38 highly variable motor unit recordings, we tested it by quantifying paired discharge behavior before and after three test interventions in participants with PD: 1) a single bout of high-speed low- resistance cycling, 2) a six week high-speed low-resistance cycling intervention, and 3) off/on medication (Levodopa – dopamine agonist). The points of interest that will be discussed include 1) tremor frequency and amplitude during constant isometric force contractions and 2) the paired motor unit discharge behavior in people with PD who are tremor-dominant.

Methods

Participants and Recruitment

Participants included people with Parkinson's disease who participated in either the acute (single session, n=10) or chronic (6 weeks, n=8) exercise intervention (see Table 4.1 for subject characteristics) and were recruited from local PD support groups. All participants reported experiencing tremor in at least one of their hands. Exclusion criteria included injury to the lower or upper extremity within the past 6 months that required medical treatment, low back pain, or uncontrolled hypertension. All participants signed an institutionally approved informed consent and provided physician's clearance if they answered yes to one or more questions in the Physical Activity Readiness Questionnaire.

Parkinson's Severity Assessment

Experienced clinicians performed the motor assessment section of Unified Parkinson's Disease Rating Scale (UPDRS) and the Hoehn-Yahr assessment. These two tools are the gold standard for assessing severity of PD motor symptoms and disease progression (Baas, Stecker & Fischer, 1993).

Table 4.1: Subject characteristics ± (SD). UPDRS: Unified Parkinson's Disease Rating Scale motor section score.

Intervention	N	Age (years)	Height (cm)	Mass (kg)	UPDRS	Hoehn-Yahr
Acute	10	61.2(11.4)	180.9(13)	79.3(11.4)	19.6(6.5)	2.31(.65)
Chronic	8	62.0(9.4)	175.4(9.1)	76.7(8.6)	18.3(6.9)	2.44(.68)

Force Tremor Measurement

In the hand most affected by tremor (self -reported), isometric force steadiness was assessed in isometric index finger abduction (IFA) contractions. Participants were seated comfortably on a stationary recumbent bicycle with their palmar surface resting on the force measuring device at standard table height. The index finger was oriented perpendicular to the measurement axis of a strain gauge force transducer (MB-25, Interface, Scottsdale, AZ, USA; Figure 4.1). The greatest force from three maximal effort isometric contractions (maximal voluntary contraction: MVC) was used for scaling of isometric conditions to %MVC units. Similar to another study (Christakos, Erimaki, Anagnostou, & Anastasopoulos, 2009) each participant performed isometric force matching tasks (10% and 20% of pre-determined MVC) using a custom force measuring device. Participants received real time feedback of their force on a computer monitor. The force matching task was as follows: 3 s ramp up to the desired force level, hold constant force at either 10% MVC (90 s) or 20% MVC (64 s), and then 3 s ramp down (Figure 4.2). At least 60 s rest was given between contractions to prevent fatigue and more time was given if necessary. Participants practiced the force matching tasks until they became comfortable with the protocol before MU recordings were taken.

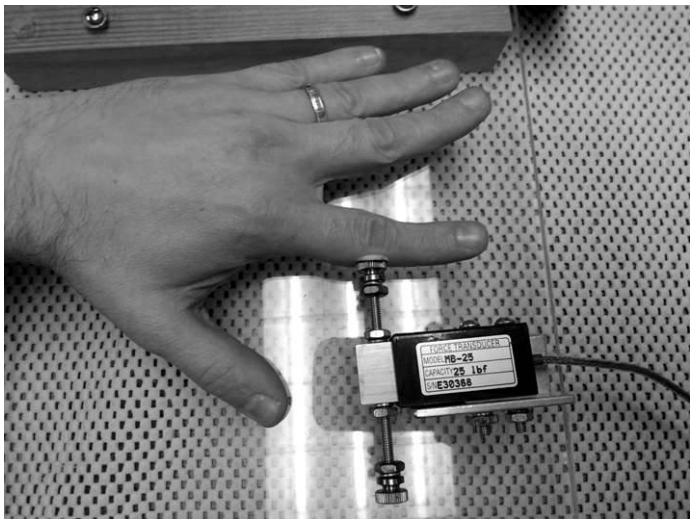


Figure 4.1: Custom force measuring device for index finger abduction.

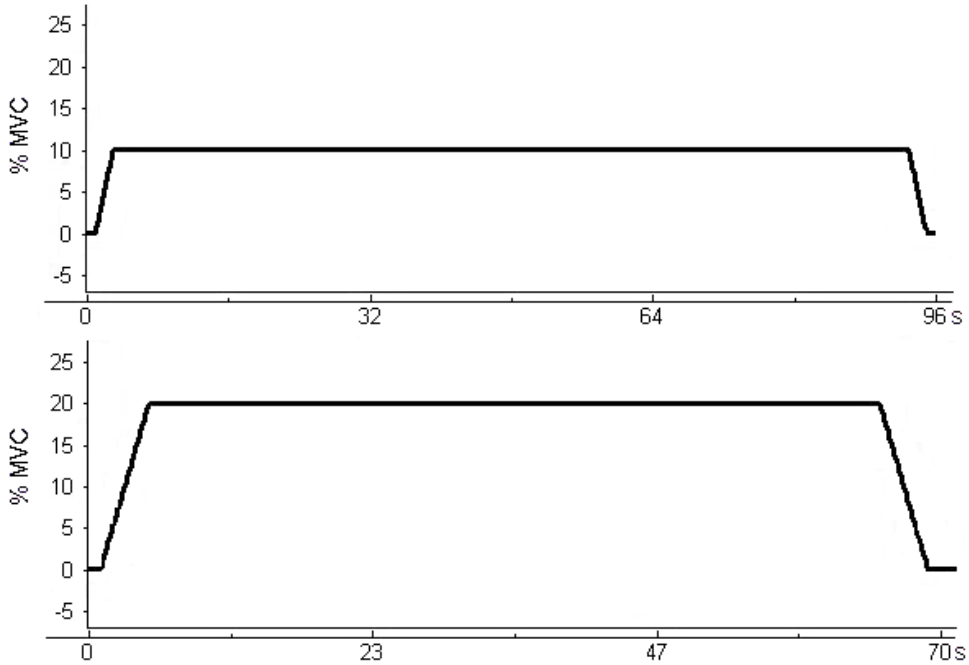


Figure 4.2: Isometric force matching trajectories. Top: 10% MVC (96 s). Bottom: 20% MVC (70 s).

Motor Unit Recordings

MU recordings were obtained from a custom needle electrode placed in the mid-belly of the first dorsal interosseous (FDI) muscle (based on palpation). This electrode remained in place during the acute exercise intervention and before and following medication as an attempt to record from the same MUs before and after treatment in two test cases. To prevent needle electrode movement, the hand and arm rested on the force measuring device throughout exercise.

Test Treatments

Acute: Once baseline MU and force recordings were obtained, participants completed approximately 25 minutes of high-speed low-resistance cycling. Exercise was performed on a stationary recumbent bicycle (Life Fitness, Platinum Club Series Recumbent Lifecycle) with no added resistance (Level 1). Exercise began with a 5 minute warm-up at preferred pedaling cadence. Participants then completed ten 20 s bouts of fast cycling (at least 20% greater than preferred pedaling cadence) with a minute of active recovery at preferred pedaling cadence between each bout of fast cycling. Exercise concluded with a 5 minute cool-down. After cycling, participants completed the same force matching tasks as described above. Force and MU activity were recorded for analysis.

Chronic: Participants trained for six weeks under the supervision of the experimenter (2 days per week = 12 total sessions) following the same protocol as explained in the Acute intervention.

Off vs. On Medication: One participant scheduled testing after overnight washout of PD medications and prior to the first morning dose. Force and motor unit recordings were taken before and following the first morning dose. The subject rested in the data collection station for 30 minutes while the medication took effect, as evidenced by subject self-report of feeling 'on' and increasingly dynamic facial expressions. During this test session, the subject's symptoms were observed by a clinical researcher with extensive experience with PD (Pretzer-Aboff et al., 2011).

Data Acquisition

Force Tremor Measurement: The methods of measurement are modeled after experiments described by Elble and Randall (1976) for isometric tasks. Briefly, the hand rested upon a custom device equipped with a strain gauge force transducer. The FDI was then aligned to the transducer at the distal interphalangeal joint against a firm bumper. The hand and other fingers rested comfortably upon the surface of the custom device (Figure 4.1).

Motor Unit Recordings: Motor unit action potentials were recorded using the same methods that have proven successful in previous experiments (Kamen & Knight, 2004; Knight & Kamen, 2005, 2007). Greater numbers of MUs and accurate spike sorting are facilitated by custom-made recording electrodes, the initial design of which originated at the Neuromuscular Research Center at Boston University (LeFever & DeLuca, 1982; LeFever, Xenakis, & DeLuca, 1982). The custom electrodes consist of four fine wires epoxied within a cannula. The uninsulated tips of the four wires are affixed in a square

array at a small side port near the tip of the needle. Differential amplification of three pairs of wires provides uniquely shaped MU action potentials (MUAP) in three channels (this is a deliberate use of crosstalk). Since MUAPs from two different MUs can present similar shapes in one channel, the additional channels make their accurate sorting possible. The integrity of spike sorting is especially important in the present population because atypical discharge behavior was expected. These electrodes are sterilized using ethylene oxide gas.

Finding Motor Unit Recording Sites: After palpation of the FDI muscle, the electrode was inserted through the skin and into the muscle at approximately the mid-belly region. Participants were then asked to produce mild isometric contractions. The electrode was subtly manipulated until the recording volume contained action potentials from one or more MUs. With adequate experience, the investigator can determine the quality of the recording site based on audio and visual feedback of the signals in real time. Once a good site was found, recordings were taken during the 10% and 20% MVC isometric force matching tasks.

Data Reduction

Force Tremor: For each participant, the amplitude and frequency of tremor was quantified in the force recordings using frequency spectral techniques described in signal processing literature (Bendat & Piersol, 1971) and in relevant tremor research (Elble & Randall, 1976; Elble, Higgins, & Elble, 2005). The approach to frequency domain analyses was based on the methods described by Elble and Randall (1976) and Elble et al.

(2005). To quantify motor performance of the force matching task, root mean squared error (RMSE) was calculated from differences between the target and actual force (10 or 20% MVC) values.

Motor Unit Spike Sorting: The three channels of MU recordings were used in custom automatic spike sorting algorithms and then user-interactive manual sorting tools. The automatic algorithms first find all spikes above threshold amplitude. Next, spikes are sorted non-specifically by amplitude and specifically by root mean squared-based template matching and then manually with a user-interactive program that has the capability to resolve MU action potentials in superposition. Following the sorting process, each MU file was independently verified by a second trained investigator. The product of spike sorting is a small file containing integer identifiers of spikes belonging to an individual MU and the associated discharge times. All subsequent analyses were based on the temporal patterns of discharge and not on the characteristics of the spikes themselves.

Measures of Paired Discharge: Paired MU discharge presents a special situation for the measures of central tendency and variance due to the bimodal distribution of inter-spike intervals (Figure 4.3). The hypotheses of interest are based on the means and variance of each separate ISI distribution (ISI-short and ISI-long). However, with inconsistent or less severe paired discharge behavior, ISIs from the disordered short-long-short ISI pattern are mixed among ISIs from non-disordered discharge. The challenge is that dependent measures of interest from ISI short and ISI long are altered by ISIs that are not from the paired discharge behavior. Therefore, the following experimental

methodology was developed and tested using MATLAB software. For each motor unit of interest, the user selected the region for analysis (typically the whole plateau region of the force trajectory).

A serial correlation plot was used to quantitatively assess clustering of the ISI - short-long-short discharge behavior. Serial correlation plots an ISI versus that ISI plus the ISI which follows it (ISI_n versus ISI_{n+1}). Once plotted, the ISI distributions form a cluster of data points and the result is a plot that depicts MU discharge behavior. In a healthy neuron, the ISI plot would reveal a single cluster of ISIs. In the presence of tremor, two distinct clusters of ISIs emerge due to the short-long period between successive MU discharges (Figure 4.4).

The "kmeans" algorithm was used to fit the data within 2-5 clusters. Once ISI distributions were put into clusters, the silhouette mean (range: 0-1, city block method) provides a measure of how well-defined clusters were. The highest average silhouette value was used as a selection criterion for the number of clusters to apply and the number of clusters could vary from one motor unit to another. After the best cluster representation was determined, ISIs from the ISI-short-long distribution were extracted as subsets of the total ISI distribution of the motor unit. The mean and standard deviation of each cluster (ISI-short and ISI-long) were then calculated. Another measure of the prevalence of paired discharge was computed as a percentage of ISIs in paired discharge behavior relative to the total number of ISIs. Two distinct modes would result in a score of 100% indicating the discharge only exhibited the paired behavior.

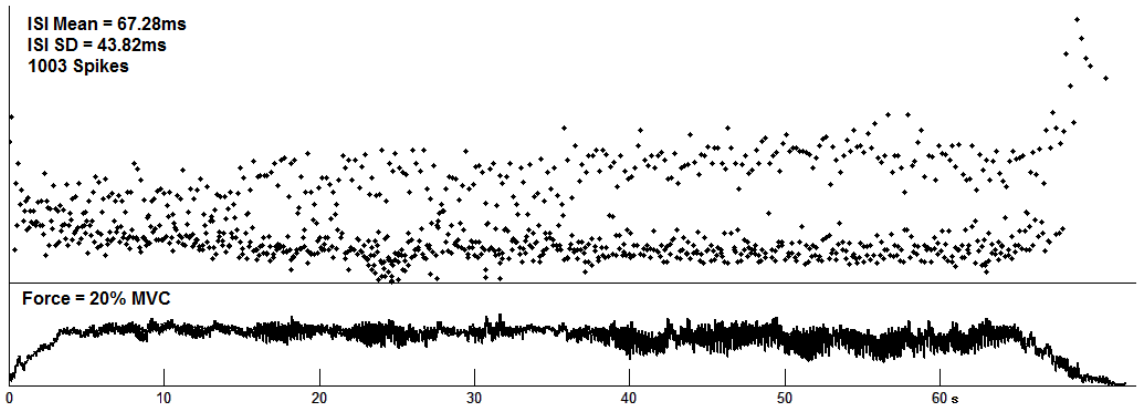


Figure 4.3: Paired discharge behavior and isometric force tremor in a person with PD. Top: Dot-plot of inter-spike intervals from a single motor unit. This recording shows distinct bands of short and long ISIs with an increasing severity of this discharge behavior reflected by increased separation of the bands and relatively low variability within them. Mean (SD) inter-spike interval (ISI) = 67.28 (43.82) ms. Bottom: Constant isometric contraction force at 20% MVC with corresponding tremor that increases with severity throughout the contraction.

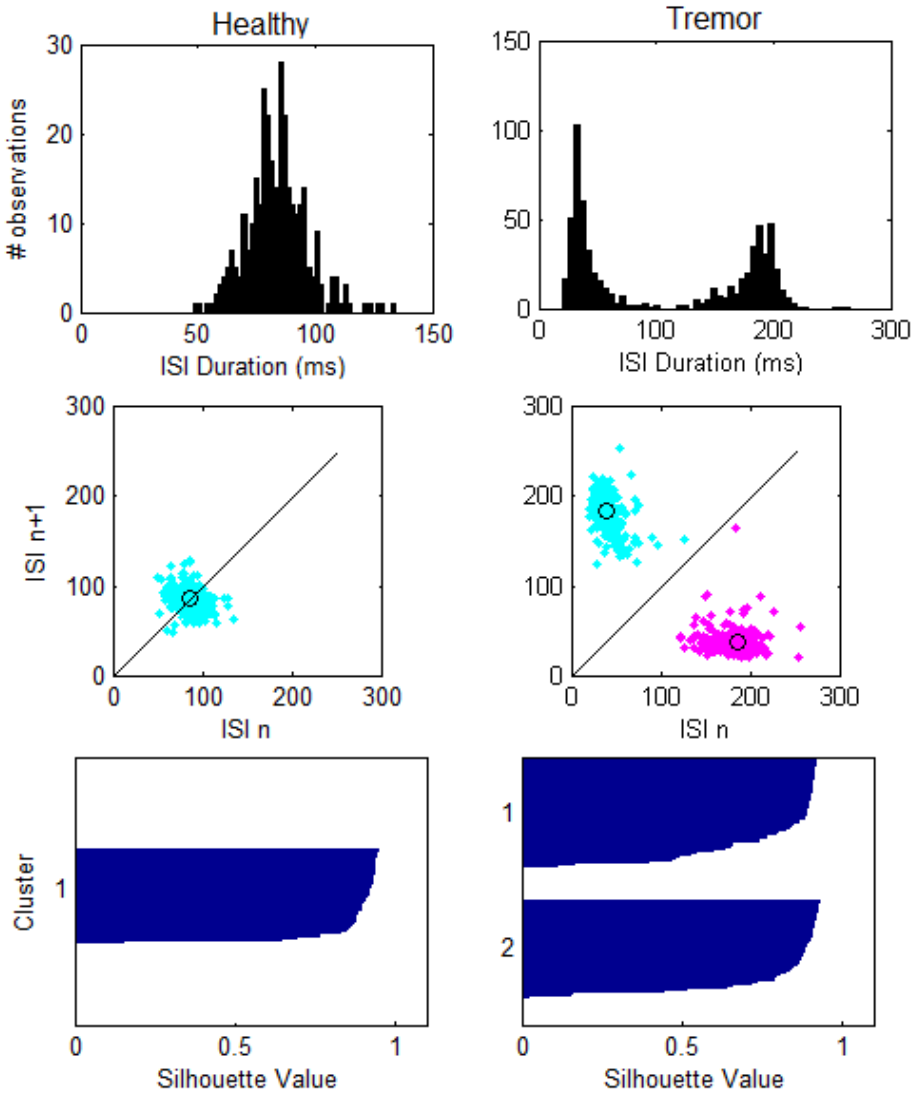


Figure 4.4: Demonstration data showing clear cases of healthy discharge behavior (left) in smooth force production and severe paired discharge behavior in tremor (right). Traditional ISI frequency histograms (top) show the typical normal distribution of ISIs (left) and the biomodal ISI distribution of paired discharge (right). The corresponding serial correlation (ISI_n versus ISI_{n+1}) plots (middle) show (light blue), short ISIs followed by long ISIs). Silhouette plots (bottom, cluster means: Healthy = .88, Tremor = .89) support well-defined clustering results in both healthy discharge behavior (left) and severe paired discharge behavior (right). The number of clusters was automatically determined based on the silhouette mean criterion. In this case of tremor, nearly 100% of ISIs are represented in the ISI short-long behavior with a highly discrete ISI distribution. The tested clustering method for isolating ISIs would not be necessary in this case.

Results and Discussion

Motor unit recordings were obtained from a total of 18 people with Parkinson's disease before and after either a single exercise session (acute) or following the six week intervention (chronic). While all participants reported experiencing hand tremor, only four of them presented with tremor during force and MU testing (acute intervention, N=3; chronic intervention N=2). One individual participated in both the acute and chronic intervention. To further validate our methodological approach (see Case Series) we also analyzed data from a person with PD who was tested after an overnight washout from PD medications (Levodopa – dopamine agonist). For the development of the tremor analysis methods we used 38 MU recordings from tremor-dominant participants. For the Case Series, 2 MU recordings were analyzed for each treatment of interest.

Development of Methods

Number of Clusters

We developed an algorithm and a criterion for determining the number of clusters in the ISI cluster plot (ISI_n versus ISI_{n+1}). Clusters represent the discharge behavior of a neuron. The criterion (silhouette mean) of cluster analysis provides a measure of how accurately each set of ISIs were clustered together. We rejected cluster results if the silhouette mean was less than 0.6 (4 ISI recordings rejected). The determination of this threshold was guided by quantitative assessment resulting from serial correlation plots. Pure paired discharge behavior would result in two distinct clusters (likely the most severe neurological case). The majority of MUs had 3 clusters (representing short, long,

and apparently normal ISI distributions). In the present sample, 5 ISI recordings had 2 clusters, 25 ISI recordings had 3 clusters, and 9 ISI recordings had 4 or 5 clusters. Using the cluster plots, we were able to identify which clusters did not represent paired discharge based on visual inspection.

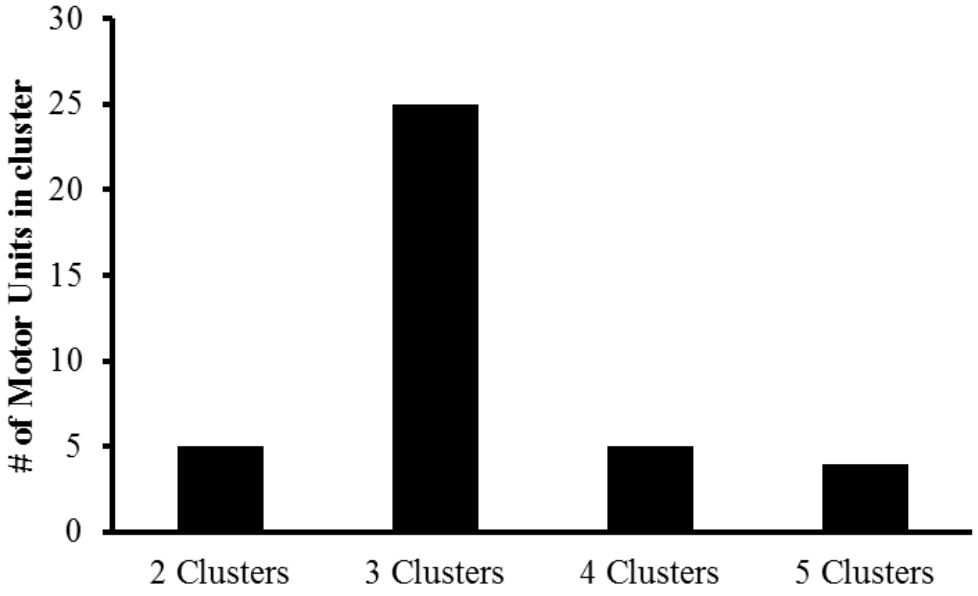


Figure 4.5: Number of motor unit recordings displaying 2, 3, 4, or 5 clusters using this algorithm. After rejecting 4 ISI series due to a low silhouette means, the final sample represented 34 motor units from 5 different individuals.

For MUs observed while near their recruitment threshold force (Figure 4.6) periods of slow firing rates were mixed together with periods of de-recruitment (not tonic, not sustained discharge). In this population and as shown in Figure 4.6 poor control (unsteady force production separate from tremor) also results in motor unit de-recruitment. For adequate analysis using the tested clustering methods, MUs need to be sufficiently above their recruitment threshold force to exhibit tonic discharge.

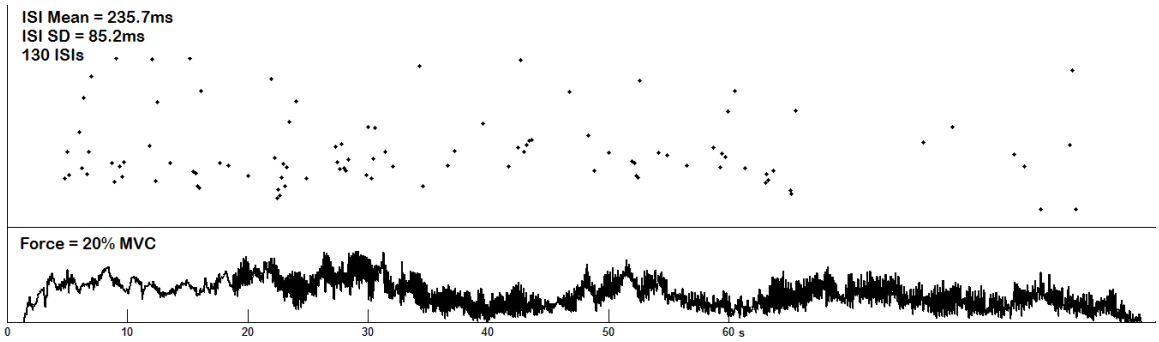


Figure 4.6: Low frequency oscillations representing poor control through 20 s, at which time tremor began and persisted through the end of the contraction. Prolonged inter-spike intervals in the upper panel (higher dots) represent periods of MU de-recruitment. Between 70 s and 90 s the force level remains low and the representative MU does not fire because it is below the recruitment threshold force. In practice, real time feedback of MU discharge could be used to guide the force level at which recordings are taken rather than specifying arbitrary force levels of 10 or 20%. In this recording the tremor amplitude and frequency were 19.9% MVC^2 and 4.59 Hz, respectively. This recording as among those rejected due to a silhouette mean below 0.6.

Visual inspection of cluster plots revealed that the 4th and 5th clusters were small sets of ISIs representing momentary de-recruitment or perhaps missed observations in the MU recording and do not provide meaningful information about the paired discharge behavior. Their presence does not undermine the analysis of the three primary clusters of interest (short, long, and apparently normal). In the same cluster results, clear paired discharge ISI clusters were visible with adequate ISI representation to examine the short-long ISI behavior.

Figure 4.7 represents the clustering results from one of the least ideal motor unit recordings (the messy data case). Although this is a recording in which the motor unit discharge was sporadic and the number of ISIs in the series was relatively few (144), the clustering method still provides an estimate of the behavior of the three clusters of interest (ISI-short, ISI-long, ISI normal). Five clusters were observed including 2 with paired discharge (cluster 3: pink and cluster 5: yellow), one with apparently normal discharge (cluster 4: red) and some observations near 300 ms representing momentary de-recruitment, and two being non-informative (cluster 1: blue and cluster 2: green). Although it is not ideal for momentary de-recruitment to be within the same cluster as the normal discharge (cluster 1: blue), the main information sought in this method is that from clusters 3 (yellow) and 5 (pink) representing the paired discharge behavior.

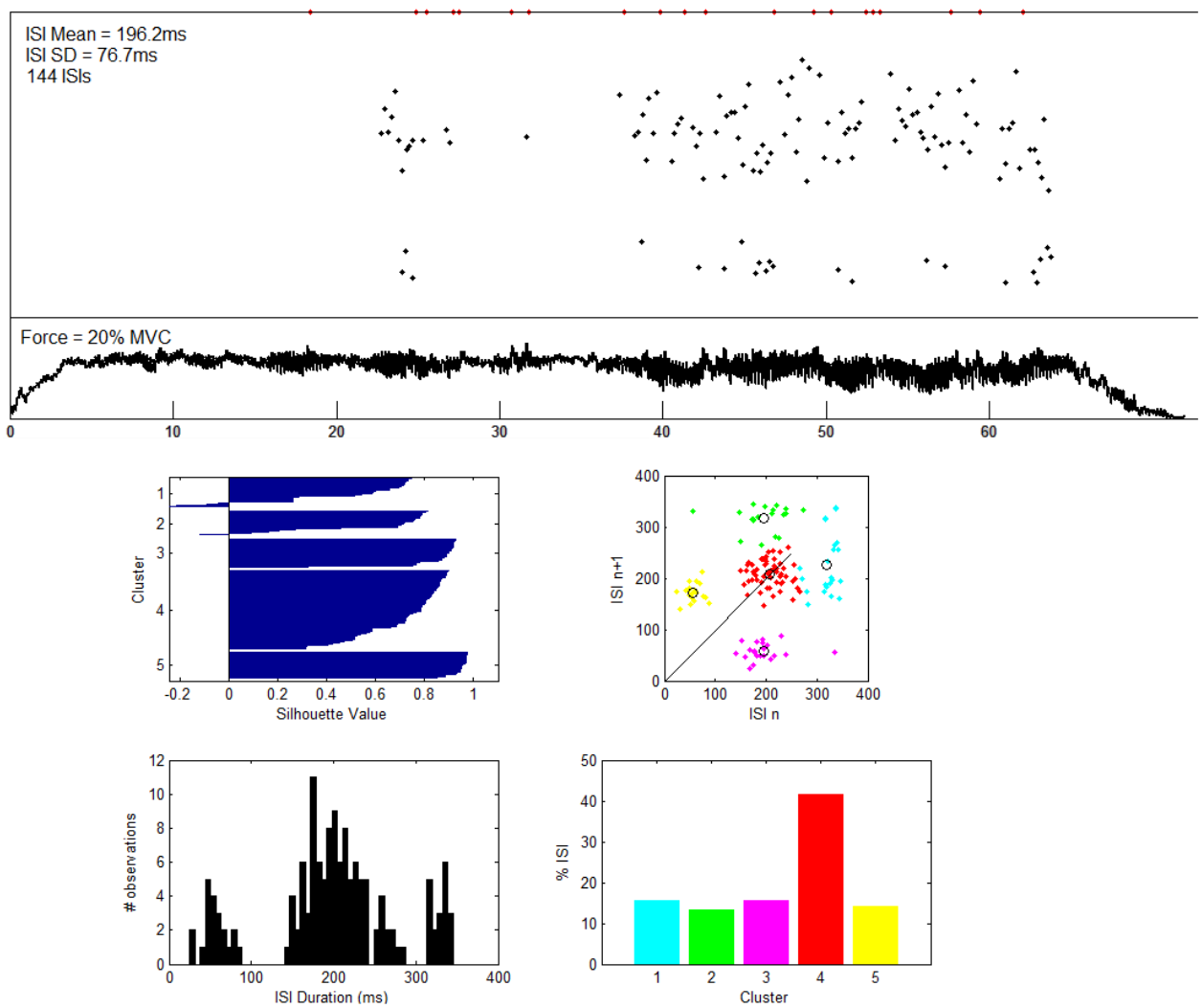


Figure 4.7: Top: ISI plot with corresponding force output below at 20% MVC. Middle Left: Silhouette results for each cluster (silhouette mean = .84). Middle Right: ISI cluster plot for short intervals (pink), long intervals (yellow), normal/long intervals (red), and two irrelevant clusters representing periods of de-recruitment or possibly missed observations (blue and green). Bottom left: ISI histogram for all observed ISIs. Bottom right: percentage that each cluster contributed to the total number of observed ISIs.

Figure 4.8 shows a better motor unit recording for analysis in which the discharge behavior is more stable (less de-recruitment) and more ISIs (341) are available for analysis. Four clusters were observed including 2 with paired discharge (cluster 2: green and cluster 3: pink), one with apparently normal discharge and some observations near 300ms representing momentary de-recruitment (cluster 1: blue), and one that is primarily de-recruitment based (cluster 4: red). Although it is not ideal for momentary de-recruitment to be within the same cluster as the normal discharge (cluster 1: blue), the main information sought in this method is that from clusters 2 (green) and 3 (pink) representing the paired discharge behavior. Another qualitative observation here is that the cluster we consider apparently normal discharge behavior (cluster 1: blue) deviates from the line of identity. Therefore there seems to be some behavior in which relatively long ISIs are followed by even longer ones still. Again, the primary information of interest comes from the distinct pink and green clusters.

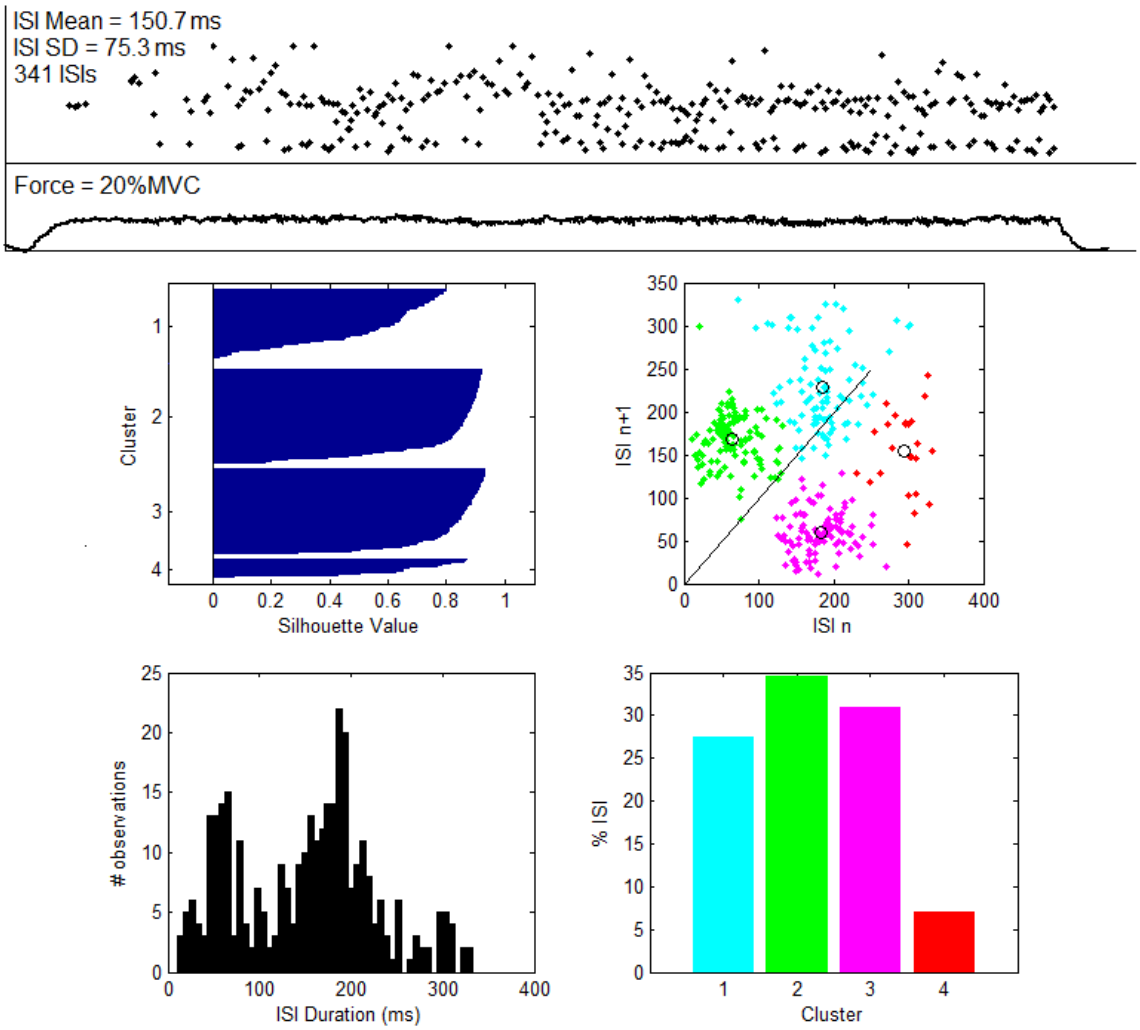


Figure 4.8: Top: ISI plot with corresponding force output below at 20% MVC. Middle Left: Silhouette results for each cluster (silhouette mean = .82). Middle Right: ISI cluster plot for short intervals (pink), long intervals (green), one cluster containing primarily normal discharge behavior and some long ISIs indicative of de-recruitment (blue) and one irrelevant cluster representing periods of de-recruitment or missed possibly observations (red).

Information content of clusters

As originally proposed, the aim was to study paired discharge behavior that underlies force tremor. Hypotheses were centered on the mean ISIs and standard deviations of expected bimodal ISI distributions. In the sample of participants we encountered, tremor was not always present at the time of testing (subjects on medications) and for those participants with tremor, the paired discharge behavior was not accurately quantifiable using traditional methods. The cluster analysis method allowed us to isolate and extract the ISI events that are specifically within paired MU discharge and separate from other discharge behavior. Table 4.2 contains all 38 MUs, their clustering statistics (number of clusters, silhouette mean, and clustering %) and the final dependent measures (means and standard deviations for each cluster). The assignment of cluster number is automatically determined by the MATLAB algorithm, "kmeans". In table 4.2, the **bold*** ISI means and standard deviations within boxes are the dependent measures of interest that represent paired MU discharge behavior.

Once cluster information is obtained, descriptive statistics applied on the different distributions provide information about the behavior of neurons. This information may prove useful in quantifying paired discharge behavior before and after interventions or as a means to track disease progression over time.

In the next section we will use three examples of different treatments to test our ability to analyze paired discharge behavior using the cluster method.

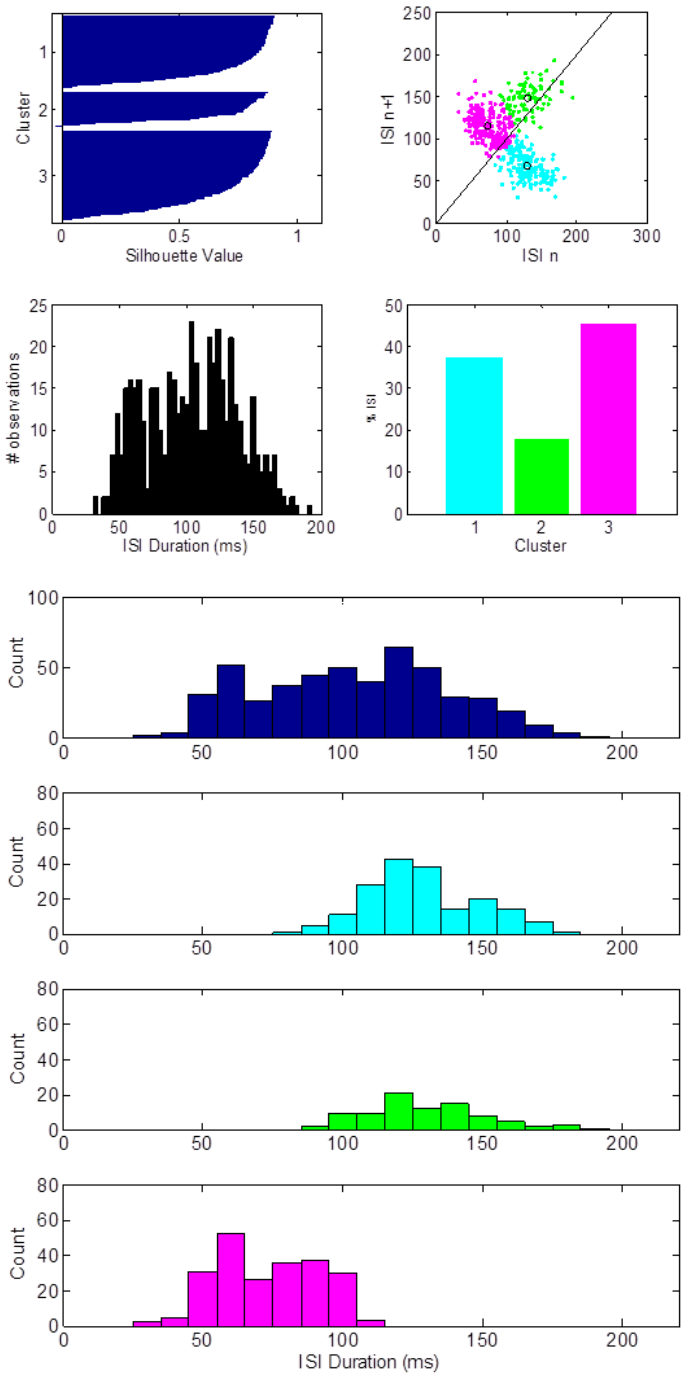


Figure 4.9: Original histograms for all ISIs (dark blue) within this recording with the isolated histograms representing each cluster of ISIs (cluster 1: light blue, cluster 2: green, cluster 3: pink).

Table 4.2: Dependent measures from 38 individual motor units. * values are mean ISI(SD) that represent paired discharge behavior (MU: Motor unit number in file, Trt: Treatment, Frc: Force level (%MVC), #ISI: Number of inter-spike intervals in file, #Clu: Number of clusters from analysis, Sil: Silhouette mean, %Pts per Cluster: percent of total points assigned to each cluster, C1: Cluster 1, C2: Cluster 2, C3: Cluster 3, C4: Cluster 4, C5: Cluster 5).

								% Pts per Cluster					Mean(SD) ISI of Cluster				
File	MU	Trt	Time	Frc	# ISI	# Clu	Sil	C1	C2	C3	C4	C5	C1	C2	C3	C4	C5
60905	2	off med	pre	10	522	3	.7	35	47	18			129(20)*	75(19)*	131(20)		
60905	3	off med	pre	10	442	3	.66	29	31	39			139(23)*	73(21)*	150(28)		
60906	1	on med	post	10	454	3	.49	30	21	49			100(11)*	85(11)	77(8)*		
60906	2	on med	post	10	376	2	.46	53	47				93(13)*	114(15)*			
60906	3	on med	post	10	480	2	.56	73	27				96(17)*	126(25)*			
66107	1	acute	pre	10	504	3	.83	13	43	45			165(31)	50(17)*	156(27)*		
66108	1	acute	pre	20	369	3	.6	26	38	36			188(42)	78(27)*	188(52)*		
66112	1	acute	post	10	392	3	.75	39	21	40			52(25)*	202(51)	183(48)*		
66112	3	acute	post	20	161	5	.82	32	9	23	5	32	205(60)	211(12)	174(11)*	202(38)	51(20)*
66113	1	acute	post	20	340	4	.72	7	31	27	35		293(26)	183(31)*	184(39)	65(29)*	
66313	3	acute	pre	10	356	3	.6	20	64	16			146(66)*	118(48)	283(45)*		
66312	1	acute/ chronic	pre	20	287	3	.61	34	32	35			82(62)*	270(60)	185(90)*		
66312	2	acute/ chronic	pre	20	272	3	.68	16	66	18			311(30)	187(34)*	206(56)*		
66312	3	acute/ chronic	pre	20	343	3	.54	36	30	34			130(76)*	44(41)*	230(65)		
66317	1	acute	post	10	100	4	.81	20	31	24	24		323(23)	163(38)*	325(16)*	167(41)	
66316	1	chronic	post	10	612	3	.73	9	43	48			152(26)	146(34)*	46(21)*		
66315	1	chronic	post	20	799	2	.65	43	57				127(33)*	48(26)*			
66508	1	acute	pre	10	374	4	.64	9	34	32	25		238(81)	47(26)*	146(40)*	154(29)	

Table 4.2 (continued): Dependent measures from 38 individual motor units. * values are mean ISI(SD) that represent paired discharge behavior (MU: Motor unit number in file, Trt: Treatment, Frc: Force level (%MVC), #ISI: Number of inter-spike intervals in file, #Clu: Number of clusters from analysis, Sil: Silhouette mean, %Pts per Cluster: percent of total points assigned to each cluster, C1: Cluster 1, C2: Cluster 2, C3: Cluster 3, C4: Cluster 4, C5: Cluster 5).

								% Pts per Cluster					Mean(SD) ISI of Cluster				
File	MU	Trt	Time	Frc	# ISI	# Clu	Sil	C1	C2	C3	C4	C5	C1	C2	C3	C4	C5
66508	2	acute	pre	10	375	3	.69	22	19	59			156(99)*	295(43)	98(49)*		
66508	4	acute	pre	10	483	3	.58	17	29	54			254(56)	118(50)*	84(43)*		
66511	3	acute	pre	10	245	3	.84	28	27	44			174(37)*	53(21)*	182(27)		
66511	4	acute	pre	10	632	3	.67	23	54	23			34(21)	39(19)*	121(30)*		
66511	5	acute	pre	10	218	4	.63	7	31	29	34		168(35)	48(27)*	141(23)*	63(25)	
66510	1	acute	pre	20	998	3	.65	32	31	37			99(19)*	41(17)	43(15)*		
66513	1	acute	post	10	158	3	.89	75	11	13			83(30)*	317(33)	102(69)*		
66513	2	acute	post	10	443	2	.88	94	6				71(28)*	184(79)*			
66515	1	acute	post	20	224	3	.65	20	22	58			219(58)*	55(48)	60(40)*		
67913	1	chronic	pre	10	765	3	.77	35	30	35			45(15)*	57(22)	149(25)*		
67913	2	chronic	pre	10	255	3	.71	29	43	28			208(48)*	242(55)	61(40)*		
67907	1	chronic	pre	20	494	3	.68	43	29	28			59(36)*	168(33)*	214(40)		
67907	2	chronic	pre	20	546	3	.75	17	44	40			203(39)	57(27)*	163(42)*		
67907	3	chronic	pre	20	758	3	.68	36	33	30			53(32)*	148(25)*	57(25)		
67907	6	chronic	pre	20	400	3	.8	46	11	43			71(68)*	55(31)	192(44)*		
67914	1	chronic	pre	20	900	3	.81	40	30	30			39(17)	128(21)*	44(15)*		
67914	4	chronic	pre	20	113	5	.69	13	14	14	49	10	193(53)	197(41)*	55(12)*	210(34)	333(3)
67908	1	chronic	post	10	660	2	.89	47	53				183(25)*	41(23)*			
67909	2	chronic	post	20	136	3	.68	29	36	36			201(60)	59(38)*	206(50)*		
67909	4	chronic	post	20	521	3	.77	41	37	22			53(48)*	164(24)*	41(18)		

Case Series

The following case series will present data from high responders in each intervention group (medications, acute exercise, and chronic exercise) to test the cluster approach to paired MU discharge behavior.

CASE 1: Off versus On Parkinson's Medication

Similar to the known group difference method (Thomas & Nelson, 1990), an off versus on medication condition was used to further validate the cluster method of MU analysis. One person with PD and known tremor volunteered for MU testing after an overnight washout from medication (subject 609 in Table 4.2). Constant isometric force recordings were obtained during the 10 and 20% MVC force matching tasks and then again 30 minutes after taking PD medications. Tremor amplitude and frequency diminished after taking a usual dose of PD medication (Figure 4.10). Paired discharge behavior was evident off medication and disappeared after taking medication. Cluster analysis was able to detect improvements in discharge behavior (Figure 4.11).

Traditional methods of ISI distribution analysis would have been based on the ISI frequency histogram (Figure 4.11: lower left of top panel). For this participant, off medications, the histogram suggests some potential paired discharge behavior with some amount of visible bimodality. In the top panel showing the ISI time series, it is evident that this participant's discharge behavior went into and out of paired discharge (most severe from 15-30 s).

In the upper panel of figure 4.11, a silhouette mean of .7 was supportive of the presence of clusters. In the lower panel (on medication), although the cluster method

forced the assignment of 3 clusters, a silhouette mean of .49 does not support their true existence. This is in agreement with the unimodal ISI frequency histogram. Because paired discharge behavior went away in this condition, unimodal distribution statistics would be adequate for these recordings from the on-medication case. .

In the lower right figures of the off-meds panel (blue histograms), the first and third histograms depict the isolated ISI distributions from which the dependent measures for hypothesis testing are obtained. Without this clustering approach these dependent measures would be altered by ISIs from parts of the recording in which there was no paired discharge behavior. The cluster approach successfully isolated the paired discharge behavior in two clusters with mean (SD) in Table 4.4. The appropriate unimodal discharge statistics for the on- meds condition are MU1: 85.8 (14.2), MU2: 102.7 (17.7), MU3: 103.7 (23.4).

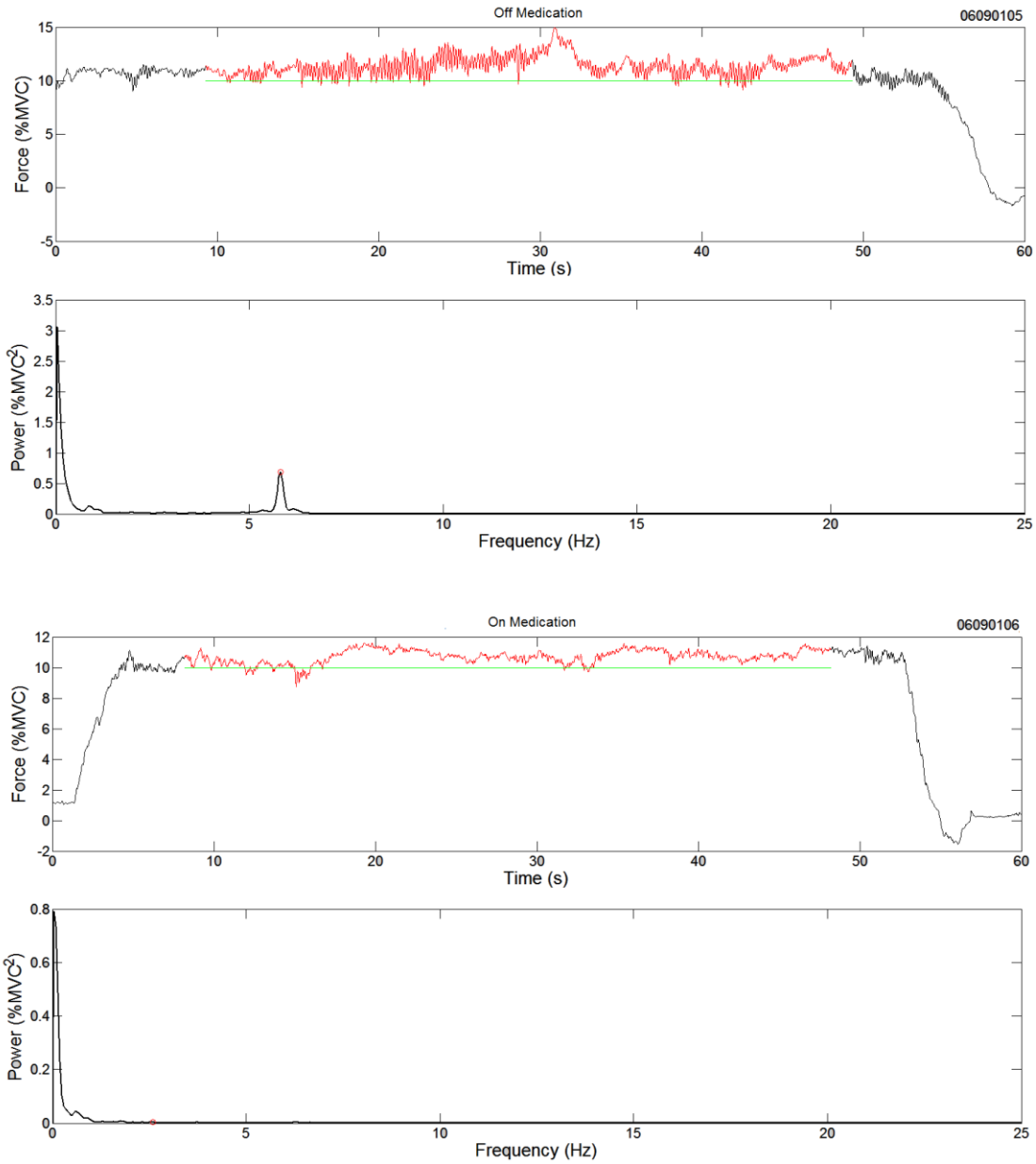


Figure 4.10: Force output and tremor frequency and amplitude from a person with PD and known tremor off (top 2 panels) and on medication (bottom 2 panels). Custom MATLAB software chose 40 s of the force trace to calculate frequency and amplitude (pre amplitude = 0.67% MVC^2, pre frequency = 5.81 Hz; post peak amplitude in the tremor frequency range from 4 to 6 Hz = 0.006% MVC^2).

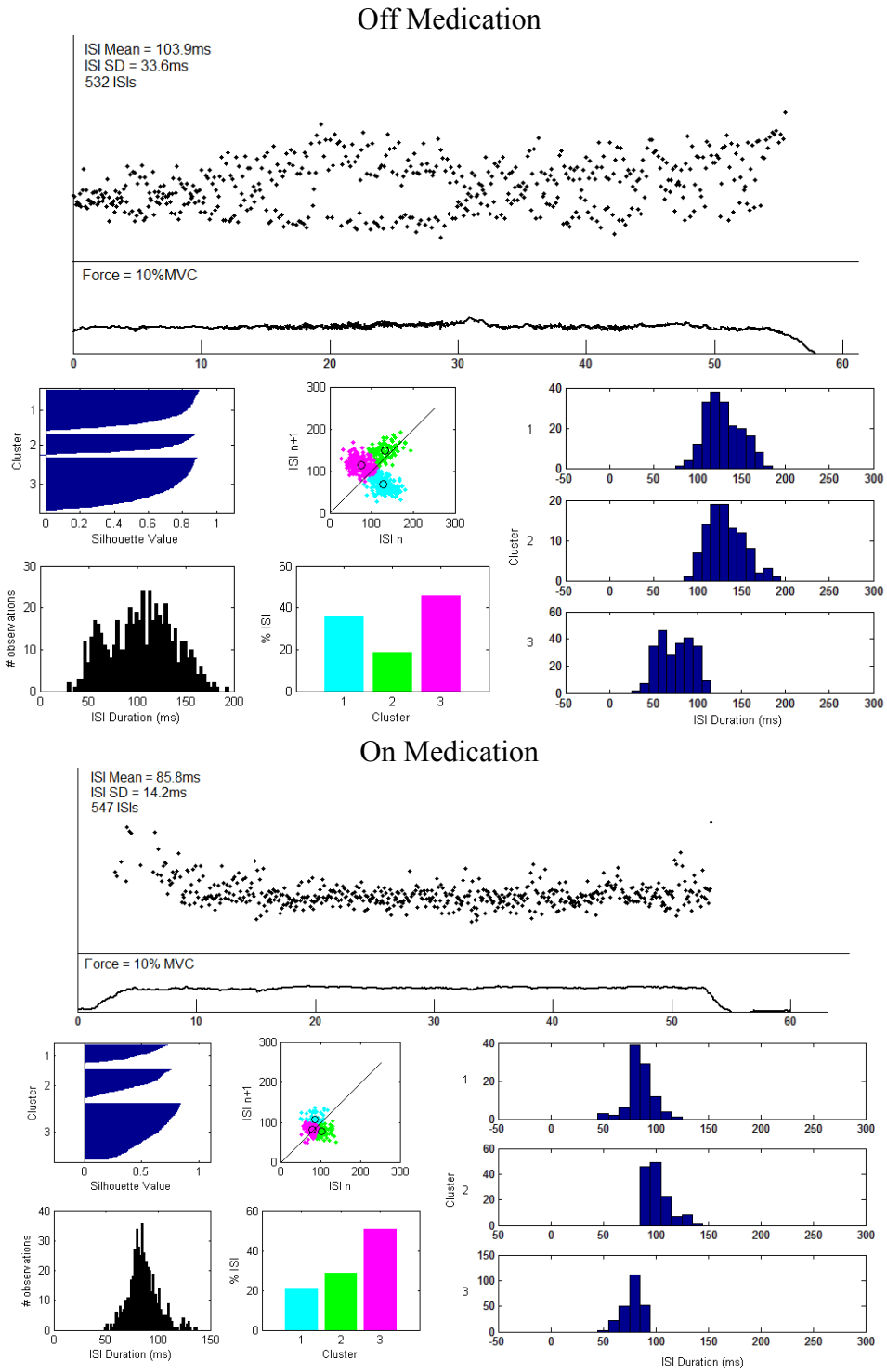


Figure 4.11: Cluster analysis results for Case 1. See text for details.

CASE 2: Acute Effects of Exercise

Constant force recordings were obtained before and after a single bout of high-speed low-resistance cycling (subject 665 in Table 4.2). Tremor amplitude and frequency decreased after exercise (Figure 4.12). Before exercise, a motor unit was observed during the most pronounced period of tremor. It exhibited severe paired discharge behavior in which visual inspection of the ISI frequency histogram would have supported direct analysis of the bimodal statistics. Nevertheless, the cluster analysis revealed the third cluster in which several longer ISIs (~200 ms) that were followed by long ISIs (~200 ms) indicating a generally slow MU discharge rate (Figure 4.13: pre intervention, green cluster). The cluster approach isolated the short and long ISIs as expected in the observed paired discharge behavior of this MU.

After cycling, normal discharge behavior was observed (Figure 4.13: post intervention, blue cluster). The two clusters (green and pink) representing paired discharge behavior approached the normal cluster region resulting in smaller force tremor amplitude. Unlike Case 1 (off/on medication), there is still some paired discharge behavior after exercise and the cluster method provides means (SD) of the two underlying clusters (Figure 4.13: post intervention, pink and green, Table 4.4). In the interpretation of these data, the improvement in tremor is associated with the short and long ISI means becoming closer as well as diminishing support for discrete clusters.

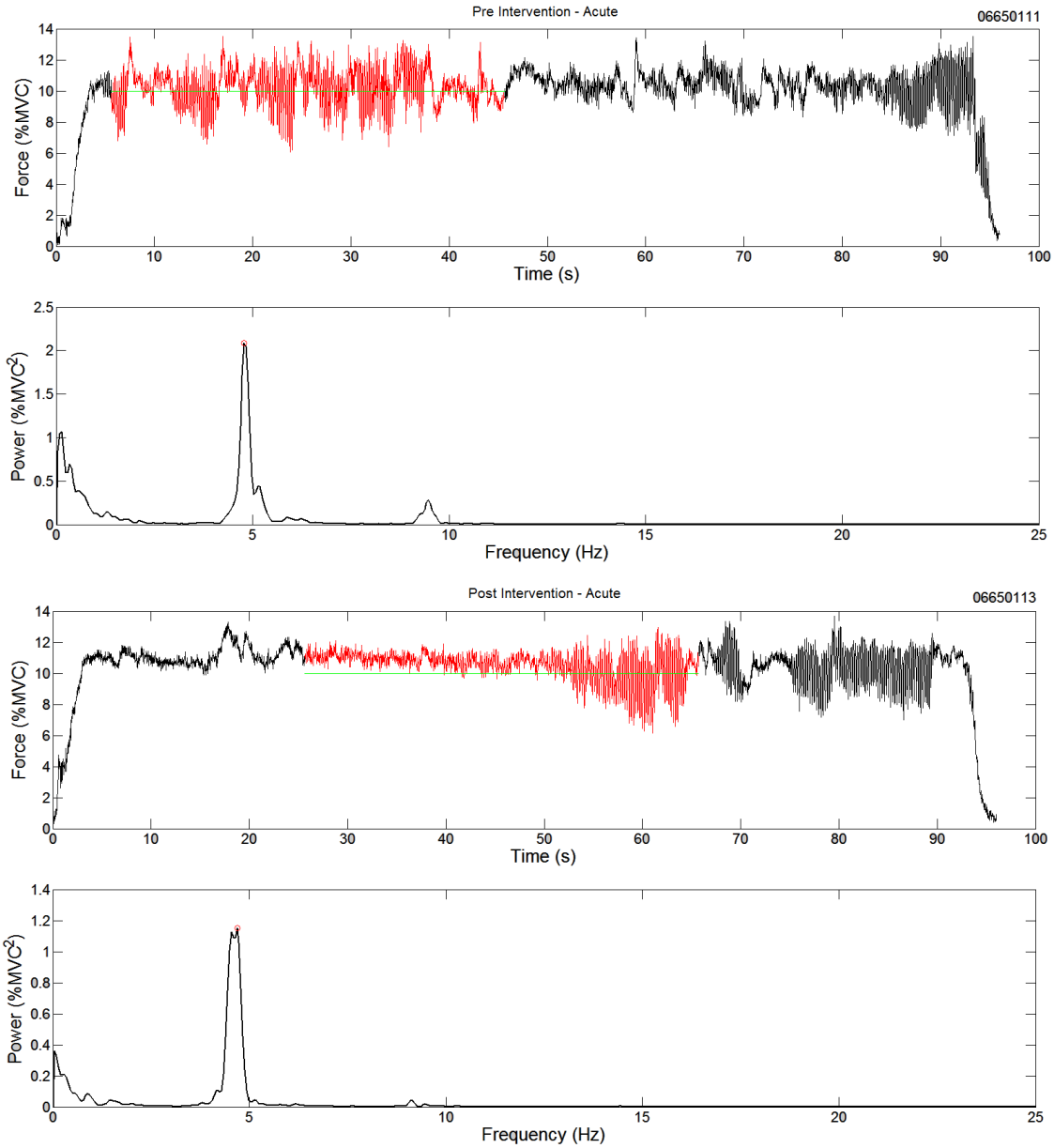
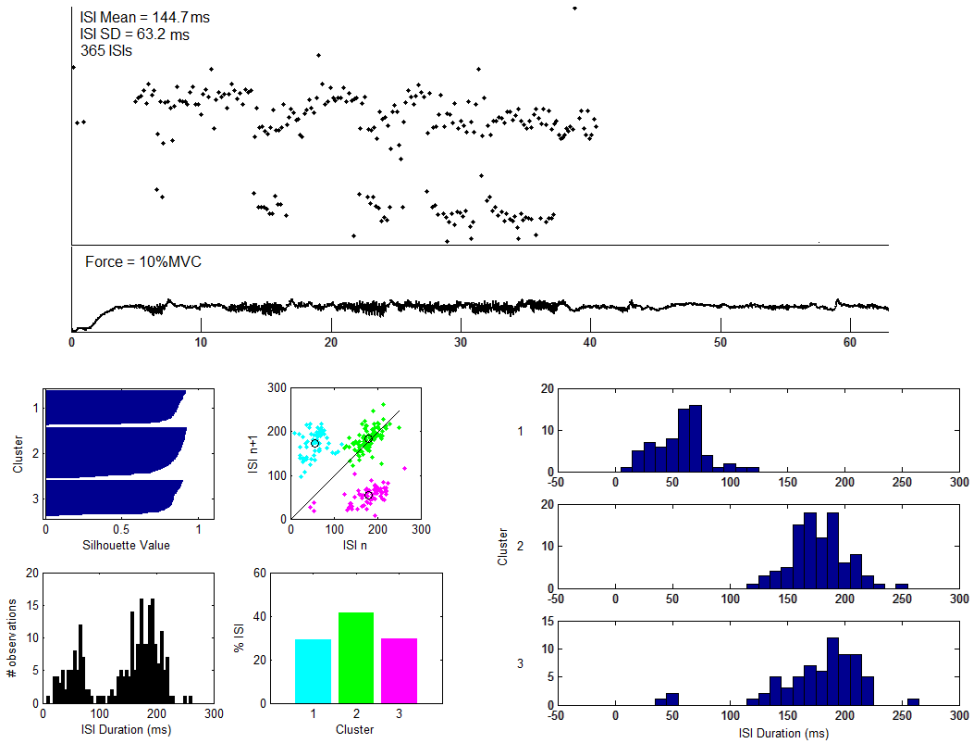


Figure 4.12: Force output and tremor frequency and amplitude from a person with PD before (top 2 panels) and after (bottom 2 panels) a single bout of cycling. Custom MATLAB software chose 40 s of the force trace to calculate frequency and amplitude (pre amplitude = 2.3% MVC^2, pre frequency = 4.89 Hz; post amplitude = 1.2% MVC^2, post frequency = 4.59 Hz).

Pre Intervention – Acute Exercise



Post Intervention – Acute Exercise

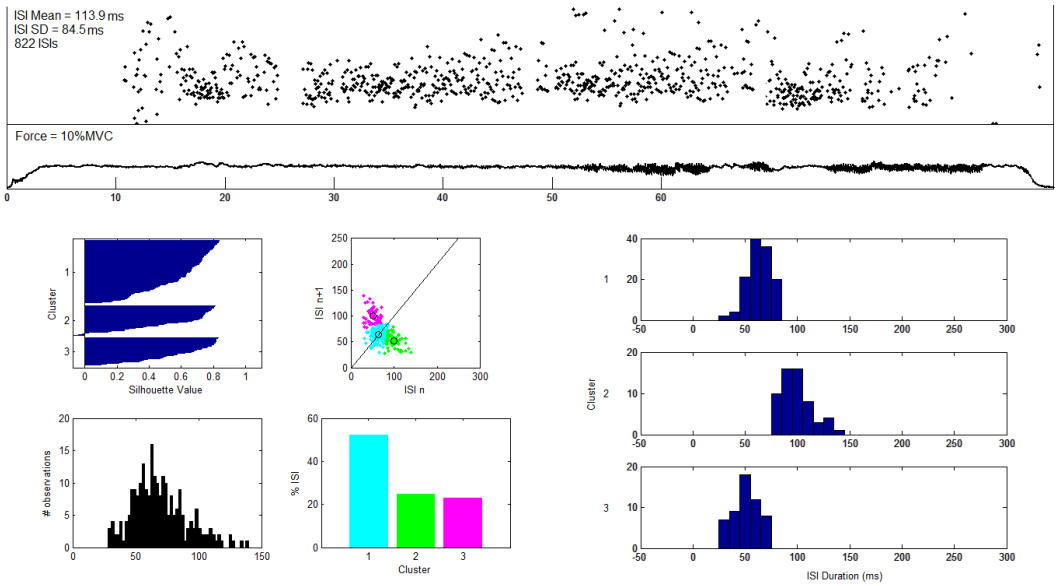


Figure 4.13: Cluster analysis results for Case 2. See text for details.

CASE 3: Chronic Effects of Exercise

Constant force recordings were obtained before and after a six week intervention of high-speed low-resistance cycling (subject 663 in Table 4.2). Tremor amplitude and frequency did not improve and, unfortunately, appeared worse after six weeks of exercise (Figure 4.14). One explanation for the lack of improvement in tremor may have been due to the timing of medication peak effectiveness relative to testing or a reduction in its effectiveness over time. Another consideration in this within subject design is that, unlike the first two subjects, we must assume that different motor units are recorded.

After exercise, paired discharge behavior was more pronounced with greater separation between bands of long and ISIs in the ISI time series as well as greater separation between clusters (Figure 4.15). Cluster analysis was successful in determining short and long ISIs within the MU discharge recordings (see Table 4.4 for means (SD) of clusters).

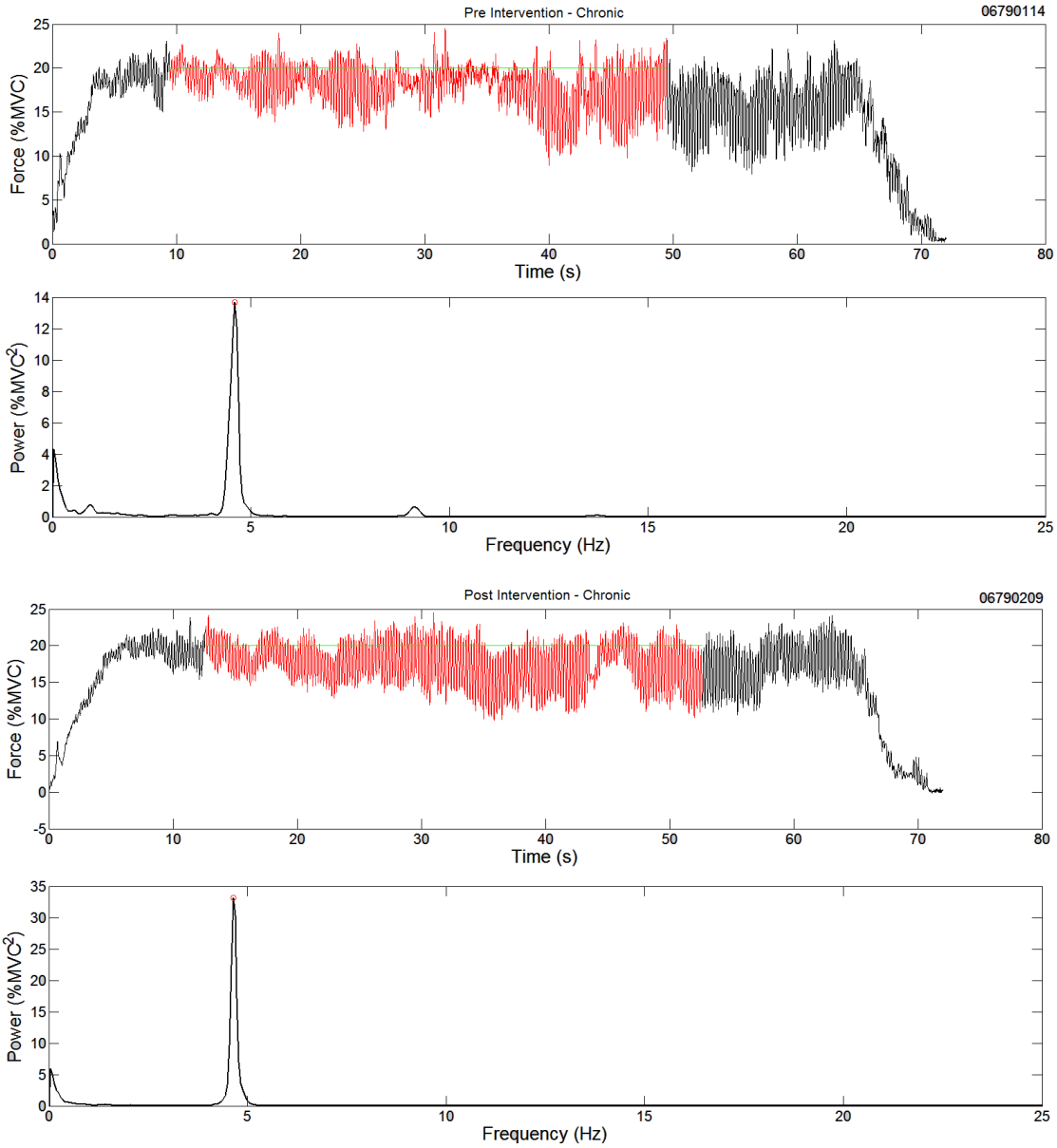
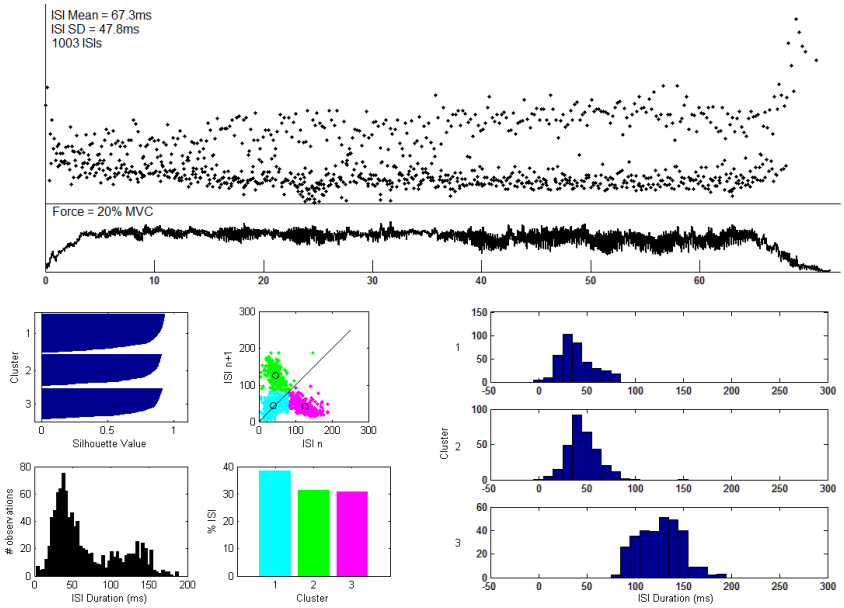


Figure 4.14: Force output and tremor frequency and amplitude from a person with PD before (top 2 panels) and after (bottom 2 panels) a six week cycling intervention. Custom MATLAB software chose 40 s of the force trace to calculate frequency and amplitude (pre amplitude = 13.7% MVC^2, pre frequency = 4.69 Hz; post amplitude = 33.1% MVC^2, post frequency = 4.64 Hz).

Pre Intervention – Chronic Exercise



Post Intervention – Chronic Exercise

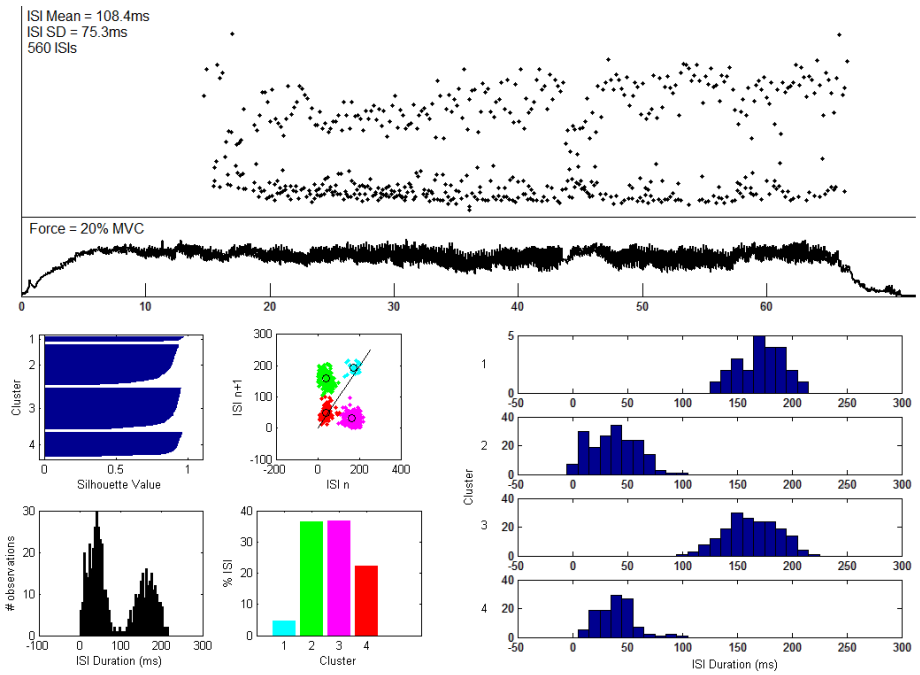


Figure 4.15: Cluster analysis results for Case 3. See text for details.

Table 4.3: Amplitude (%MVC^2: percentage of maximal voluntary contraction squared), frequency (Hz: hertz), and root mean squared error (RMSE) of tremor pre and post intervention. Percent change depicts the amount and direction of change.

Intervention	Pre Intervention Tremor			Post Intervention Tremor			% Change		
	Amp (%MVC^2)	Freq (Hz)	RMSE	Amp (%MVC^2)	Freq (Hz)	RMSE	Amp (%MVC^2)	Freq (Hz)	RMSE
Off/On Meds	0.67	5.81	1.61	0.006	2.25	2.96	-99.1	-61.3	83.9
Acute	2.31	4.79	1.63	1.24	4.59	1.16	-80.6	-4.1	-29.3
Chronic	13.66	4.59	2.99	33.11	4.64	3.91	-81.8	-5.3	-66.9

Table 4.4: Means (SD) for short and long inter-spike intervals, the percent that the two combined contribute to the overall motor unit discharge behavior (MUDB), and difference between short and long intervals shows the amount of separation between these measures.

Intervention	Pre Intervention MUDB				Post Intervention MUDB			
	Short ISI (ms)	Long ISI (ms)	%	Short-Long Diff (ms)	Short ISI (ms)	Long ISI (ms)	%	Short-Long Diff (ms)
Off/On Meds	75(19)	129(20)	82	54	85(11)	100(11)	50	15
					Unimodal: 86(14)		100	0
Acute	54(21)	174(37)	55	120	71(28)	184(79)	100	113
Chronic	44(15)	128(17)	60	84	59(38)	206(50)	71	147

Conclusion

Paired motor unit discharge results in tremor. The current data set was useful for the development and testing of an improved method for studying such discharge behavior. It was highly variable and consisted of recordings of mixed quality. Based on qualitative assessment of serial correlation plots, a silhouette mean greater than 0.6 is a good initial criterion to support the presence of clusters and paired discharge. In the most severe cases, 2 clusters of short and long ISIs are revealed and correspond with the bimodal distribution in frequency histograms that would be expected. In less severe cases of tremor, or when the behavior goes in and out of tremor, the paired discharge behavior is more challenging to isolate and analyze. When 2 clusters were observed but no tremor was present, we found it was because the silhouette mean was too low and excluded those MUs from analysis. When 3 or more clusters were observed, we used visual inspection to determine which clusters corresponded with short and long ISIs and described them separately using values of central tendency and variance.

The majority of ISI series in this study had three clusters with two of them representing ISI short-long and ISI long-short and the third being apparently normal discharge (albeit slow). To further validate this methodological approach, a subject with known tremor was tested off and on PD medication. Although the tremor was not severe in magnitude or consistent throughout the recording, the cluster approach isolated paired discharge behavior that was far less evident in the traditional ISI histogram approach (Figure 4.16). Once cluster information is obtained, descriptive statistics for different

distributions provide information about the behavior of neurons. This information may prove useful in quantifying paired discharge behavior before and after interventions or as a means to track disease progression over time. Considering the high success of the on versus off meds case, this methodological approach may be of high interest to pharmaceutical researchers.

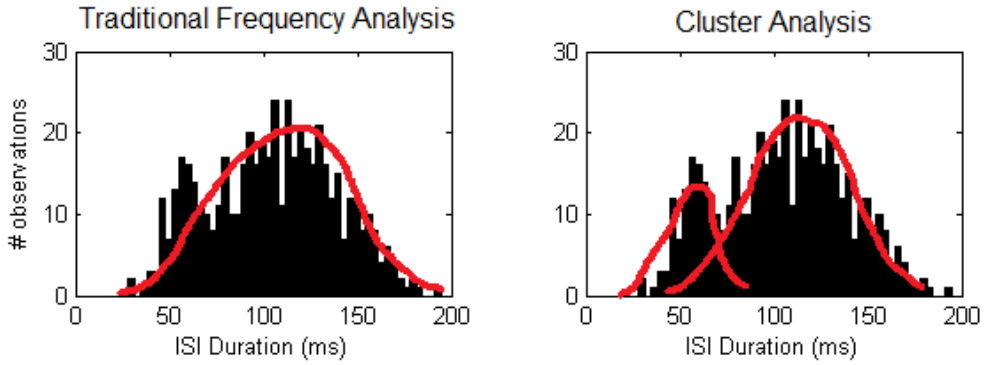


Figure 4.16: Left: Traditional frequency analysis would attempt to fit a unimodal curve to the data. Right: Cluster analysis can decipher between different modes in ISI histograms.

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Appendix A

EFFECTS OF A SINGLE BOUT OF HIGH-SPEED LOW-RESISTANCE CYCLING ON TREMOR IN PARKINSON'S DISEASE

The purpose of this appendix is to present part of the data collected in support of Aims 4 and 5: to determine the effect of an acute bout of exercise on tremor in people with Parkinson's disease. Tremor is defined as involuntary, rhythmic oscillatory muscle contractions in one or more body parts and is one of the primary symptoms in Parkinson's disease (PD). Although there are medications aimed toward reducing tremor and other PD symptoms, they not only lose effectiveness as the disease progresses, but also have severe side effects (e.g. dyskinesia, insomnia, increases in high risk behaviors, etc.). Drug-related side effects, along with PD related symptoms, further diminish the quality of life of a PD patient. Therefore, there is a need for a non-drug treatment that could be either a supplement or an alternative to the traditional medical and pharmaceutical approach toward PD.

A quality aspect of mobility is the smoothness with which muscular contractions or posture can be maintained. This is impaired in people with PD through the manifestaion of muscle tremors which occur at a frequency between 4 and 6 Hz (Jankovic, 2008). The presence and severity of tremor varies greatly between individuals. The amplitude and frequency of tremor in isometric contractions is known to be affected by anxiety, fatigue, pharmacological interventions and deep brain stimulation. Elek et al. (1991) examined the relationship between characteristics of paired motor unit (MU)

discharge and tremor amplitude in pathological and voluntary tremor. The conclusion was that paired discharge was not necessarily due to a MU pathology, but a response to impaired input in which the motor neurons produce paired pulses in response to abnormally strong excitation (Bawa & Calancie, 1983; Elek et al., 1991). More recently, using funtional magnetic resonance imaging (fMRI) , Helmich et al. (2011) suggested that the basal ganglia triggers a cerebellar circuit that results in the production of tremor.

Speed training has recently become a valuable training method for people with PD (Ridgel, Vitek, & Alberts, 2009). Individuals who completed incremental speed-dependent treadmill training showed improvements in mobility after a single intervention (Pohl et al., 2003; Herman et al., 2007; Cakit, Saracoglu, Genc, Erdem, & Inan, 2007). Tremor, manual dexterity, and motor function improved in a study involving PD patients pedaling on a tandem bike with an assistant pedaling in front to augment the pedaling rate however, the specific neural adaptations remain unclear (Ridgel et al, 2009). While keeping in mind the benefits of speed training in PD, we selected a high speed-low-resistance recumbent cycling program to address the symptom of tremor.

Until recently, exercise was not recommended for people with PD. It was believed that the pathology causing PD would worsen with physical activity and exercise could not have positive measurable effects on PD symptoms (see review: Hirsch & Farley, 2009). However, recent research in both human and animal models has disproved this belief. Various exercise routines aimed toward improving strength (Hass, Collins, & Juncos, 2007), aerobic capacity (Bergen, Toole, Elliott, Wallace, Robinson, & Maitland, 2002) and speed (Pohl, Rockstroh, Ruckriem, Mrass, & Mejrjolz, 2003; Alberts, Linder,

Penko, Lowe, & Phillips, 2011; Herman, Giladi, Gruendlinger, Hausdorff, 2007) have been shown to be effective for improving PD related symptoms. Among these routines, speed training has recently become a valuable intervention strategy for people with PD (Ridgel, Vitek, & Alberts, 2009). Individuals who completed incremental speed-dependent treadmill training showed improvements in mobility after a single intervention (Pohl et al., 2003; Herman et al., 2007; Cakit, Saracoglu, Genc, Erdem, & Inan, 2007). Tremor, manual dexterity, and motor function improved in a study involving people with PD pedaling on a tandem bike with an assistant pedaling in front to augment the pedaling rate however, the specific neural adaptations remain unclear (Ridgel et al, 2009). While keeping in mind the benefits of speed training in PD, we selected a high speed-low-resistance recumbent cycling program to address the symptom of tremor. This exercise was chosen for the following reasons: 1) it is safer compared to exercises done on treadmills and upright bicycles for people with PD who are known to have balance deficits; 2) it is cost and space effective; 3) it can be self-administered 4) it places relatively little stress on the muscular and cardiovascular system (Sayers, 2007); 5) the compliance to high-speed low-intensity training may be higher compared to that of traditional strength training programs (Sayers, 2007).

There is sparse literature on the abnormal MU discharge behavior in PD tremor with even less evidence on the effects of exercise on MU discharge behavior in PD tremor. By stimulating the motor cortical areas of the brain with high speed, rhythmic movements, this may elicit adaptations in the central nervous system to deliver peripheral MU action potentials in a more normal fashion.

The purpose of this study was to compare motor unit control mechanisms before and after an acute bout of exercise. While all participants (Table A.1) reported experiencing hand tremor, only three of them presented with tremor during force and MU testing. Due to the lack of tremor-dominant subjects, data from those who did exhibit tremor (Tables A.2 & A.3) will be presented (see Chapter 4 for detailed methods). Briefly, participants completed force matching tasks used to obtain tremor force and MU data before and after a single bout of high-speed low-resistance cycling.

Table A.1: Subject characteristics ± (SD). UPDRS: Unified Parkinson's Disease Rating Scale motor section score.

N	Age (years)	Height (cm)	Mass (kg)	UPDRS	Hoehn-Yahr
10	61.2(11.4)	180.9(13)	79.3(11.4)	19.6(6.5)	2.31(.65)

Table A.2: Individual subject data from tremor-dominant participants include values for tremor amplitude (percentage of maximal voluntary contraction), frequency (Hz: hertz), root mean squared error (RMSE), and percent change pre to post cycling.

Subj	Force (%MVC)	Pre Cycling Tremor			Post Cycling Tremor			% Change		
		Amp (%MVC)	Freq (Hz)	RMSE	Amp (%MVC)	Freq (Hz)	RMSE	Amp (%MVC)	Freq (Hz)	RMSE
665	10	2.31	4.79	1.63	1.24	4.59	1.16	-46.3	-4.1	-29.3
	20	0.33	6.20	1.56	0.07	6.29	1.46	-79.3	1.6	-6.4
661	10	3.58	3.96	1.72	3.89	4.05	1.59	8.56	2.5	-7.5
	20	2.79	4.98	4.87	1.02	4.15	4.73	-63.49	-16.7	-2.9
663	10	3.81	4.88	4.64	5.13	17.4	7.95	34.75	255.7	71.2
	20	13.04	4.69	7.95	NA	NA	NA	NA	NA	NA

Table A.3: Individual subject data from tremor-dominant participants mean(SD) inter-spike intervals (ISI) for short and long ISIs during paired motor unit discharge, percent that both ISIs contribute to all ISIs within the MU recording, and the difference between short and long intervals shows the amount of separation between these measures. Post cycling data were unusable for subject 663 in the 20% recording.

Subj	Force (%MVC)	Pre Cycling MUDB				Post Cycling MUDB			
		Short ISI (ms)	Long ISI (ms)	%	Short-Long Diff (ms)	Short ISI (ms)	Long ISI (ms)	%	Short-Long Diff (ms)
665	10	47(26)	146(40)	66	99	83(30)	102(69)	88	19
	20	41(17)	99(19)	63	58	60(40)	219(58)	78	18
661	10	50(17)	156(27)	88	106	52(25)	183(48)	79	131
	20	78(27)	188(52)	74	110	65(29)	183(31)	66	118
663	10	68(48)	146(66)	84	78	163(38)	167(41)	56	4
	20	44(41)	130(76)	66	86	NA	NA	NA	NA

An acute bout of exercise had a positive effect on tremor in two participants with no effect on the third participant. One confounding variable to take into account is medication efficacy. The presented data were from people who took Levodopa, a dopamine agonist. There is a window of time that this medication has optimal effectiveness and may have contributed to the lack of tremor seen in other participants. In subject 3, tremor got worse after exercise. This may have been due to the Levodopa losing its effectiveness. Future studies should attempt to assess the potential benefits of high-speed exercise on tremor after an overnight washout from medications.

Another factor that may have contributed to the lack of tremor observed during testing is the effect that increasing load has on tremor. It has been shown that while many people with PD experience tremor while muscles are at rest, when the muscle is loaded, tremor decreases or disappears (Homberg, Hefter, Reiners, & Freund, 1987). Results from this pilot set of data were inconclusive due to the small sample and future studies should aim to grow the sample in order to inform exercise recommendations for people with PD.

Excluding the first chapter, we organized this dissertation material to present papers that are either already published or will be submitted for publication. We believe that the present material could serve as a set of pilot data in the development of another full-scale study including a larger sample of tremor-dominant people with PD, rather than a set of data that could be published in its present form. Therefore, it was presented within an appendix.

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Appendix B

QUESTIONNAIRES

The Activities-specific Balance Confidence (ABC) Scale

Administration:
The ABC can be self-administered or administered via personal or telephone interview. Larger typeset should be used for self-administration, while an enlarged version of the rating scale on an index card will facilitate in-person interviews. Regardless of method of administration, each respondent should be queried concerning their understanding of instructions, and probed regarding difficulty answering specific items.

Instructions to Participants:
For each of the following, please indicate your level of confidence in doing the activity without losing your balance or becoming unsteady from choosing one of the percentage points on the scale form 0% to 100%. If you do not currently do the activity in question, try and imagine how confident you would be if you had to do the activity. If you normally use a walking aid to do the activity or hold onto someone, rate your confidence as it you were using these supports. If you have any questions about answering any of these items, please ask the administrator.

Instructions for Scoring:
The ABC is an 11-point scale and ratings should consist of whole numbers (0-100) for each item. **Total the ratings (possible range = 0 – 1600) and divide by 16 to get each subject's ABC score.** If a subject qualifies his/her response to items #2, #9, #11, #14 or #15 (different ratings for "up" vs. "down" or "onto" vs. "off"), solicit separate ratings and use the lowest confidence of the two (as this will limit the entire activity, for instance the likelihood of using the stairs.)

- 80% = high level of physical functioning
- 50-80% = moderate level of physical functioning
- < 50% = low level of physical functioning (Myers AM, 1998)
- < 67% = older adults at risk for falling; predictive of future fall (LaJoie Y, 2004)

1. Powell, LE & Myers AM. The Activities-specific Balance Confidence (ABC) Scale. *J Gerontol Med Sci* 1995; 50(1): M28-34
2. Myers AM, Fletcher PC, Myers AN, Sherk W. Discriminative and evaluative properties of the ABC Scale. J Gerontol A Biol Sci Med Sci. 1998;53:M287-M294.
3. Lajoie Y, Gallagher SP. Predicting falls within the elderly community: comparison of postural sway, reaction time, the Berg balance scale and ABC scale for comparing fallers and non-fallers. Arch Gerontol Geriatr. 2004;38:11-26.

The Activities-specific Balance Confidence (ABC) Scale

For each of the following activities, please indicate your level of self-confidence by choosing a corresponding number from the following rating scale:

0% 10 20 30 40 50 60 70 80 90 100%

no confidence **completely confident**

"How confident are you that you will not lose your balance or become unsteady when you…

1. …walk around the house? ____%

2. …walk up or down stairs? ____%

3. …bend over and pick up a slipper from the front of a closet floor ____%

4. …reach for a small can off a shelf at eye level? ____%

5. …stand on your tiptoes and reach for something above your head? ____%

6. …stand on a chair and reach for something? ____%

7. …sweep the floor? ____%

8. …walk outside the house to a car parked in the driveway? ____%

9. …get into or out of a car? ____%

10. …walk across a parking lot to the mall? ____%

11. …walk up or down a ramp? ____%

12. …walk in a crowded mall where people rapidly walk past you? ____%

13. …are bumped into by people as you walk through the mall?____%

14. … step onto or off an escalator while you are holding onto a railing? ____%

15. … step onto or off an escalator while holding onto parcels such that you cannot hold onto the railing? ____%

16. …walk outside on icy sidewalks? ____%

SF-36(tm) Health Survey

Instructions for completing the questionnaire: Please answer every question. Some questions may look like others, but each one is different. Please take the time to read and answer each question carefully by filling in the bubble that best represents your response.

Name: _____

Date: _____

1. In general, would you say your health is:

□ □Excellent
□ □Very good
□ □Good
□ □Fair
□ □Poor

2. Compared to one year ago, how would you rate your health in general now?

□ □Much better now than a year ago
□ □Somewhat better now than a year ago
□ □About the same as one year ago
□ □Somewhat worse now than one year ago
□ □Much worse now than one year ago

3. The following items are about activities you might do during a typical day. Does your health now limit you in these
activities? If so, how much?

a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.
□ □Yes, limited a lot.
□ □Yes, limited a little.
□ □No, not limited at all.

b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf?
□ □Yes, limited a lot.
□ □Yes, limited a little.
□ □No, not limited at all.

c. Lifting or carrying groceries.
□ □Yes, limited a lot.
□ □Yes, limited a little.
□ □No, not limited at all.

d. Climbing several flights of stairs.
□□Yes, limited a lot.
□□Yes, limited a little.
□□No, not limited at all.

e. Climbing one flight of stairs.
□□Yes, limited a lot.
□□Yes, limited a little.
□□No, not limited at all.

f. Bending, kneeling or stooping.
□□Yes, limited a lot.
□□Yes, limited a little.
□□No, not limited at all.

g. Walking more than one mile.
□□Yes, limited a lot.
□□Yes, limited a little.
□□No, not limited at all.

h. Walking several blocks.
□□Yes, limited a lot.
□□Yes, limited a little.
□□No, not limited at all.

i. Walking one block.
□□Yes, limited a lot.
□□Yes, limited a little.
□□No, not limited at all.

j. Bathing or dressing yourself.
□□Yes, limited a lot.
□□Yes, limited a little.
□□No, not limited at all.

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

a. Cut down the amount of time you spent on work or other activities?
□□Yes □□No

b. Accomplished less than you would like?
□□Yes □□No

c. Were limited in the kind of work or other activities

□□Yes □□No

d. Had difficulty performing the work or other activities (for example, it took extra time)

□□Yes □□No

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

a. Cut down the amount of time you spent on work or other activities?

□□Yes □□No

b. Accomplished less than you would like

□□Yes □□No

c. Didn't do work or other activities as carefully as usual

□□Yes □□No

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

□□Not at all
□□Slightly
□□Moderately
□□Quite a bit
□□Extremely

7. How much bodily pain have you had during the past 4 weeks?

□□Not at all
□□Slightly
□□Moderately
□□Quite a bit
□□Extremely

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

- ☐☐Not at all
- ☐☐Slightly
- ☐☐Moderately
- ☐☐Quite a bit
- ☐☐Extremely

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks.

a. did you feel full of pep?

- ☐☐All of the time
- ☐☐Most of the time
- ☐☐A good bit of the time
- ☐☐Some of the time
- ☐☐A little of the time
- ☐☐None of the time

b. have you been a very nervous person?

- ☐☐All of the time
- ☐☐Most of the time
- ☐☐A good bit of the time
- ☐☐Some of the time
- ☐☐A little of the time
- ☐☐None of the time

c. have you felt so down in the dumps nothing could cheer you up?

- ☐☐All of the time
- ☐☐Most of the time
- ☐☐A good bit of the time
- ☐☐Some of the time
- ☐☐A little of the time
- ☐☐None of the time

d. have you felt calm and peaceful?

- ☐☐All of the time
- ☐☐Most of the time
- ☐☐A good bit of the time
- ☐☐Some of the time
- ☐☐A little of the time
- ☐☐None of the time

e. did you have a lot of energy?

- ☐☐All of the time
- ☐☐Most of the time
- ☐☐A good bit of the time
- ☐☐Some of the time
- ☐☐A little of the time
- ☐☐None of the time

f. have you felt downhearted and blue?

- ☐☐All of the time
- ☐☐Most of the time
- ☐☐A good bit of the time
- ☐☐Some of the time
- ☐☐A little of the time
- ☐☐None of the time

g. did you feel worn out?

- ☐☐All of the time
- ☐☐Most of the time
- ☐☐A good bit of the time
- ☐☐Some of the time
- ☐☐A little of the time
- ☐☐None of the time

h. have you been a happy person?

- ☐☐All of the time
- ☐☐Most of the time
- ☐☐A good bit of the time
- ☐☐Some of the time
- ☐☐A little of the time
- ☐☐None of the time

i. did you feel tired?

- ☐☐All of the time
- ☐☐Most of the time
- ☐☐A good bit of the time
- ☐☐Some of the time
- ☐☐A little of the time
- ☐☐None of the time

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

- ☐☐All of the time
- ☐☐Most of the time
- ☐☐Some of the time
- ☐☐A little of the time
- ☐☐None of the time

11. How TRUE or FALSE is each of the following statements for you?

a. I seem to get sick a little easier than other people

- ☐☐Definitely true
- ☐☐Mostly true
- ☐☐Don't know
- ☐☐Mostly false
- ☐☐Definitely false

b. I am as healthy as anybody I know

- ☐☐Definitely true
- ☐☐Mostly true
- ☐☐Don't know
- ☐☐Mostly false
- ☐☐Definitely false

c. I expect my health to get worse

- ☐☐Definitely true
- ☐☐Mostly true
- ☐☐Don't know
- ☐☐Mostly false
- ☐☐Definitely false

d. My health is excellent

- ☐☐Definitely true
- ☐☐Mostly true
- ☐☐Don't know
- ☐☐Mostly false
- ☐☐Definitely false

Appendix C

INFORMED CONSENT DOCUMENTS

Title: Quickness Training in Seniors and Chronic Conditions

Investigators: Maria Bellumori, MS and Christopher A. Knight, Ph.D.
SUBJECT NAME: _____

1. PURPOSE / DESCRIPTION OF THE RESEARCH

You are being asked to participate in a research project at the University of Delaware. The purpose is test whether a 6-week exercise program can improve your physical *quickness*. Such quickness relates to movements like catching an object before it falls or crossing a street quickly, and is important for many daily tasks and fall prevention.

The exercise program involves brief bouts of high speed cycling on a stationary bicycle. Although your strength will be measured as part of the research project, the cycling program only uses fast, low-force contractions (the bike is set so that you do not have to push hard on the pedals). The intent of this type of exercise program is to minimize the amount of muscle soreness while attempting to improve the function of your nervous system.

You will be one of at least 20 adults who are over the age of 59 years. Testing will occur at the Human Performance Lab on the Newark campus of the University of Delaware. The exercise program will occur at the Fitness Center within the Newark Senior Center. To conduct a valid test of the exercise program, we need to compare the quickness measures between ten people who participate in the exercise program to the same measures from another set of ten people who have not done the exercise program but are similarly tested. You will be randomly assigned to either group. However, we will provide the exercise program for all participants and test the results in both groups as detailed below. So, even if you are in the non-exercise group, you will eventually receive the same exercise program.

Group 1: Participants will be tested at week 1, participate in the exercise training program for six weeks and then be tested again at week 8. Four weeks later (week 12), you will be tested one last time. This requires 12 weeks of involvement.

Group 2: Participants will be tested at weeks 1 and 8, followed by 6 weeks of exercise training, and then a third (post training) test and a final follow-up test. During the six weeks between weeks 1 and 8, you will be asked to maintain your usual patterns of physical activity and exercise. This testing schedule requires 19 weeks of involvement.

Week	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Group 1	Test	Exercise Training Program						Test				Test							
Group 2	Test	Usual Physical Activity						Test	Training						Test				Test

Testing Sessions: Testing will be conducted at the University of Delaware in room 156 of the Human Performance Laboratory. This is located at 541 S. College Avenue on the side of the Rust Ice Arena. You will be asked to wear shorts and a short sleeve shirt during testing. You can wear the same footwear that you do for exercise. If you arrive by car, a temporary parking permit will be provided.

Testing Days: Once in the laboratory, you will participate in the following test schedule, ***which is expected to last less than 90 minutes***.

1. Paper and pencil tests about your ability to move, your independence and quality of life. One survey will be about your readiness to participate in the exercise program. Another test will ask about your confidence during activities that involve balance. You will complete two additional surveys if you have a disability or movement disorder such as Parkinson's disease or stroke. One of these surveys is about disability in general and the other will be specific to your condition. This may require 30 minutes of time and an investigator will assist you with some of these surveys. The following are two example questions:

    a. *How confident are you that you will not lose your balance or become unsteady when you walk up or down a ramp?*
    b. Or, if you happen to be a participant with Parkinson's disease: *How often in the last three months have you had trouble with signing your name in public?*

2. Strength tests: We will measure the strength of your legs and arms. With your leg or hand, you will push as hard as you can against force sensors that do not move. For the legs, you will be seated in a comfortable testing chair with seat belts that help you to remain stable. For the arms you will push down on something resembling a walking stick. Your strength will be measured three times in the legs and three times in the arms.

3. Quickness tests: For both the legs and arms you will be tested with the same equipment that is used for strength tests. We will measure the speed with which you can produce small, medium and large forces. We will record many (~100) of these 'force pulses' in both the legs and arms. You will perform them in manageable sets that allow you adequate rest.

4. Muscle electrical activity: If you show improvements due to the training, we will be very much interested in why they happened. Therefore, during strength and quickness testing, you will have sensors taped to the skin over a muscle in your upper arm or on your thigh. These sensors record the small electrical currents that your brain uses to cause your muscles to perform. This technique does not give you an electrical shock. Rather, it records your body's electrical activity.

5. You will perform a walking test called the Timed Up and Go in which you are timed as you rise from an arm chair, walk 3 meters, turn, walk back, and sit down again. You will also perform a test in which you place 9 small pegs into small holes on a piece of wood. Using each hand, you will perform reaction time and finger tapping tests.

Exercise Program: The exercise training sessions will be held in the Fitness Center of the Newark Senior Center. These sessions will be supervised by trained students from the Department of Kinesiology and Applied Physiology. Exercises will be performed on a stationary upright or reclined bicycle, depending on your preference. Exercise sessions will occur at least twice per week for a minimum of twelve sessions. During the first session, your preferred pedaling speed will be determined. Fast cycling will be initially defined as 20% faster than your preferred speed, and adjusted as necessary based on your needs. Exercise sessions will begin with a 5 minute warm up at your preferred speed. Then you will complete 10 bouts of fast cycling which last 20 seconds each. Between fast bouts you will have 60 seconds of active recovery during which you pedal at your preferred speed. You may have longer recovery if needed. You will be verbally encouraged by the experimenter to stay within your target pedaling ranges. The session will conclude with a 5 minute cool down at self-selected speed. Each session will last approximately 30 minutes. When you show signs of improvement your fast cycling pace may be increased. Together, the speed and resistance of your cycling exercise will be adjusted to keep your exercising heart rates below 150 beats per minute. Investigators will monitor this by feeling your pulse on your wrist.

2. CONDITIONS OF SUBJECT PARTICIPATION

Information obtained from this study will be kept strictly confidential. You will not be individually identified, except by a subject number that is known only to the investigators. Any records of personal information will be stored in a locked cabinet. After three years any personal identifiers will be destroyed. All data files consisting of force and nervous system recordings will be de-identified and kept indefinitely for teaching purposes or secondary analyses. While the results of this research may be published and presented at conferences, your name or identity will not be revealed.

In the event of physical injury, you will receive first aid. If there are indications of a medical emergency, 911 will be called. If you require additional medical treatment, you

will be responsible for the cost. You are free to withdraw from the study at any time without penalty.

3. EXCLUSION CRITERIA

Participation requires that you are a member of the Newark Senior Center Fitness Center and that you complete a physical activity readiness questionnaire (PAR-Q). Responses on the PAR-Q may require you to obtain physician's clearance to participate in the exercise program. You will be excluded from participation if you are not a member of the fitness center and if you have not provided updated physician's clearance (if necessary). You will also be excluded from participation if you are unable to understand spoken instructions or communicate with the investigators.

4. RISKS AND BENEFITS

POSSIBLE RISKS:

Soreness: Even though the exercise program is designed to avoid forceful contractions, the strength tests still present some risk of muscle soreness. If you do become sore, such soreness is typically mild to moderate and will only last a few days.

Disappointment: If you are randomly assigned to the group that has to wait 8 weeks before participating in our exercise program, you may be disappointed. As you complete the surveys about physical function or quality of life, you may become saddened as you think about your present condition.

Skin Irritation: During recordings from your muscles, sensors will be taped to your skin and a special gel will be applied to improve the recording. Although all materials are hypoallergenic, your skin may show mild redness as a result. This redness is like that seen after removal of a bandage and it is temporary.

POSSIBLE BENEFITS:

Although this exercise program is experimental, and the responses of individual persons may vary widely, we anticipate that most people will improve their physical quickness and related aspects of function.

5. CONTACTS

Any questions can be directed to Christopher A. Knight, PhD, Associate Professor, Department of Kinesiology and Applied Physiology (302-831-6175). Questions regarding the rights of individuals who agree to participate in this research study may be directed to the Chair of the Human Subjects Review Board at the University of Delaware (302-831-2137).

6. SUBJECT'S ASSURANCES

I have read the above informed consent document. The nature, demands, risks and benefits of the project have been explained to me. I knowingly assume the risks involved, and understand that I may withdraw my consent and discontinue my participation in this study at any time without penalty of loss of benefit to myself. A copy of this consent document has been given to me.

7. CONSENT SIGNATURES

Participant's Signature: _____

Participant's Name (printed): _____
Date: _____

Project Title: Effects of Exercise on Parkinson's Tremor

Investigators: Maria Bellumori, MS and Christopher A. Knight, PhD

Subject Name: _____

1. PURPOSE/DESCRIPTION OF THE RESEARCH

You are being asked to participate in a research project at the University of Delaware. The purpose is to learn the effects of exercise on Parkinson's tremor. Depending on your availability and interest, we will test the effects of A) a single exercise session or B) a six week exercise program. Even though our main interest is tremor, we will also take other measurements of your function.

You are being asked to participate because you are aged between 21 and 79 years and have been diagnosed with PD. Depending on your answers to some questions about your health or physical activity habits, you might be excluded from participating in this project or you might be asked to provide written documentation of your physician's clearance. This will be explained in section 3 of this form. If you are healthy enough to participate and if you do not have any health issues that would make your results hard to interpret you can be included in the project. You will be one of between 20 and 50 other participants in this study.

This study has two possible schedules for participation. In Schedule A, we test the effects of a single exercise session on Tremor. In Schedule B, we test the effects of a single exercise session and a 6-week program on tremor and other measures of function. The exercise is free and supervised. The schedules are explained in more detail below. All exercise sessions and testing will be performed on the Newark campus of the University of Delaware. We will give you specific directions and parking instructions when we schedule your first visit.

<u>Schedule A. Effects of a single exercise session</u>: You will visit the laboratory one time for 60-90 minutes. During this visit, you will complete some paperwork, have your tremor tested, perform bicycling exercise for 30 minutes, and then have your tremor tested again. For the tremor test, a small needle will be inserted in a muscle of your hand. The needle is like one a neurologist might use for diagnosis. This session will last approximately 60-90 minutes.

<u>Schedule B. Effects of a 6-week exercise program (see table below)</u>: You will visit the laboratory 17 times over approximately 9 weeks. This experience has several measures of your function so the first visit is to help you become familiar with the tests and their instructions. During the second visit, we will take real measures of your function. In visit 3, we will measure your tremor before and after an exercise session on a stationary bike. From weeks 3-8, there will be two 30-minute exercise sessions per week. For the 2

visits with tremor tests, a small needle will be inserted in a muscle of your hand. The needle is like one a neurologist might use for diagnosis. We will give you a paper calendar of appointments and there is reasonable flexibility to accommodate your other activities.

~Week 1		~ Week 2	~ Week 3-8	~ Week 9	
Visit 1 Familiarization Visit	Visit 2 Functional Tests	Visit 3 Tremor Test, 30 minutes cycling, Tremor Test	Visits 4-15 Exercise Sessions (2 / week for 6 weeks)	Visit 16 Functional Tests	Visit 17 Tremor Tests
40 min.	40 min.	60-90 min.	30 min. each	40 min.	30 min.

Which part of this project would you like to sign up for? Please write your initials next to your choice.

_____ Schedule A: Effects of a single exercise session

_____ Schedule B: Effects of a 6-week exercise program

Location

The Exercise Intervention Lab is located at 5 Innovation Way, Newark, DE 19716. Visitor parking is directly in front of the building and you will be greeted at the front door upon arrival.
You will be asked to provide your own transportation. For your comfort, you should wear or bring shorts for exercise and test sessions. A large restroom with a chair is available near the lab. Once in the laboratory, you will perform several tests that are described below.

Test Sessions

A needle test is involved. When you move, messages from your brain are sent to your muscles as small electrical impulses. These messages are the main part of this project and we will insert a needle into a muscle in your hand to record them. The needle is smaller than one used for a blood draw. Nothing is injected into or withdrawn from your body. This test is similar to one that is used routinely in a neurologist's office. If you are not comfortable with needle procedures like blood draws, you should not participate in this project.

Tests:

6. Paper and pencil surveys. You will begin by completing brief surveys about your history of physical activity and exercise, your ability to move, your independence and quality of life. One survey is a simple tool to help us identify any risks of your participation in testing. Another survey will help us to identify any pre-existing health problems that would exclude you from participation.

7. Strength tests: We will measure the strength of your hands. In one test you will squeeze a device that measures your grip strength. In another test, you will press on a device that measures the strength of just your index finger.

8. Muscle electrical activity: During testing, you will have sensors taped to the skin over a muscle in your hand. The sensors will have a small coating of gel that does not cause allergic responses. When the sensors are removed, there is sometimes redness on the skin like when you remove a bandage.

9. Needle Recordings: A special needle with four fine wires in it will be inserted in a muscle in your hand. This needle is removed immediately after a desirable recording site is found leaving the hair-like wires in the muscle for the remainder of testing. For the first tremor test, the wires are left in the muscle while you do your exercise session. This is so that we can get recordings before and after the session. To reduce the chance of the wires being pulled out during exercise, your arm will be secured comfortably to a padded arm rest. For the second tremor test (for those completing the full exercise program, the wires are only in the muscle for the time required to obtain 3 good recordings (< 15 minutes).

   When the needle goes through the skin, it feels about the same as during a blood draw. Once in the muscle, the feeling has been described as dull or unnoticeable. Sometimes the needle ends up in an uncomfortable position. This is almost always fixed by adjusting its position very slightly. If the discomfort cannot be fixed, the needle is taken out. You might be asked whether we can try a second insertion in a slightly different location on the same muscle. While the needle is in your muscle, you will be asked to press on the force device with 10% of your strength. You will push this hard for 90 seconds so that we can record your tremor or force steadiness. Your muscle force will be shown to you on a computer monitor. You will be asked to perform this task about 3-5 five times within a test session.

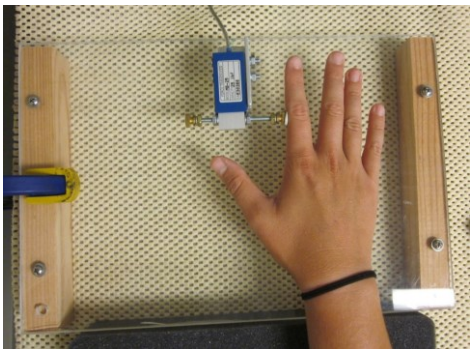

Figure 1. Force Device

10. Function: You will perform one walking test in which you are timed as you rise from an arm chair, walk 3 meters, turn, walk back, and sit down again. In a second timed walking test you will walk six meters as fast as possible. A third test tells us about your balance. You will be timed as you step through four squares that are marked on the floor with tape. You will also perform a test for your hands in which you are timed while you place 9 small pegs into small holes on a piece of plastic.

11. Reaction time: When you see a light of the correct color, you will lift your finger off of a button as fast as you can.

The Exercise Program

This exercise sessions use high speed cycling with the bike set at the easiest levels. Our intent is to activate your neurons (nervous system) while avoiding muscle or joint soreness. Exercise sessions will occur within our Exercise Intervention Laboratory. These sessions will be supervised by researchers or trained students from the Department of Kinesiology and Applied Physiology. Exercises will be performed on a stationary reclined bicycle. Exercise sessions will occur twice per week for a total of twelve sessions and some flexibility is allowed for scheduling conflicts.

During the first session, your preferred (comfortable) pedaling speed will be determined. Fast cycling will be about 20% faster than your preferred speed and adjusted as necessary. Exercise sessions will begin with a 5 minute warm up at your preferred speed. Then you will complete 10 bouts of fast cycling which last 20 seconds each. Between fast bouts you will have 60 seconds of recovery during which you pedal at your preferred speed. You may have longer recovery if needed. You will be verbally encouraged by the experimenter to stay within your target pedaling ranges. The session will conclude with a 5 minute cool down at your preferred speed. Each session will last approximately 30 minutes. During the full exercise program (Schedule B), your fast cycling speed may be increased as you improve. The intensity of your exercise will be adjusted to keep your heart rate below 70% of the maximal heart rate that is predicted for your age. Investigators will monitor this by feeling your pulse on your wrist every few minutes.

2. RISKS AND BENEFITS

Risks:

- Some joint or muscle soreness may occur due to the strength tests or during exercise. Such soreness is temporary.
- Like any blood draw or needle based technique, infection is a rare possibility. Like any blood draw or needle based technique, bruising is a possibility.
- Like any blood draw or needle based technique, hematoma is a rare possibility. The risk of hematoma is less than that during a blood draw because the needle is inserted in the muscle rather than in a vein.
- There is risk of injuries such as muscle strains and tears.
- Like any exercise, physical exertion increases the risk of heart attack, stroke or death.
- There is risk that you may fall during tests of your balance.

Possible Benefits:

Exercise benefits every physiological system as well as social, physical and mental well-being. Although they may not be noticeable, there are direct benefits of performing the exercises involved in this research. Through participation in this experiment, you may learn more about the relationship between exercise and the management of your symptoms.

3. CONDITIONS OF SUBJECT PARTICIPATION

You are free to withdraw from the study at any time without penalty. If we learn of any new information that might relate to your willingness to continue, you will be notified promptly.

Your information from this project will be kept strictly confidential. Nobody will be told that you were part of this project. All of your results will be labeled with a number code that is known only to the investigators. Any records of personal information will be stored in a locked cabinet or protected computer file. We will keep your contact information only to follow-up with you about this project. We will not give your contact information to anyone else. We are required to keep your records for three years after this project is over. After three years, if we do not believe that we will need to contact you again, all personal identifiers will be destroyed. Some of your data will be kept for teaching purposes or to answer new scientific questions. The results of this research may be published and presented at conferences.

For, presentation, teaching or subject recruitment materials, we might ask to take your photograph. If you agree, we will ask you to sign a photo release form.

In the event of physical injury, you will receive first aid. If there are indications of a medical emergency, 911 will be called. You will be responsible for the cost of any medical treatment.

Many of the tests in this project require physical effort. Therefore, to be part of this study, you have to be considered healthy enough to perform the exercise tests. Also, you must be free of any pre-existing conditions that would affect our ability to understand your results (exclusion criteria). We might need your physician's help to determine if you are healthy enough to participate.

If you are aged from **65 to 69 years**, you will fill out a form called a PAR-Q. If any of your responses identify risks for participating in physical activity, we will ask you to get **physician's clearance** to join our project. In this case, we will give you letter to the Physician and this Informed Consent Document. If no risks are identified and you have no exclusion criteria listed below, you will be invited into the study.

If you are aged from **70 to 79 years**, you need to complete the same PAR-Q form **and** we will ask you to get your **physician's clearance** to participate. If you provide written documentation of your physician's clearance and you have no exclusion criteria listed below, you will be invited into the study.

4. FINANCIAL CONSIDERATIONS

None.

5. EXCLUSION CRITERIA

- You will be excluded from the project if you are younger than 21 or older than 79 years.

- Participation requires completion of a physical activity readiness questionnaire (PAR-Q). You will be excluded from the project if you answer 'Yes' to any of the questions and you do not give us written proof that your physician has cleared you for physical activity.

- You will be excluded from participation if you are over 69 years of age and you do not give us written proof that your physician has cleared you for physical activity.

- You will be excluded from participation if you have any of the following

Insulin dependent diabetes
Inability to communicate with investigators
Unexplained dizziness in the last 6 months
Recent (< 3 months) myocardial infarction
Known orthostatic hypotension
Muscle or joint conditions that can be worsened by the exercise or testing

Termination of Participation by Investigator: Your participation in this project will be ended if you report or display any symptoms that are associated with cardiovascular distress or if you report joint or muscle soreness that is greater than that expected during exercise.

You will be asked to leave the project if you display any abusive, unsafe or disrespectful behavior that is directed towards project staff or other participants.

6. CONTACTS

If you have any questions about the research project or its procedures, you can contact the investigator, Christopher A. Knight, PhD at 302-831-6175 or caknight@udel.edu.

If you have questions or concerns regarding the rights of individuals who agree to participate in research please contact the Chair of the Institutional Review Board (IRB) at the University of Delaware (302-831-2137).

7. SUBJECT'S ASSURANCES

Your participation in this research study is voluntary and you may withdraw at any time. If you choose not to participate or withdraw from the study before its completion, you will not lose any benefits to which you are otherwise entitled.

8. CONSENT SIGNATURES

Participant's name (printed): _____ Date: _____

Participant's signature: _____