BEHAVIORAL AND NEUROPHYSIOLOGICAL STUDIES OF HAND DEXTERITY IN HEALTH AND PARKINSON'S DISEASE

by

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Dedication

To God, my parents and two little sisters

for their unconditional love and support

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Abstract

This dissertation focuses on behavioral differences in dynamic grip force control at the edge of instability between healthy older adults and individuals with Parkinson's disease (PD), and underlying neurophysiological mechanisms of dynamic grip force control in healthy young adults. By pushing the motor system to its limit of sensorimotor performance with a spring compression task, we aimed to develop more sensitive clinical measures, which detect 1) differences in motor severity between the hands in well-managed mild to moderate PD and 2) disease state from non-disease states, based on the ability to control dynamic grip force.

We measured the compression force level (F), and force variability at low (<4Hz, voluntary control, F_LF) and high frequency (4-12Hz, involuntary control, F_HF) bands for the more-affected and less-affected hand in PD and their relationship with motor severity, measured by Unified Parkinson's Disease Rating Scale (UPDRS) motor examination. Our results revealed significantly lower F in the more-affected hand (p= 0.019), greater F_LF in the more-affected hand (p= 0.042), but no difference in F_HF between hands by a 10,000-iteration permutation test. The greater F_LF in the more-affected hand was significantly correlated with the UPDRS motor scores (total motor, rho= -0.44, p= 0.04; hand only, rho= -0.52, p= 0.016), revealing the force variability decreased as motor severity increased. Because of greater heterogeneity of motor severity among PD participants, we further tested if the difference in force variability between two hands (ΔF_LF and ΔF_HF) was associated with symptom severity. The results showed a decrease in ΔF_LF as motor severity increased (total motor, rho= -0.46, p= 0.04). Interestingly, as non-hand motor symptoms (e.g. gait and balance) increased,

ΔF_LF and ΔF_HF significantly decreased, which suggests that the measure of dynamic grip force control may also reflect systemic motor impairment.

As the measures of dynamic grip force control clearly revealed differences in control strategies between the more-affected and less-affected hand in well-managed mild to moderate PD, we used the same measures in healthy older adults to test how well these measures could distinguish disease state (PD) from non-disease state (control). We used percentile ranks for each hand in PD and Receiver Operating Characteristic (ROC) curves to test if force measures could be a potential diagnostic tool. Our results revealed that F_LF and F_HF were more sensitive to separate PD from the control group than F, using these methods. The F_LF in the less-affected hand showed that 13 out of 20 individuals were ranked at above 80^{th} percentile with respect to these measures from the control group, and F_HF in the more affected hand showed 14 out of 20 individuals were ranked at above 80^{th} percentile. The UPDRS motor scores for the individuals clustering above 80^{th} percentile had little to no influence on the ranking of force variability with respect to force variability in healthy individuals. Our results of ROC curve showed that both F_LF and F_HF had good performance, revealing area values of 0.845 and 0.833 respectively, which indicates that F_LF and F_HF have a 84.5% and 83.3% chance of accurate diagnosis respectively. Therefore, measures of force variability might be a useful tool as an adjunct to current clinical diagnostic measures, considering these participants were well managed with medications.

Individuals with PD exhibit altered corticospinal excitability in primary motor cortex (M1). The greater force variability in PD might be associated with changes in corticospinal excitability in M1. In the healthy brain, bilateral activity of M1 was

observed during unimanual dynamic force control tasks, however, there has been no investigation of the neurophysiological mechanisms underlying dynamic grip force control. Therefore, studying the corticospinal excitability in M1 ipsilateral to a task hand in healthy individuals will be helpful to understand neuropathological changes in PD. We measured 1) corticospinal excitability in the right M1 by motor evoked potentials (MEP) in the left first dorsal interosseous (FDI), 2) mirror EMG activity in the left FDI, and 3) ipsilateral silent period (ISP) in the right FDI, to determine if interhemispheric inhibition (IHI) would influence the control of dynamic grip force with different dexterity demands in three motor tasks (the unstable spring, stable spring, and dowel compression). We found a significant increase (almost twofold) in MEP during the unstable spring task, but not in the stable spring, compared to the dowel task. Modulation of corticospinal excitability in the right M1 was independent from the effect of IHI, revealing no changes in ISP among three tasks. We also found no correlations between MEP amplitudes and mirror EMG activity. This suggests that dynamic grip force control during stabilizing highly unstable objects may require fundamentally different neural mechanisms from other stable grip or isometric contraction tasks that have been used for previous studies of IHI. Furthermore, increasing corticospinal excitability in M1 ipsilateral to a task hand by unimanual dexterous task may be useful for neurorehabilitation for bilateral recovery in hemiparesis such as stroke and cerebral palsy.

Chapter 1

Overview

Parkinson's disease (PD) is the second most common neurodegenerative disease, characterized by depletion of dopamine due to impaired basal ganglia. Approximately one million people suffer and about 60,000 people are newly diagnosed with PD each year in the US, however, a definitive diagnostic assessment is not available; about 80% of striatal dopamine is already lost at the onset of motor symptoms. The lack of sensitive clinical assessment might hinder early diagnosis and management of PD. Current clinical assessments focus on evaluation of motor symptoms, rather than on the impairment of sensorimotor function, which precedes overt motor symptoms.

Dynamic control of fingertip force by pushing the motor system to a limit of performance may allow us to measure true impairment of sensorimotor function in PD, which provides a way to detect subtle changes in motor function with disease progression. This idea is encouraging as the basal ganglia are known to be involved in grip force control, and their involvement is modulated by the degree of instability of the object during dynamic grip force control.

Therefore, the overall objectives of the dissertation are 1) to investigate dynamic control of fingertip force in PD by pushing the motor system to a limit of sensorimotor control, to test a potential application of this as clinical assessment and 2) to investigate typical neural mechanisms underlying dynamic grip force control in healthy individuals to understand the pathological neural mechanisms in PD. To respond to the objectives, three studies with the following specific aims were completed.

Specific Aim 1. To test if measures of dynamic grip force control can reflect differences in motor severity between the more- and less-affected hands in PD. We hypothesized that force variability measured by the standard deviation of force fluctuations at low frequency (< 4Hz, F_LF) and RMS of force fluctuations at high frequency (4-12Hz, F_HF), which includes tremor frequency bands, would be better correlated with the motor examination scores of Unified Parkinson's Disease Rating Scale (UPDRS) of the more-affected hand than the less-affected hand.

Specific Aim 2. To test the discriminability of measures of dynamic grip force control between healthy older adults and individuals with well-managed mild to moderate PD as a potential biomarker. We hypothesized that F_LF and F_HF would be better discriminators than the compression force level (F), measured by percentile rank and Receiver Operating Characteristic (ROC) curves.

Specific Aim 3. To test underlying neural mechanisms of involvement of M1 ipsilateral to the manipulating hand during dynamic grip force control in healthy young adults. We hypothesized that corticospinal excitability in the ipsilateral M1 would increase the most during unstable spring compressions, which require the greatest dexterity demands. We also hypothesized that interhemispheric inhibition from the ipsilateral M1 to contralateral M1, measured by ipsilateral silent periods in the task hand, would decrease during unstable spring compression.

Statement of Problem

Precision grip is a vital hand function for activities of daily living, particularly those that require picking up and manipulating small objects. Object manipulation requires dynamic grip force control, which involves rapid regulation of fingertip force vectors (magnitudes and directions), while maintaining finger postures or making finger movements during manipulation of objects (Valero-Cuevas, Smaby, Venkadesan, Peterson, & Wright, 2003). The ability to stabilize an object is critical to dexterous manipulation and tool use because dynamic interactions with a physical environment often generate instability in the motor system (Burdet et al., 2006; Johansson, 1996; Valero-Cuevas et al., 2003; Venkadesan, Guckenheimer, & Valero-Cuevas, 2007). Therefore, dexterous manipulation requires continuous dynamic fingertip force to achieve action goals without dropping the object.

The inability to control dynamic grip force control can therefore result in impaired hand function, affecting one's independence and quality of life. Individuals with Parkinson's disease (PD) experience difficulties in hand function, and although dynamic grip force control is important for dexterous manipulation, this ability in PD is not well understood. Moreover, the link between the ability to control the instability and hand function is understudied.

Furthermore, there is no defined diagnostic assessment for PD. By the time PD symptoms become overt, 30-70% of substantia nigra neurons and up to 80% of dopamine in the striatum are lost (Bernheimer, Birkmayer, Hornykiewicz, Jellinger, & Seitelberger, 1973; Cheng, Ulane, & Burke, 2010; Dauer & Przedborski, 2003; Fearnley & Lees, 1991). Studies have confirmed the role of basal ganglia (BG) in precision grip control in

planning and parameterization of force control (Prodoehl, Corcos, & Vaillancourt, 2009). Therefore, a simple motor task that maximizes engagement of BG may be able to reveal any abnormal behaviors before 80% of dopamine is lost. Dynamic grip force control at the edge of instability may allow us to detect such behavioral difference in PD, with a potential to develop more sensitive measures to detect motor symptoms in PD.

Background

Neuropathology of Parkinson's disease

The neural structure first affected by the etiology of PD would be sensorimotor circuitry (Alexander & Crutcher, 1990; Alexander, DeLong, & Strick, 1986; Redgrave et al., 2010), which is evident by the first recognition of disease as motor symptoms, described in "An Essay on Shaking Palsy" by James Parkinson in 1817 (Parkinson, 2014). The well-known cause of PD is a depletion of dopamine in the striatum (putamen and caudate). The putamen and caudate are terminal neural structures of the nigrostriatal pathway, projected from substantia nigra neurons (Cheng et al., 2010). The loss of the substantia nigra pars compacta neurons in PD leads to dopamine depletion in the striatum, specifically dorsolateral putamen (Cheng et al., 2010; Dauer & Przedborski, 2003; Jankovic, 2008). The dorsolateral or posterior putamen projects its pathway to sensorimotor cortex via the thalamus, which forms a closed loop of cortical-BG-cortical circuitry, and regulates sensorimotor functions such as 'stimulus-response habitual control' (Alexander & Crutcher, 1990; Redgrave et al., 2010).

About 70-90% patients noticed their first symptom as resting tremor in a hand (Weintraub, Comella, & Horn, 2008). Impaired hand function is common in PD (Lukos, Poizner, & Sage, 2014). In the homunculus of the sensorimotor cortex, the somatotopic

body representation of fingers is large since fingers require more sophisticated sensorimotor control (Kandel, Schwartz, & Jessell, 2000, p. 344). A large area of somatotopic finger representation is also seen in the striatum, especially in the putamen (Gerardin et al., 2003). Fingers might be vulnerable body structures that are easily influenced by the damaged sensorimotor circuitry because of their anatomically large representation. Measuring changes in sensorimotor function in hands may reflect changes in overall motor function with a disease progression.

Basal ganglia in precision grip networks

Studies have confirmed that BG is involved in precision grip force control. Based on neuroimaging evidence, BG roles in planning and parameterization have been proposed. The anterior part of BG: caudate, anterior putamen, and external segment of globus pallidus (GPe), is more involved in planning, such as prediction and selection of grip force while the posterior part of BG: posterior putamen, internal segment of globus

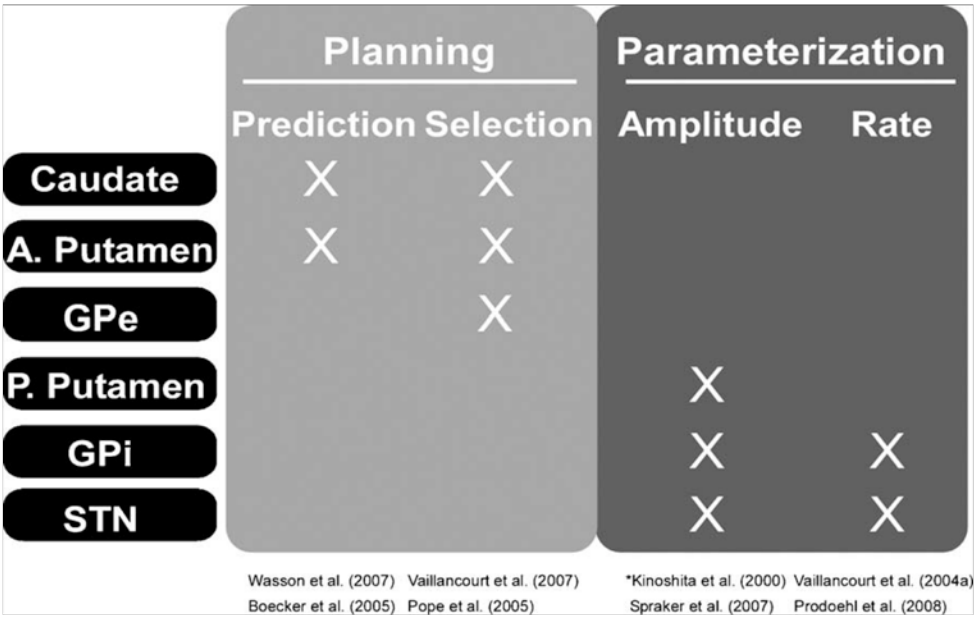

Figure 1.1 The model of basal ganglia in planning and parameterization of grip force control (retrieved from Prodoehl et al., 2009).

pallidus (GPi), and subthalamic nucleus (STN), is more involved in the parameterization of grip force such as amplitude and rate of force control (Fig. 1.1).

Precision grip networks include both cortico-cortical networks and cortico-subcortical networks (Fig. 1.2) (Prodoehl et al., 2009). Animal and human studies have suggested that ventral premotor cortex (PMv), primary motor cortex (M1), and anterior intraparietal area (AIP) of parietal cortex are strongly coupled during visually guided precision grip tasks (Davare, Kraskov, Rothwell, & Lemon, 2011; Prodoehl et al., 2009). AIP sends visual information of properties of an object to PMv, PMv processes the information and plans for finger shaping or positioning about 200ms before initial contact of the object, and then, PMv sends motor commands to M1 for motor execution (Davare, Andres, Cosnard, Thonnard, & Olivier, 2006; Davare et al., 2011; Davare, Montague, Olivier, Rothwell, & Lemon, 2009). PMv also plays a role in predicting grip force, and

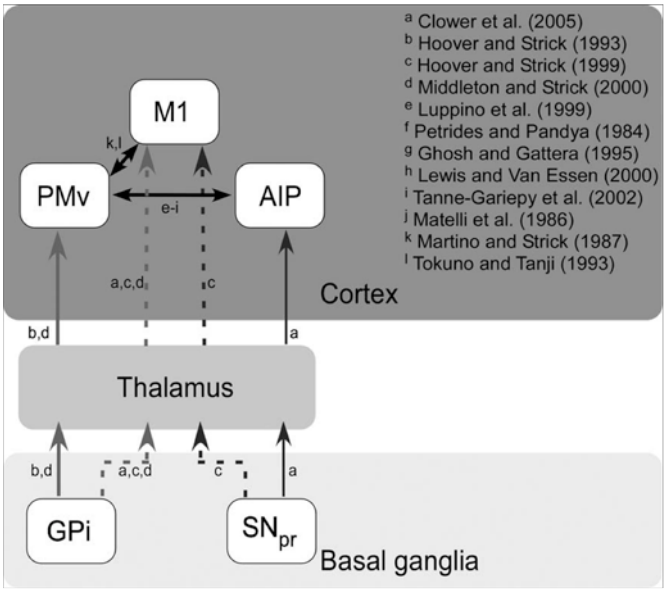

Figure 1.2 Cortico-cortical and cortico-subortical precision grip networks (retrieved from Prodoehl et al., 2009). The cortico-cortical network includes ventral premotor, primary motor cortex, and anterior intraparietal area, and the Cortico-subcortical network includes thalamus and basal ganglia output neurons: internal globus pallidus and substantia nigra pars reticulata.

AIP detects grip force errors and corrects them by integrating sensory input (Dafotakis, Sparing, Eickhoff, Fink, & Nowak, 2008). The cortico-cortical circuits interconnect the output nuclei of BG, internal globus pallidus (GPi) and substantia nigra pars reticulata (SN_{pr}), forming closed cortico-striatal circuits for precision grip force control (Prodoehl et al., 2009).

Sensorimotor control of stable grip force in PD

Sensorimotor control of grip force is essential to object manipulation (Flanagan, Bowman, & Johansson, 2006). The ability to control fingertip force during stable precision grip has been studied in PD for both aspects of predictive and reactive sensorimotor control (Stewart J Fellows et al., 1998; Gordon et al., 1997; Ingvarsson, Gordon, & Forssberg, 1997; Nowak & Hermsdörfer, 2006). The summary of observations is as followings: 1) excessive grip force, 2) slow movement in grip-lift force generation, 3) greater reliance on visual information, 4) intact predictive grip force control, 5) intact scaling of grip force with visual information of objects, 6) intact anticipatory control by expected perturbation, 7) intact early muscle response to reactive grip force control (~65ms), and finally 8) abnormal late muscle response to reactive grip force control (140 - 210ms).

These findings suggest that individuals with PD might have intact predictive grip force control, but possibly use compensatory strategies such as an increased reliance on visual feedback (Gordon, Ingvarsson, & Forssberg, 1997) or switching the control mechanism to associative circuitry, which engages the frontal cortex for planning and goal-directed control (Redgrave et al., 2010). The abnormal late muscle response was observed during reactive grip force control, in which parameterization is critical against

unpredictable perturbations. The abnormal late muscle response between 140 and 210ms might be indicative of abnormal sensorimotor control at the cortical level. The findings suggest that assessment tests that require reactive grip force control may reveal true impairment of sensorimotor control by engaging the sensorimotor cortico-BG-cortical closed loop.

For the last three decades, people have attempted to understand sensorimotor control in grip force control in PD. However, it has been challenging to study dynamic grip force control until the last decade, when a device that is capable of measuring continuous sensorimotor control of grip force was developed, the Strength-Dexterity test (Valero-Cuevas et al., 2003).

Measurements of Dexterous Manipulation

The Strength-Dexterity (S-D) test. The Strength-Dexterity (S-D) test, which involves compressing a spring device with the thumb and index finger, makes it possible to measure hand dexterity in humans. The Strength-Dexterity (S-D) test requires compressing a slender spring with the thumb and the index finger as far as possible and maintaining the compression for 3-5 seconds, followed by releasing the spring (Dayanidhi, Hedberg, Valero-Cuevas, & Forssberg, 2013; Valero-Cuevas et al., 2003). The spring is prone to buckling, which makes it challenging to compress fully, and it only requires < 3N for full compression (Dayanidhi, Hedberg, et al., 2013). The S-D test provides an unpredictable and perturbed environment to the thumb and the index finger. As an individual compresses the spring without buckling, the instability of the spring increases by its nature, and so it becomes more challenging for the fingers to maintain their posture against the spring.

The S-D test has been used to measure hand dexterity in development, aging, and pathological populations including thumb osteoarthritis, children with pollicization, and Parkinson's disease (Dayanidhi, Hedberg, et al., 2013; Dayanidhi & Valero-Cuevas, 2014; Lawrence, Fassola, Werner, Leclercq, & Valero-Cuevas, 2014; Lightdale-Miric et al., 2015). This test has shown its sensitivity to detect continuing development of dynamic grip force control until adolescence as well as an early decline of dynamic grip force control, starting middle age (Dayanidhi, Hedberg, et al., 2013; Dayanidhi & Valero-Cuevas, 2014). A study measured how people with PD performed the S-D test, however, it lacked demographic information in order to link performance of dynamic grip control with motor severity, and ignored differences in motor symptoms between more-affected and less-affected hand (Lawrence et al., 2014). Therefore, a more controlled study is needed.

Involved neural networks for stabilizing unstable objects

Manipulating compliant objects with the dominant hand tends to elicit bilateral neural activity, which is a more extended network than that for static precision grip control. These neural substrates include the precentral gyrus, postcentral gyrus, medial frontal gyrus, inferior parietal lobule, cingulate cortex, thalamus, putamen, caudate, and cerebellum (Holmström et al., 2011; Mosier, Lau, Wang, Venkadesan, & Valero-Cuevas, 2011; E. L. Pavlova et al., 2015; Talati, Valero-Cuevas, & Hirsch, 2005). These areas include precision grip network of PMv-AIP-M1 and BG (Holmström et al., 2011; Mosier et al., 2011; E. L. Pavlova et al., 2015; Talati et al., 2005). When people compressed different levels of instability of springs, brain activity levels in certain areas were modulated. For example, activity levels in PMv and BG increased with greater instability

of springs, and greater bilateral activation in putamen was seen during a sustained compression (Mosier et al., 2011). Furthermore, the main effect on control of high instability was seen in bilateral M1 (Holmström et al., 2011). The evidence suggests that compressing unstable spring at one's maximal instability elicits the greatest engagement of BG. Individuals with PD would therefore be expected to exhibit greater degrees of atypical behaviors as their BG is damaged.

Changes in neurophysiological functions in PD

Altered corticospinal excitability in M1 has been reported in PD when measured by transcranial magnetic stimulation (TMS) (Berardelli, Rona, Inghilleri, & Manfredi, 1996; Cantello, Tarletti, Varrasi, Cecchin, & Monaco, 2007; Lefaucheur, 2005; Ridding, Rothwell, & Inzelberg, 1995; Spagnolo et al., 2013). TMS is a form of non-invasive brain stimulation (Hallett, 2007; Merton & Morton, 1980; Siebner & Rothwell, 2003) that can directly measure corticospinal excitability from M1 by motor-evoked potentials (MEP): motor responses measured by electromyography (EMG) (Bestmann & Krakauer, 2015; Di Lazzaro, Ziemann, & Lemon, 2008; Hallett, 2007; Siebner & Rothwell, 2003). With different TMS protocols, individuals with PD demonstrate 1) increase in corticospinal excitability at rest, 2) decrease in intracortical inhibition measured by paired-pulse TMS with short inter-stimulus intervals (short interval intracortical inhibition, SICI), 3) decrease in intracortical excitation by paired-pulse TMS with long inter-stimulus intervals (intracortical facilitation, ICF), 4) decrease in duration of cortical silent period, and 5) shorter duration of ipsilateral silent period in the less-affected hand. The observations of changes in motor corticospinal excitability in PD are consequences of damaged BG and impaired sensorimotor cortico-striatal circuitry, which may cause

variability in motor outputs, for example force variability in dynamic grip force control.

In order to understand neurophysiological changes in PD, it is important to understand intact neurophysiological function in healthy individuals during dynamic grip force control. To the best of our knowledge, there has been no investigation of neurophysiological functions during dynamic grip force control, using TMS. As fMRI studies revealed bilateral activity in M1 during spring compressions with high instability (Holmström et al., 2011; Mosier et al., 2011; E. Pavlova et al., 2015), studying neurophysiological changes in the ipsilateral M1 to a task hand is particular interesting. The increased blood-oxygen-level-dependent (BOLD) signals do not elucidate if M1 is excitatory or inhibitory, therefore, measures of corticospinal excitability with TMS will be useful (Foltys et al., 2003; Kobayashi, Hutchinson, Schlaug, & Pascual-Leone, 2003). Furthermore, communication between hemispheres during unimanual tasks also affects corticospinal excitability in the ipsilateral M1; in particular, interhemispheric inhibition (IHI) has been widely studied during simple unimanual tasks because of its functional role to suppress mirror movement in the resting hand during tasks (Cincotta & Ziemann, 2008; Ferbert et al., 1992; Giovannelli et al., 2009; Liepert, Dettmers, Terborg, & Weiller, 2001). The effect of IHI during unimanual dynamic grip force control is not clearly understood; therefore, we aimed to determine if IHI is modulated by different dexterity demands during unimanual dynamic grip force control (see chapter 4). Understanding normal neurophysiological control during dynamic grip force control will help us to understand pathological changes in PD for future studies.

Significance of Research

Parkinson's disease (PD) is the second most common neurodegenerative disease,

affecting about 1-2% of the population over age of 65 in the US (de Lau & Breteler, 2006; Guttmacher, Collins, Nussbaum, & Ellis, 2003; Weintraub et al., 2008). The prevalence increases up to 3-5% over age of 80-85 (Guttmacher et al., 2003; Weintraub et al., 2008). According to the statistics from the Parkinson's Disease Foundation, annual direct and indirect costs for PD are nearly $25 billion in the US. Well-managed patient care potentially reduces direct and indirect medical costs (Dowding, Shenton, & Salek, 2006; Weintraub et al., 2008), which increase with disease progression (Dowding et al., 2006; Keränen et al., 2003). Moreover, there is need to develop sensitive clinical measures for better management of PD.

Therefore, the studies in the dissertation aimed to develop a clinically useful and more sensitive assessment to detect PD motor symptoms with high resolution by characterizing behavioral differences during dynamic grip force control. Furthermore, studying underlying neural mechanisms of dynamic grip force control in the healthy brain will help us to understand neurophysiological changes in PD, which could expand the potential rehabilitation regimen. The knowledge gained from these studies could therefore have a positive impact on clinical patient management, reducing direct and indirect medical costs for disease management over the life expectancy of patients.

Dissertation outline

Chapter 2

This chapter compares force variability in dynamic grip force control between more- and less-affected hands in PD and its relationship to motor severity. This work was published in *Frontiers in Aging Neuroscience* in August 2015. Co-authors are Na-hyeon

Ko, Chris M Laine, Beth E Fisher, and Francisco J Valero-Cuevas (corresponding author). My contributions are data collection, data analysis, writing the full manuscript, and generating tables and figures; Dr. Laine, a post-doctoral fellow, contributed to data analysis and writing the manuscript. This work was directed by Professors Fisher and Valero-Cuevas.

Chapter 3

This chapter describes the use of force variability measures in dynamic grip force control to distinguish disease state (PD) from non-disease state (controls), as a potential biomarker. The manuscript is in preparation, targeting *Frontiers in Aging Neuroscience,* as a follow-up manuscript of chapter 2. Co-authors are Chris M Laine, Na-hyeon Ko, Meng-Fen Tsai, and Francisco J Valero-Cuevas (corresponding author). My contributions are data collection, data analysis, generating figures, and writing the manuscript; Dr. Laine, contributed to data analysis and writing the full manuscript; Meng-Fen contributed to data analysis, generating figures, and writing the manuscript. This work was directed by Professor Valero-Cuevas.

Chapter 4

This chapter examines neurophysiological changes in the primary motor cortex ipsilateral to a manipulating hand of dynamic grip force control in young healthy individuals. The manuscript is in preparation, targeting the *Journal of Neuroscience*. Co-authors are Na-hyeon Ko, Chris M Laine, Francisco-Valero-Cuevas (corresponding author), and Beth E Fisher. My contributions are study design, data collection, data analysis, generating figures, and writing the full manuscript; Dr. Laine contributed to data

collection, data analysis, and writing the manuscript. This work was directed by Professors Valero-Cuevas and Fisher.

Chapter 5

This chapter concludes the dissertation studies and discusses future directions.

Chapter 2

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Force Variability During Dexterous Manipulation in individuals with Mild to Moderate Parkinson's Disease

Na-hyeon Ko, Chris M Laine, Beth E Fisher, and Francisco J Valero-Cuevas

Abstract

Parkinson's disease (PD) is a progressive neurodegenerative disease affecting about 1–2% of the population over the age of 65. Individuals with PD experience gradual deterioration of dexterous manipulation for activities of daily living; however, current clinical evaluations are mostly subjective and do not quantify changes in dynamic control of fingertip force that is critical for manual dexterity. Thus, there is a need to develop clinical measures to quantify those changes with aging and disease progression. We investigated the dynamic control of fingertip forces in both hands of 20 individuals with PD (69.0 ± 7.4 years) using the Strength–Dexterity test. The test requires low forces (<3 N) to compress a compliant and slender spring prone to buckling. A maximal level of sustained compression is informative of the greatest instability the person can control, and thus is indicative of the integrity of the neuromuscular system for dexterous manipulation. Miniature sensors recorded fingertip force (F) during maximal sustained compressions. The force variability during sustained compression was quantified in two frequency bands: low (<4 Hz, F_LF) and high (4–12 Hz, F_HF). F_LF characterizes variability in voluntary fluctuations, while F_HF characterizes variability in involuntary

fluctuations including tremor. The more-affected hand exhibited significantly lower F and lower F_LF than those in the less-affected hand. The more-affected hand showed significant negative correlations between F_LF and the Unified Parkinson's Disease Rating Scale motor scores for both total and hand-only, suggesting that greater force variability in the voluntary range was associated with less clinical motor impairment. We conclude the nature of force variability in the voluntary range during this dynamic and dexterous task may be a biomarker of greater motor capability/flexibility/adaptability in PD. This approach may provide a more quantitative clinical assessment of changes of sensorimotor control in individuals with PD.

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease in the United States, affecting about 1-2% of the population over age of 65 (de Lau & Breteler, 2006; Guttmacher et al., 2003; Weintraub et al., 2008). Loss of hand dexterity and impaired sensorimotor control of grip force have been reported in PD (Fellows, Noth, & Schwarz, 1998; Gordon, 1998; Gordon et al., 1997; Ingvarsson, Gordon, & Forssberg, 1997; Lawrence et al., 2014; Lukos et al., 2014; Nowak & Hermsdörfer, 2006). The gradual impairment of dexterous manipulation leads to difficulties in daily activities such as buttoning, eating, extracting money from a wallet, or signing a check (Lukos et al., 2014). Loss of these abilities will negatively impact qualify of life (Lukos et al., 2014).

The Unified Parkinson's Disease Rating Scale (UPDRS) is the most well-established and accepted assessment in PD (Goetz et al., 2008; Ramaker, Marinus, Stiggelbout, & van Hilten, 2002). The motor examination portion of the UPDRS (part III) provides a global motor severity score, but does not measure force control. The ability to dynamically regulate both the magnitude and direction of fingertip force vectors is fundamental for dexterous manipulation (Cole & Abbs, 1988; Valero-Cuevas et al., 2003; Valero-Cuevas, Zajac, & Burgar, 1998), and can be revealing of sensorimotor processing capability in older adults (Lawrence et al., 2015). This ability progressively deteriorates with the progression of PD, but the physiology of this process is not well understood. Therefore, it is critical to develop a sensitive measure of the neural control of fingertip force vectors in PD. Such a measure would add an informative and currently missing component to the current set of clinical assessment tools used for PD.

In the past, quantification of dynamic dexterous manipulation ability in PD has been difficult because of lack of appropriate techniques (Lukos et al., 2014). The Strength-Dexterity test was developed to quantify dynamic dexterous manipulation in general, and has been used to measure finger dexterity in healthy individuals (4-89 years) and those suffering from pathological conditions such as carpometacarpal osteoarthritis, Parkinson's disease, and children with pollicized hands (Dayanidhi, Hedberg, et al., 2013; Dayanidhi & Valero-Cuevas, 2014; Lawrence et al., 2014; Lightdale-Miric et al., 2015; Vollmer et al., 2010). The previous study of dynamic dexterous manipulation in PD, however, did not consider different degrees of motor symptoms between the hands (Lawrence et al., 2014) despite the fact that lateralized motor impairment is common in PD (Lukos et al., 2014). Differences in dynamic force control between the more- and less-affected hands could be highly informative, given that motor symptoms likely affect dynamic dexterous manipulation.

Measures of dynamic force control during the Strength-Dexterity test might reveal sensorimotor impairment in PD. fMRI studies have shown that the basal ganglia are active during the sustained spring compressions of the Strength-Dexterity test (Mosier et al., 2011; E. L. Pavlova et al., 2015) (in press). In addition, the blood-oxygen-level dependent (BOLD) signals in the putamen increased as the spring became more unstable (Mosier et al., 2011). Given that disruption of the basal ganglia result in motor impairment in PD, and that the basal ganglia are known to be involved in the spring task, it is likely that measuring the dynamic control of fingertip forces during performance of the Strength-Dexterity test may provide a sensitive index of manual sensorimotor control in PD.

Therefore, the purpose of this study was to explore differences in dynamic control of fingertip forces between the more affected and less affected hands in individuals with PD. If such differences exist, it would indicate that measures of force during the spring task hold a potential as markers of symptom severity that may not be evident with traditional clinical testing. As a further evaluation of this potential, spring force measures were correlated with the well-established clinical assessment of motor impairment, the UPDRS. Thus, we respond to the goal of this Research Topic to develop clinical measures to enable future studies of the mechanisms of declining motor control in aging and disease.

Methods

Participants

A total of 20 individuals with PD (69.0 ± 7.4 yrs, 11M, 9F) participated in the study. Given the observational, cross-sectional nature of this study, we included patients with a diagnosis of PD who were functionally independent (regardless of their medication status) and demonstrated intact cognitive functions and excluded patients with musculoskeletal symptoms including pain and fatigue as well as a history of other neurological disorders and surgical procedures affecting the thumb and index finger. The study was approved by the Institutional Review Board at the University of Southern California. Informed consent was obtained from all participants. The average disease duration for 20 individuals with PD was 6.0 years (± 4.1 years), and all participants were physically independent and Hoehn and Yahr stages 1-3. Eighteen participants were on PD medications while two participants did not take PD medications. We included

participants both on- and off-medication because our study represents a cross-sectional and exploratory investigation of dynamic fingertip force control in the general population of functionally independent patients with PD. The more-affected side was determined by UPDRS motor examination and self-report from patients asked, *'which hand has been giving you more trouble in daily activities?'* UPDRS motor scores were only obtained from a subset of 13 patients. Thus, the more-affected side was self-reported from seven patients whose UPDRS scores were not available and also from two patients whose UPDRS scores were the same for both hands. Handedness was also measured by the Edinburgh Handedness Inventory at the screening. However, a subsequent multiple regression analysis revealed handedness did not influence dynamic fingertip force control (see Appendix A). This is in line with findings reported for the healthy population (Lawrence et al., 2014).

Instrumentation for dynamic fingertip force measurement

The Strength-Dexterity test was used to measure dynamic sensorimotor control of fingertip force from the thumb and index finger. The test required compressing a slender spring with the thumb and index fingers without allowing it to buckle (Fig. 2.1) (Dayanidhi, Hedberg, et al., 2013; Valero-Cuevas et al., 2003). The specifications of the custom spring (Century Springs Corp., Los Angeles, CA) were the following: 1) free length = 3.96 cm, 2) solid length = 0.69 cm, 3) force range = 0 - 2.84N, 4) stiffness = 0.86N/cm, and 5) the diameter of end caps were 0.95cm (Fig 2.1) (Dayanidhi, Hedberg, et al., 2013). The spring was designed to be impossible to compress fully, and thus the maximal compression participants could achieve was less than 3N (Dayanidhi, Hedberg, et al., 2013). As the spring is compressed, it becomes increasingly unstable in a nonlinear

way (Venkadesan et al., 2007), making it unpredictable and also making the particular dynamics of each sustained compression unique. The maximal level of compression that is sustained reflects the integrity of the sensorimotor system, which controls fingertip force and direction during object manipulation (Dayanidhi, Hedberg, et al., 2013; Dayanidhi & Valero-Cuevas, 2014; Lawrence et al., 2014).

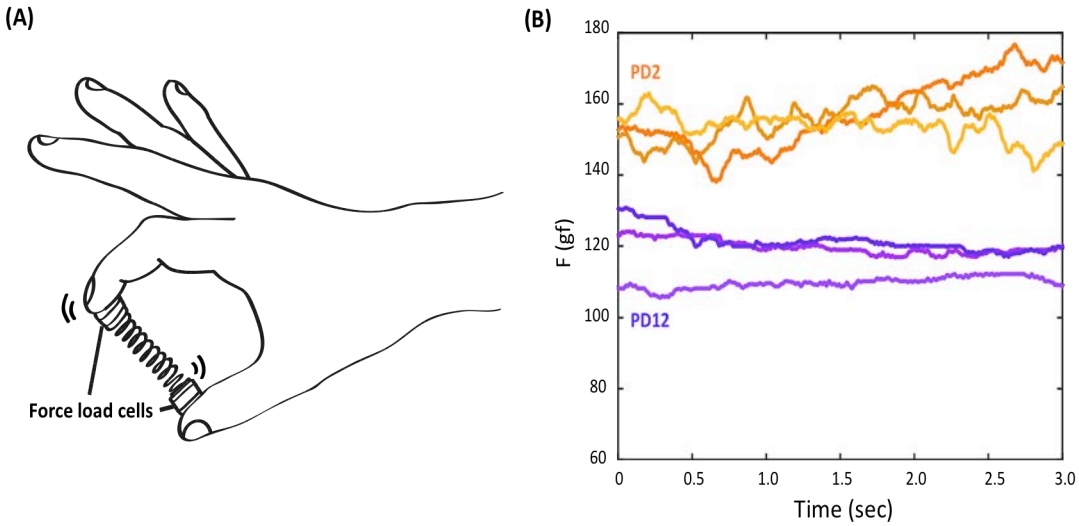

Figure 2.1. The Strength-Dexterity test and raw force data examples of three trials from the more-affected hand of two PD participants with different UPDRS hand motor scores. (A) Participants compress a slender spring prone to buckling as much as they can to its solid length, sustain the compression for 5 seconds, and release the compression. The force data were recorded from miniature load cells at the tips of spring. (B) Orange lines: the top three force traces during a hold phase from PD2 with UPDRS hand motor score, 7. Purple lines: the top three force traces during a hold phase from the more-affected hand of PD12 with UPDRS hand motor score, 15.

Experimental procedure

The participants were seated comfortably with their forearm supported by a foam pad. They were asked to pick up the spring with the thumb and index finger and familiarize themselves with the properties of the spring. As in our prior studies, the

number of trials was varied among patients as needed in order to make them familiar with the test and produce relatively consistent performance with each attempt. They were asked to either open or curl the other three fingers so as not to touch or assist the index finger. The instruction given to the participants was *"compress the spring as much as possible without buckling, hold the compression for 5 seconds, and release the compression"*. We measured both affected and less-affected hands. All participants were tested with their less-affected hand first to ensure that they fully understood the task before testing with the more-affected hand. Since the task requires dynamic control of an unpredictable object, it is unlikely that the testing order would influence performance. Only hold periods where force was held stable for at least 3 seconds were used for further analysis. The goal of the experiment was to obtain the highest compression force possible. The three trials with the highest compression forces (per hand) and variability were used for each analysis. We chose to analyze only the three best trials per subject to minimize potential sources of variance related to learning, task-familiarization, and sub-maximal (overly cautious) efforts.

Data collection and analysis

Customized miniature load cells (ELB4–10, Measurement Specialties, Hampton, VA, USA) at the end caps were used to measure fingertip force in the compression direction. The load cells were connected to a signal conditioner and USB-DAQ (National Instruments, Austin, TX, USA). The signals were sampled at 400Hz with a custom-written MATLAB (MathWorks, Natick, MA, USA) program.

For a particular sustained compression period to be used in further analysis, the compression force was required to remain within one standard deviation of mean force

recorded during the attempt (Dayanidhi, Hedberg, et al., 2013).

In addition to measuring the maximal mean sustained compression force for each trial, force variability was analyzed at two frequency bands to distinguish slow voluntary force fluctuations (< 4Hz) from fast involuntary force fluctuations (4-12Hz) that include tremor, a well-known symptom in PD. The first was aimed at quantifying voluntary fluctuations in force, produced as the subjects attempted to control the buckling of the spring by dynamically altering the magnitude and direction of their fingertip forces. These voluntary fluctuations occur at low frequencies (<4 Hz) (Miall, Weir, & Stein, 1993; Slifkin, Vaillancourt, & Newell, 2000; Vaillancourt, Slifkin, & Newell, 2001). We quantified them simply as the standard deviation of the sustained compression force after applying a 4 Hz low-pass filter (zero-phase, 4^{th} order Butterworth) to the force. Standard deviation is a commonly reported measure because of its simplicity, compatibility with prior literature on force control in PD (Slifkin & Newell, 1999; Vaillancourt et al., 2001; Vaillancourt, Slifkin, & Newell, 2002), and lack of dependence on the duration of the hold period or the mean value of the signal. We did remove any linear trend for each sustained compression prior to calculation of standard deviation to prevent it potential inflation by such slow trends. This measure of low frequency force dynamics is referred to herein as F_LF.

The second measure of force dynamics was aimed at quantifying faster, involuntary fluctuations, which include tremor oscillations and noise from the motor system. For this analysis, the force signal during each sustained compression was band-pass filtered between 4 and 12 Hz (zero-phase, 4^{th} order Butterworth) and the RMS of the resulting signal was calculated. The RMS of the band-pass filtered force trace gives a

value, which is directly comparable and mathematically related to the signal power in the frequencies present. The most common way to quantify 'tremor-band' activity is by a measure of spectral power (McAuley & Marsden, 2000; Vaillancourt et al., 2001), thus, our analysis is in keeping with standard methodology while taking advantage of the simplicity and robustness of time-domain calculations of signal variance. This measure of high frequency force dynamics is referred to herein as F_HF.

Statistical analysis

To quantify differences in each measure of force between the more- and less-affected hands, we first checked all distributions for normality using a Lilliefors test. Force measures that showed non-normal and skewed distributions were normalized using a log transformation before testing for differences of means. To test for differences in means, we used a 10,000 iteration permutation test on paired-differences (Hooton, 1991; Ludbrook, 1994). This test directly determines the probability that the mean paired-difference between two data sets could have occurred by chance (i.e., after randomly changing the sign of each paired-difference). We chose this nonparametric test over a repeated measures ANOVA design for its robustness and lack of assumptions regarding the distribution of variances across subjects and trials. The method directly tests the null hypothesis that hand designation, such as more-affected vs. less-affected, had no effect on the force measurement.

Where differences were found between hands at the group level, we determined the directional consistency of the effect at the subject level by calculating an average difference in each force measure per subject. If significantly more than 50% of subjects showed a directional difference across hands according to a binomial test, we considered

the effect to be generalizable at the subject level. If not, we can assume that a subset (e.g. those with more severe symptoms) were primarily responsible for the group effect.

Finally, we tested all force measures—and the magnitude of their differences across hands—for correlation with the UPDRS motor scores obtained for a subset of 13 participants out of the original 20. In particular, we tested for correlation to (i) the entire UPDRS motor score, (ii) the UPDRS hand-only score for the more-affected and the less-affected hands, and finally (iii) the UPDRS motor score excluding all hand scores (non-hand motor score). Given that UPDRS tremor scores have received recent attention as potentially descriptive for PD classification (Stebbins et al., 2013), we also tested our force measures for correlation with UPDRS hand-tremor scores. These were calculated as the sum of the postural tremor, kinetic tremor, and rest tremor amplitude evaluations within the UPDRS. To be conservative, we used the nonparametric Spearman's rho rank correlation, with the significance of each coefficient determined by a permutation test. This test calculated the correlation between force measures and UPDRS scores before and after shuffling the UPDRS score assignments across subjects, replacing the scores from one subject with the scores from another. The probability that the correlation coefficient obtained could have occurred by chance was thus directly calculated from 10,000 sets of shuffled data. This permutation process allowed all 3 trial replicates for the 13 subjects to be used, rather than reducing the data set to 13 mean values. This allowed us to test for the significance of correlations in a conservative and assumption-free way.

In this study, we calculate a large number of correlations. Because each test is deemed significant at the 95% confidence level, we can expect that 5% of independent tests might show significance by chance. This is important if we interpret the occurrence

of a single significant result to imply clinical utility for the Strength-Dexterity test. We do not specifically make this claim, nonetheless, we used a binomial test to determine if the number of significant correlations observed could have occurred by chance given the number of statistical tests. The approach directly addresses the problem of multiple comparisons without requiring the global adjustment of confidence levels.

Results

Force measures

We found significant group differences in dynamic fingertip force control between the more- and less-affected hands during the Strength-Dexterity test. The basic group-level differences in F, F_LF, and F_HF are as follows:

Mean compression force (F). The mean compression force measured from the more-affected hand was significantly lower (i.e., worse) than that of the less-affected hand (p=0.019) (Fig. 2.2, A). Interestingly, although the difference was significant at the group level, 60% of individual participants showed greater (i.e., better) F in the less-affected hand. For 20 participants, 60% is essentially chance-level according to a binomial test, thus, a difference between hands in compression force was not, on average, directionally consistent across PD patients.

Standard deviation of force fluctuations <4Hz (F_LF). The mean of F_LF was significantly lower in the more-affected hand (p=0.042) than in the less-affected hand at the group level (Fig. 2.2, B). Only 50% of tested individuals displayed greater mean F_LF in the less-affected hand than in the more-affected hand, indicating a subgroup-driven effect rather than a general feature of PD.

Root mean square of force at 4-12Hz (F_HF). No significant mean difference was found for F_HF between hands.

The heterogeneity of symptom severity among individuals may have influenced these results and is further explored below at the individual level.

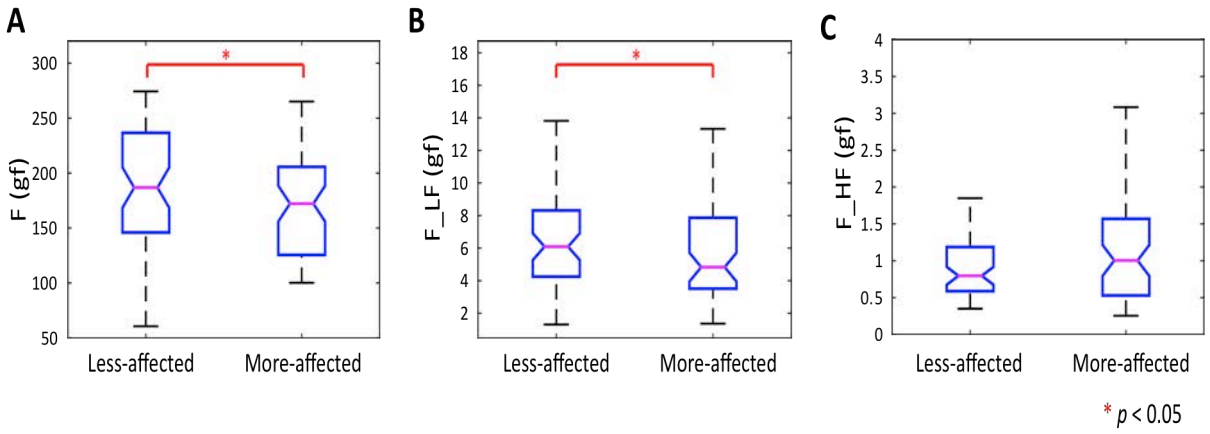

Figure 2.2 Force measure comparisons between less-affected and more-affected hands. (A) Greater mean force compression in less-affected hand (B) Greater force variability at low frequency (F_LF) in less-affected hand (C) No difference in force variability at high frequency (F_HF) between hands. A 10,000-iteration permutation test on paired-differences was used to test mean differences between hands.

UPDRS motor scores and force measures

The MDS-UPDRS (the revised version by the Movement Disorder Society) motor examination scores were obtained from 13 of the 20 participants by a trained and certified clinician. Twelve participants were on medication while one participant (PD1) in the early stage of disease voluntarily delayed drug therapy. The total motor scores ranged from 7 - 53 among the 13 participants (Table 2.1). The lower the UPDRS motor scores, the less the motor impairment.

Correlations between the UPDRS total motor score and force measures (F, F_LF, and F_HF). Table 2.2 summarizes Spearman's rho rank correlation coefficients

and *p*-values between the UPDRS total motor scores and force measures between two hands at the group level. Only F_LF showed a significant correlation in the more-affected hand (rho=-0.44, *p*=0.04).

Table 2.1 Clinical characteristics of 13 patients with Parkinson's disease

PD no.	Age	Sex	Disease duration (year)	Affected hand	H & Y stage	UPDRS motor score			Medication
						Total	More-affected hand	Less-affected hand	
1	70	F	2	R	1	32	12	6	Off
2	70	M	0.4	R	1	7	7	0	On
3	55	F	3	R	1	32	14	6	On
4	66	M	0.33	L	2	26	11	7	On
5	73	F	7	R ≤ L	2	17	4	3	On
6	76	F	8.75	L ≤ R	2	27	8	8	On
7	65	F	8	L	2	22	7	5	On
8	72	F	3.75	R	2	53	17	12	On
9	71	M	3	L	2	41	12	9	On
10	68	M	4	R	2	34	9	6	On
11	71	M	4	R ≤ L	3	52	12	12	On
12	80	M	2.5	R	2	43	15	8	On
13	75	F	7	R	2	28	12	9	On

Correlations between the UPDRS hand-only motor score and force measures.

For the UPDRS hand-only motor score, we considered a set of 7 hand-related items from the full assessment list: rigidity, finger tapping, hand movements, pronation/supination, postural tremor, kinetic tremor, and resting tremor amplitude. The UPDRS hand-only motor score for the more-affected hands ranged from 4 - 17, and from 0 - 12 for the less-affected hand. Once again, only F_LF (rho=-0.52, *p*=0.016) showed a significant correlation in the more-affected hand (Fig. 2.3). That is, greater variability of voluntary

Table 2.2. Spearman's rho coefficients (ρ) and *p*-values between UPDRS motor scores and force measures.

	More-affected hand						Less-affected hand					
UPDRS	**Motor**		**Hand only**		**Non-hand**		**Motor**		**Hand only**		**Non-hand**	
	Rho	***p*-value**	**Rho**	***p*-value**	**Rho**	***p*-value**	**Rho**	***p*-value**	**Rho**	***p*-value**	**Rho**	***p*-value**
F	-0.11	0.35	-0.22	0.23	-0.20	0.25	-0.006	0.49	0.096	0.37	-0.16	0.29
F_LF	-0.44	***0.04**	-0.52	***0.016**	-0.39	0.062	-0.024	0.46	-0.16	0.24	0.05	0.43
F_HF	-0.26	0.16	-0.14	0.30	-0.42	0.060	0.18	0.25	0.067	0.41	0.16	0.28

*$p < 0.05$, statistical significance is determined by a 10,000 iteration permutation test.

force fluctuations was associated with less motor impairment measured by UPDRS total and hand-only motor scores.

Correlations between the UPDRS non-hand motor score and force measures. To quantify the general, non-hand related, motor impairment such as gait and balance, the hand-only motor score for both hands was subtracted from the UPDRS total motor score. The UPDRS motor score without the hand scores negatively correlated with both F_LF (rho=-0.39, p=0.062) and F_HF (rho=-0.42, p=0.06) for the more-affected hand, although these correlations fell just short of statistical significance. Interestingly, these correlations were not found in the less-affected hand (Table 2.2).

Correlations between the UPDRS tremor score and force measures. We derived a tremor score per each hand by summing scores from three UPDRS tremor-related items: postural tremor, kinetic tremor, and rest tremor amplitude. The tremor

scores ranged from 1 - 7 for the more-affected hand, and 0 - 4 for the less-affected hand. We found no significant correlations between tremor scores and any of our force measures.

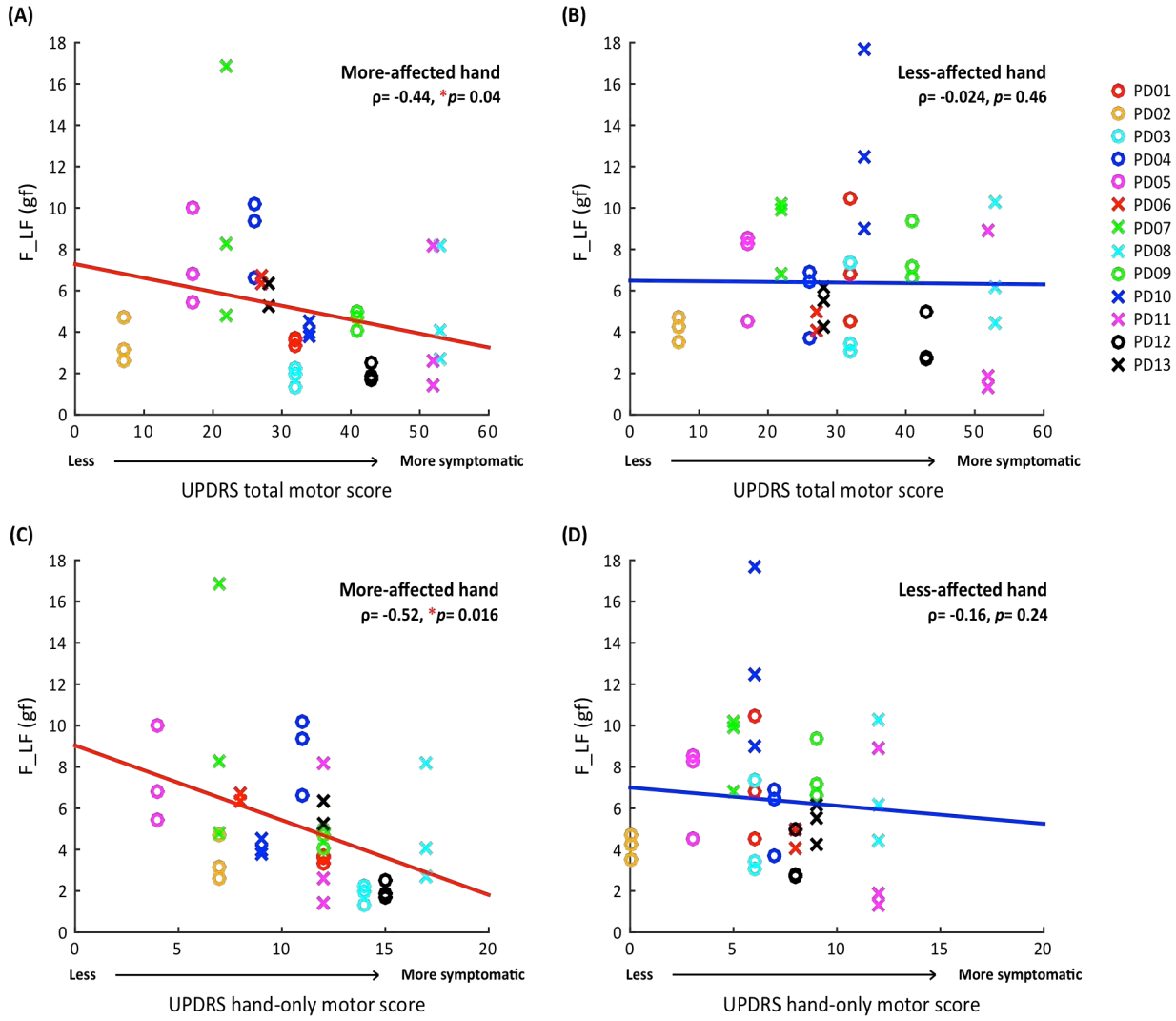

Figure 2.3. Correlations between magnitudes of voluntary force fluctuations and UPDRS total and hand-only motor scores for both hands. (A) Greater voluntary force fluctuations correlated with less total motor impairment in the more- affected hand. (B) No significant correlation between voluntary force fluctuations and UPDRS total motor score in the less-affected hand. (C) Greater voluntary force fluctuations associated with less hand-related motor impairment in the more-affected hand. (D) No significant correlation between voluntary force fluctuations and UPDRS hand-only motor score in the less-affected hand. (*$p < 0.05$, Statistical significance of each Spearman's coefficient was determined by a 10,000 iteration permutation test. The linear fit was only for visual representations.)

Correlations between the UPDRS total motor score and between-hand difference in F, F_LF, and F_HF. Because only a subset of all participants influenced the group differences in F and F_LF, (60 and 50%, respectively), due to heterogeneity of symptom severity among participants, we tested if the between-hand differences in force and force variability for each individual were correlated with overall motor impairment level. Table 2.3 summarized Spearman's rho rank correlation coefficients and *p*-values between the UPDRS motor scores and between-hand difference in force measures at the individual level. The between-hand differences in force measures were calculated as the more-affected minus the less-affected hand in magnitude. A significantly negative correlation was again found only between the overall UPDRS motor score and ΔF_LF (rho= -0.46, p=0.039) (Figure 2.4). Less difference in F_LF between hands was associated with increased overall motor impairment.

Correlations between the UPDRS non-hand motor score and between-hand difference in F, F_LF, and F_HF. We determined if the magnitude of difference in force measures between the two hands were correlated with the more systemic and non-hand related motor symptoms covered by the UPDRS motor examination. A significantly

Table 2.3. Spearman's rho coefficients (ρ) and *p*-values between UPDRS motor scores and between-hand difference in force measures.

UPDRS	Motor		Non-hand	
	Rho	*p*-value	Rho	*p*-value
ΔF	-0.083	0.38	-0.009	0.49
ΔF_LF	-0.46	***0.04**	-0.47	***0.032**
ΔF_HF	-0.39	0.076	-0.48	***0.039**

*$p < 0.05$, statistical significance is determined by a 10,000 iteration permutation test.

negative correlation was found for ΔF_LF (rho = -0.47, p=0.032) (Fig. 2.4) once again, indicating that decrease in differences between hands corresponded to greater non-hand motor symptom severity such as impairment of balance and gait. But additionally, ΔF_HF now showed a significant negative correlation (rho = -0.48, p=0.039) (Table 2.3) with UPDRS, indicating that larger differences between hands in involuntary force fluctuations corresponded to less systemic motor impairment.

Because a large number of correlations were tested for statistical significance, we used a binomial test (Dodge, 2008) to determine if the overall proportion of correlations exceeding the 95% confidence level was greater than would be expected given the

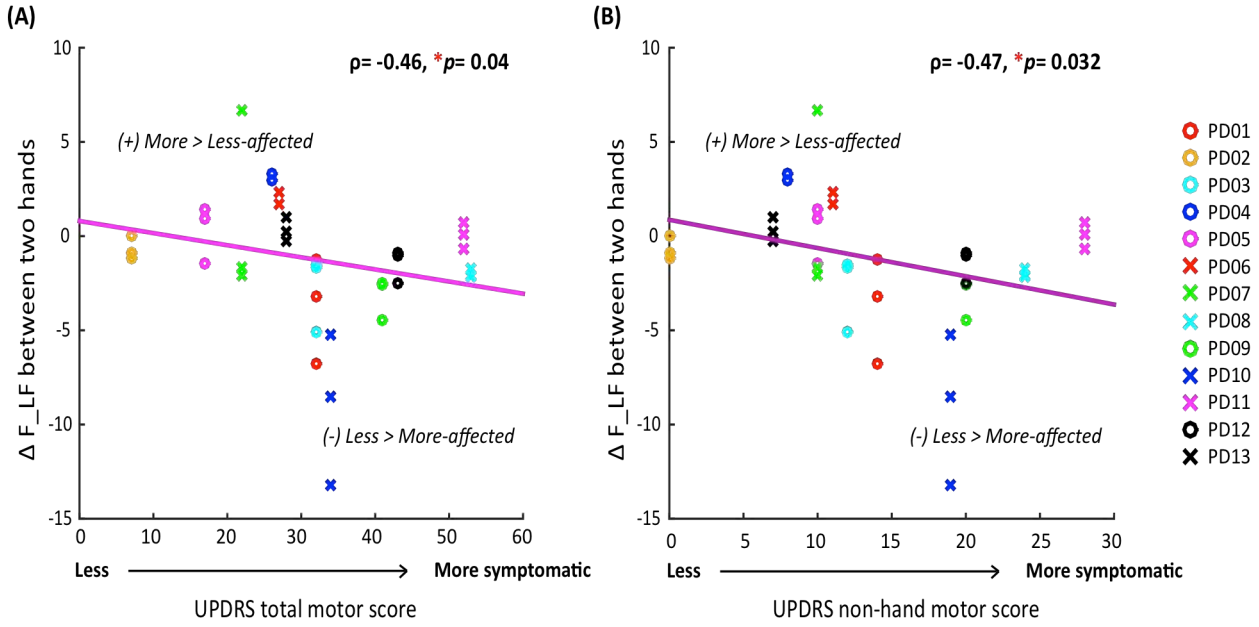

Figure 2.4. Correlations between differences in voluntary force fluctuations between the more-affected and less-affected hands and UPDRS motor scores. (A) Decrease of between-hand difference in ΔF_LF was significantly correlated with greater total motor impairment. (B) Decrease of between-hand difference in ΔF_LF was significantly correlated with greater non-hand motor impairment. (*p < 0.05, Statistical significance of each Spearman's coefficient was determined by a 10,000 iteration permutation test. The linear fit was only for visual representations.)

number of tests executed. Many of our tests are not independent, however, to be extremely conservative, we assumed 24 independent tests (every test in Tables 2.2 and 2.3). The binomial probability that we would have obtained 5 significant results by chance is p=0.00019. Of course, reducing the number of independent tests can only strengthen our results.

Discussion

Measures of dynamic force control during the Strength-Dexterity test, an inherently dynamical and dexterous task, revealed characteristic differences between the more- and less-affected hands in PD, an aging population with progressively declining hand function. The purpose of the paper was to explore force control strategies during a dynamic and dexterous task. Measurements of dynamic finger force may begin to fill the need for more objective and sensitive measures of sensorimotor function to better chart the progression of disease and gauge treatment. Note that although we speak of maximal sustained compression forces and variability therein, these maximal forces are all < 3N (< 10% maximal static pinch force). The Strength-Dexterity test is predicated on the notion that studying precision manipulation with the fingertips at low force magnitudes while pushing the motor system to a limit of dynamical performance (i.e., the edge of instability) is informative of the integrity and deficits in the neuromuscular mechanisms for sensorimotor control in manipulation (Dayanidhi, Hedberg, et al., 2013; Dayanidhi & Valero-Cuevas, 2014; Duff, Aaron, Gogola, & Valero-Cuevas, 2015; Lawrence et al., 2015; Lawrence et al., 2014; Venkadesan et al., 2007).

The main finding of the study concerns the force fluctuations at low frequencies

(in the voluntary range < 4Hz, F_LF) seen during the maximal level of sustained compression. We found lower variability at these frequencies was associated with greater severity of motor impairment measured by the UPDRS total and hand-only motor scores. Thus, measures of force variability during the performance of the Strength-Dexterity test hold potential as objective clinical assessment tool in PD, and may be a useful addition to current clinical assessments for characterizing and tracking the severity of both hand and general motor impairment.

Many individuals with PD naturally show greater motor impairment in one hand compared with the other (Jankovic, 2008; Lukos et al., 2014). Because of this, we sought to identify group differences in dynamic force control between the more- and less-affected hands. We found that the more-affected hand compressed the unstable spring with less force and with reduced low-frequency force fluctuations (< 4 Hz) compared with the less-affected hand. Slow fluctuations in force relate mostly to active and voluntary strategies and adjustments to stabilize the unstable object. Since the instability of the spring increases with compression force, our finding of decreased compression force in the more-affected hand implies reduced ability to control instability (Venkadesan et al., 2007). This reduced control of instability appears to influence both compression force and force variability. However, our data suggest that compression force and low-frequency force variability may reflect relatively independent aspects of stability control in PD because a subsequent analysis showed no significant correlation between compression force and low-frequency force variability (more-affected side: rho=0.32, p=0.11, less-affected side: rho=0.25, p=0.2). Interestingly, force fluctuations at higher frequencies (4-12Hz), which includes tremor (Jankovic, 2008; Vaillancourt et al., 2001),

a well-known symptom in PD, were not different between the two hands. PD may also be classified into tremor dominant and postural instability/gait difficulty groups with UPDRS measures (Stebbins et al., 2013). Given the potential importance of tremor for disease categorization, we also explored the relationship between UPDRS tremors scores and force measures. We found no significant correlations, indicating that our measures are not directly affected by tremor symptoms measured in the UPDRS. These findings suggest that force variability during the Strength-Dexterity test is most sensitive to impairment of voluntary rather than reflexive and involuntary aspects of sensorimotor control.

We examined if the force measures (F, F_LF, and F_HF) reflected hand-specific motor symptom severity. We found that the F_LF, low-frequency force fluctuations significantly negatively correlate with UPDRS measures only in the more-affected hand. This indicates that greater low-frequency fluctuations during the Strength-Dexterity task are associated with less impairment level of the more-affected hand. The same significant correlation was found for the UPDRS total motor score. The UPDRS non-hand motor score showed this same trend, albeit at a non-significant level.

The inevitable diversity of symptom severity in our participants may have affected our group comparisons. Therefore, we analyzed differences in force dynamics between hands. This within-subject analysis showed that it was mostly the participants with greater impairment that exhibited decreased F_LF in the more-affected hand relative to the less-affected hand. This was also the case for the UPDRS non-hand motor score. The latter finding is particularly interesting, because it suggests that ΔF_LF between hands may be indicative of systemic and general motor dysfunction.

Furthermore, the difference in high frequency force fluctuations (ΔF_HF) between hands correlated only with the UPDRS non-hand motor score. It may be that high frequency force fluctuations could reflect mostly systemic and general motor impairment. The magnitude of maximal sustained compression force, F, although different across hands on average, did not correlate well with any UPDRS measure. Thus, force fluctuations during the sustained compressions are likely more informative of neural control capabilities than the level of compression itself.

Given that low-frequency force fluctuations were smaller in hands with greater levels of motor impairment, it is reasonable to speculate that the reduced variability represents a loss of compensatory mechanisms employed by PD patients to control instabilities with the more-affected hand. Previous research showed greater variability in various force generation tasks in PD patients relative to controls (Sheridan, Flowers, & Hurrell, 1987; Stelmach, Teasdale, Phillips, & Worringham, 1989; Vaillancourt et al., 2002). While increased force variability in PD might indicate impairment under some conditions, the within-subject design of the present study compels an alternative interpretation of force variability. In some contexts, motor variability may reflect flexibility or adaptability of motor systems (Vereijken, 2010). Variability in a physiological process is thought to be necessary to adapt to unpredictable environmental changes, and this capability decreases with aging (Lipsitz & Goldberger, 1992). In the present task of controlling an unstable compliant object, the correlation between increased clinical motor impairment and reduced force variability may represent a progressive failure of the PD motor system to employ flexible/adaptive strategies for stabilizing the spring. Thus our findings have important consequences to our

understanding of variability and motor impairment in PD because it shows that not all variability is detrimental. We suggest, therefore, that such changes in variability with disease progression during a highly dynamical and complex stabilization task (i.e., as the system is pushed to some limit of performance) are informative of motor impairment in PD.

It is also possible that individuals with PD employ a fundamentally different motor strategy when using their more-affected hand relative to their less-affected hand. The Strength-Dexterity task requires mainly online somatosensory feedback to control the unstable spring. It is reported that in general, individuals with PD rely more heavily on visual feedback to guide motor actions (Cooke, Brown, & Brooks, 1978; Gordon et al., 1997; Redgrave et al., 2010). We, however, have seen reliance on slower and less effective visuomotor corrections only when tactile sensation is removed in healthy individuals (Venkadesan et al., 2007). Greater reliance on visual feedback could enhance force variability (Shadmehr, Smith, & Krakauer, 2010), however, the advantages and disadvantages of visual strategies in the context of our study are unknown. Thus, it could be that the reduced force variability in the more-affected hand reflects a compensatory adaptation to impaired tactile and proprioceptive control.

The reflexive/reactive/low-level component of dexterous manipulation, however, is relatively preserved in PD. Reactive force control by a perturbation during in-hand manipulation takes about 70ms (Cole & Abbs, 1988; Johansson & Cole, 1992), and continuous updating of somatosensory information and motor response may even shorten to about 40-50ms (Johansson, Häger, & Riso, 1992). The PD motor system seems to preserve intact neural control for early reflexive responses to the perturbation (Fellows et

al., 1998; Ingvarsson et al., 1997). Furthermore, the short latency reflex is intact in PD (Cody, MacDermott, Matthews, & RICHARDSON, 1986; Rothwell, Obeso, Traub, & Marsden, 1983). In our study, high frequency force fluctuations, which may reflect this reflexive/reactive/low-level component of task performance, were not different between the more and less affected hands. Only the difference in this measure between hands was significantly correlated with UPDRS non-hand motor score. This would seem to support the idea that PD influences the active/voluntary/high-level aspects of dexterous manipulation more so than reflexive/reactive/low-level of control aspects.

Interestingly, both ΔF_LF and ΔF_HF between the two hands showed a significant negative correlation with non-hand related motor scores (i.e., systemic and gross motor function (Lawrence et al., 2014). These findings suggest that dynamic fingertip forces measured within the context of a voluntary task may still provide information about the degree of systemic motor impairments such as alteration of posture, gait, and balance, suggesting some commonality of neural circuitry in the system. Motor impairment in posture, gait, and balance is common in individuals with PD (Jankovic, 2008; Jankovic & Kapadia, 2001; Weintraub et al., 2008). The potential for the Strength-Dexterity test to provide information about systemic and gross motor control is attested to by the findings, in which dexterity measures tended to be correlated between the fingers and legs of an individual (Lawrence et al., 2014).

Measures of dynamic force control within the Strength-Dexterity test reflect the degree of hand motor impairment in individuals with PD, potentially fulfilling the need for more objective measures of sensorimotor function. Measuring force variability when the motor system is pushed to a limit of performance (as in the Strength-Dexterity test)

may represent a valuable strategy in assessing motor control in both health and disease. Our measures appear to be informative of symptom severity in PD, however, further research is required to determine the effects of disease progression and medication level on performance of the Strength-Dexterity test. We also hope to enable future studies of its underlying mechanisms by developing measurements of force variability or other measures of performance during well-defined tasks. Such measures may prove valuable for monitoring changes in motor impairment, determining dosages for medication, appropriate parameters for deep brain stimulation, or even for early detection of PD. What's more, such dynamical tasks may also be used for rehabilitation to improve sensorimotor function in dexterous manipulation in clinical populations by challenging the motor system at the edge of instability.

Acknowledgments

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Chapter 3

[In preparation for submission to *Frontiers in Aging Neuroscience*]

Dynamic Force Control Separates Healthy Individuals from Those with Mild to Moderate Parkinson's Disease

Christopher M. Laine, Na-hyeon Ko, Meng-Fen Tsai, and Francisco J. Valero-Cuevas

Abstract

In this study, we compare the dynamic control of pinch force in elderly adults to that of individuals with mild to moderate Parkinson's disease (PD). The magnitude and variability of fingertip forces were recorded as participants compressed a custom-designed spring prone to buckling. We have previously shown that the force variability measured during this task correlates with the Unified Parkinson's Disease Rating Scale (UPDRS). In this study, we evaluate the potential of the same measures of fingertip force control to discriminate healthy participants from those with mild to moderate Parkinson's disease. We found that the variability of pinch force during compression of the custom-spring was sensitive to the presence of the condition itself, regardless of symptom severity. Further, we show that symptom-severity and the presence of PD each influence force variability differently, and thus, the test may have potential for both early detection and symptom tracking. This study serves as a proof of principle, justifying future research into dynamic force control as a potential biomarker of PD.

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease (Bernheimer et al., 1973; Dauer & Przedborski, 2003) and affects 1-2% of the population over age 65 in the U.S. (de Lau & Breteler, 2006; Guttmacher et al., 2003; Weintraub et al., 2008). There is currently an urgent need for the development of biomarkers which can be used for detection, characterization, and tracking of neural degeneration for PD (de Lau & Breteler, 2006; Jankovic, 2008; Weintraub et al., 2008). By the time PD symptoms become overt, 30-70% of substantia nigra neurons and up to 80% of dopamine in the striatum/putamen are lost (Bernheimer et al., 1973; Cheng et al., 2010; Dauer & Przedborski, 2003; Fearnley & Lees, 1991).

Goal-directed actions, which require a high degree of precision, such as precision grip force control, recruit a multitude fronto-parietal and/or cortical-striatal-cerebellar neural structures (Holmström et al., 2011; Mosier et al., 2011; E. Pavlova et al., 2015; Talati et al., 2005). Accordingly, tasks, which demand speed, accuracy, and precision are likely to display control deficits long before more basic activities of daily living are disrupted. The way in which control deficits manifest during execution of demanding tasks may be informative of the underlying neural mechanisms disrupting appropriate sensorimotor integration. Unfortunately, there are no standardized methods, which are specifically designed to push sensorimotor integration capabilities to a clinically-informative limit.

Our group has developed and extensively characterized one possible solution to this problem. We have shown that compression of a custom-designed spring, which is impossible to compress fully because it tends to buckle as it is compressed (Dayanidhi,

Hedberg, et al., 2013; Dayanidhi & Valero-Cuevas, 2014; Valero-Cuevas et al., 2003), can push the motor system to the 'edge of instability' (Venkadesan et al., 2007). This task, called the Strength-Dexterity (S-D) test requires only minimal compression force (<3 N), yet engages a wide variety of neural structures beyond those typically involved in the generation of a simple precision pinch (Holmström et al., 2011; Mosier et al., 2011; E. Pavlova et al., 2015; Talati et al., 2005).

Recently, we have also shown that the over-time variability of compression force in this task is sensitive to motor symptom severity in mild to moderate PD (Ko, Laine, Fisher, & Valero-Cuevas, 2015). In that study, force variability was shown to correlate with the Unified Parkinson's Disease Rating Scale (UPDRS) motor scores, and accordingly, we suggested that the S-D test might hold potential as a diagnostic biomarker (Ko et al., 2015). We did not, however, compare S-D test performance between healthy individuals and those with PD. Therefore, we could not evaluate the sensitivity of the S-D test to the presence of PD. Such information is necessary to determine if S-D test measures hold potential for early detection of PD, or if they are better suited to quantify motor symptom progression within the diagnosed population. In this study, we have compared the S-D test performance of our original cohort of patients with a set of similarly-aged healthy control participants.

Our results show that measures of S-D test performance are sensitive to disease presence, perhaps even more so than symptom severity. Importantly, we show that disease presence and symptom progression influence S-D test measures in different ways. We interpret these results in light of underlying neural deficits and compensation strategies.

Methods

Participants

A total of 30 individuals participated in this study; twenty with Parkinson's disease (11M, 9F, 69.0 ± 7.4yrs, Hoehn and Yarh stages 1-3), and ten healthy individuals (5 Male, 5 Female, 65 ± 7.5yrs) (Table 3.1). Of the twenty participants with PD, 13 had been rated using the UPDRS scale (6M, 7F, 70 ± 6.2yrs, UPDRS motor scores of 7-53). The mean time since diagnosis was 6.0 ± 4.1 years over the full set of PD participants. All PD participants were functionally independent and demonstrated normal cognitive functions as measured by the mini-mental state examination (scores 25-30). We excluded people with ongoing musculoskeletal symptoms and pain in the thumb and index finger as well as a history of neurological disorders and surgery that affected the finger movement. Eighteen of twenty patients were on medication. Full details concerning the symptom ratings and S-D test performance of each patient has been previously described (Ko et al., 2015). This group was intended to represent the general population of functionally independent patients with PD. All participants gave informed, written consent prior to participation, and all procedures were approved by the Institutional Review Board at the University of Southern California. The instrumentation and S-D test recording methodology has been described previously (Ko et al., 2015) and is summarized below.

Table 3.1. Demographics of Participants.

	N	Gender	Age (yr)	Year since DX	Motor severity	Dominant/ affected side
Control	10	5M 5F	65.0 ± 7.5	NA	NA	10R 0L
PD all	20	11M 9F	69.0 ± 7.4	6.0 ± 4.1	H&Y 1-3	11R 9L
PD w/ UPDRS	13	6M 7F	70.0 ± 6.2	4.1 ± 2.6	UPDRS motor 7-53	8R 5L

Instrumentation

The Strength-Dexterity test uses a custom spring (Century Springs Corp., Los Angeles, CA, USA) designed to be nearly impossible to compress entirely. As it is compressed, the spring tends to buckle, requiring the magnitude and direction of fingertip forces to be continually adjusted in order to maintain control. Miniature load cells (ELB4–10, Measurement Specialties, Hampton, VA, USA) were attached to both ends of the spring and used to measure the applied force of thumb and index finger. For analysis, the forces recorded from the two fingers were averaged. Signal sampling rate was set at 400 Hz.

The Strength-Dexterity (S-D) test

The S-D test requires compressing a slender spring prone to buckling with the thumb and index finger (Fig. 3.1), while the other fingers were either curled or fully extended in order to prevent their involvement in the task. Each participant compressed the spring as much as possible without buckling and sustained the compression level for

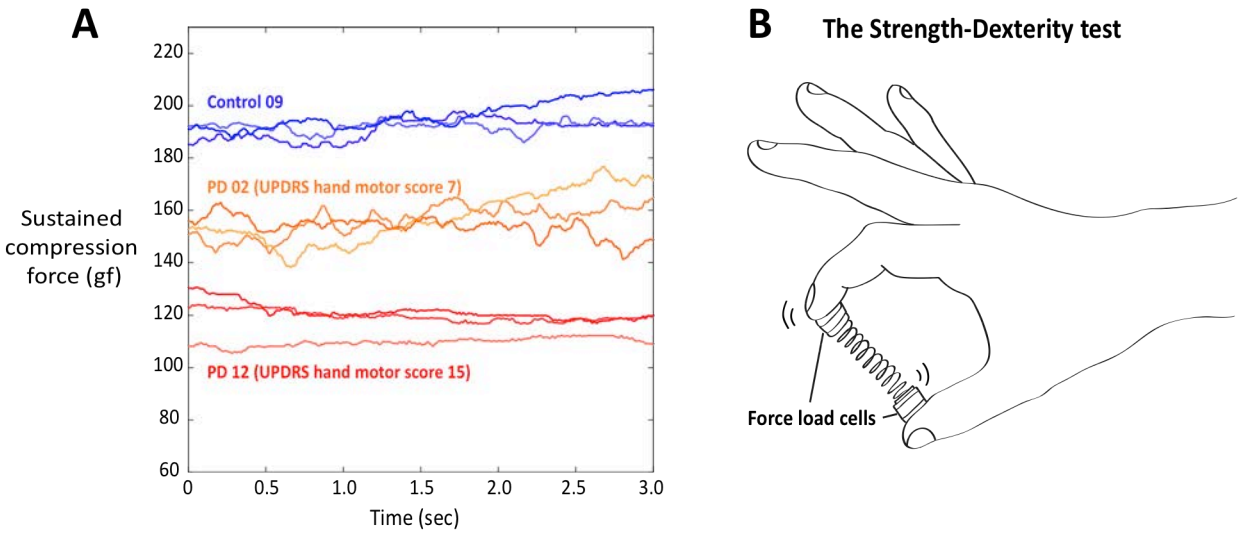

Figure 3.1. The Strength-Dexterity test. (A) Raw force traces of three trials for a healthy individual (blue), a patient with PD with less hand impairment (orange), and a patient with PD with more hand impairment (red). (B) The Strength-Dexterity test requires compressing the spring with the thumb and index finger, as much as possible without buckling, holding the compression for 5 seconds, and releasing the compression.

five seconds. The practice trials were given to participants as needed to familiarize with the task. We started recording when a consistent performance with each trial was observed. The trials with sustained compression force lasting for three seconds were extracted for further analysis.

Force data analysis

We quantified three force measures: 1) mean compression force level (F) during sustained compressions, 2) standard deviation (SD) for low frequency, voluntary fluctuation (< 4Hz, F_LF) and 3) root mean square (RMS) for high frequency, involuntary fluctuation (4-12Hz, F_HF), which includes tremor frequency and fast twitches. For F_LF, raw signals were low-pass filtered at 4Hz with 4^{th} order butterworth filter and detrended to remove any linear slopes. For F_HF, the signals were band pass filtered at 4-12Hz with 4^{th} order butterworth filter. As described previously, we used SD for the low frequency partly because of historical precedent to have a non-zero mean (Ko et al., 2015). In practice, the difference between SD and RMS was negligible but for better consistency with our previous study, we used the same procedure here. For statistical analysis, we used the three highest values of each measure per each hand.

We used a 10,000 iteration permutation test to compare the means of our S-D test measures across groups. The tests were implemented in MATLAB (MathWorks, Natick, MA, USA). Permutation tests allow for a conservative and assumption-free statistical analysis of data which is especially well suited for the type of data collected in the present study (Hooton, 1991; Ludbrook, 1994).

Percentile Rank. A statistical difference is not, however, a measure of effect size or discriminability between two data sets, which are important considerations when

evaluating a measure as a potential biomarker. To address these issues, we first pooled all data collected from the healthy participants (for each measure) and used the resulting distribution to recast each measurement collected from the PD participants as a percentile rank. In other words, if a given variability measure collected from an individual with PD was larger than 80% of the measurements collected from the control group, then that measure would be ranked at the 80^{th} percentile. The 80^{th} percentile is a common value within biomarker literature for identifying at-risk populations (Laine et al., 2015; McKie et al., 2014; Wang et al., 2004). The mean percentile ranking was determined per measure and per hand for each PD participant.

Receiver Operating Characteristic (ROC) curves. Finally, we constructed Receiver Operating Characteristic (ROC) curves for each measure, determined per hand, as above. An ROC curve is constructed by sweeping a 'threshold' from the smallest to the largest measured value within a data set. In our case, values above the moving threshold were classified as belong to the PD group. As the moving threshold passed each new value (from either group), the proportion of healthy individuals who would be misdiagnosed was plotted against the proportion of PD participants who were correctly identified. To derive a single value per measure for each participant, we used the data from the hand, which showed the largest magnitude of force and variability (per individual, regardless of handedness or more-affected side). We calculated the area under the ROC curve to determine the accuracy of the measure as a potential diagnostic test, as is common in ROC analysis (for review see (Eng, 2005)). We used the trapezoid method to integrate the area under our constructed curves. An area of 0.5 indicates a useless measure (equal chance of correct vs. incorrect diagnosis) while an area of 1 indicates

perfect discrimination (100% correct diagnosis, 0% incorrect diagnosis).

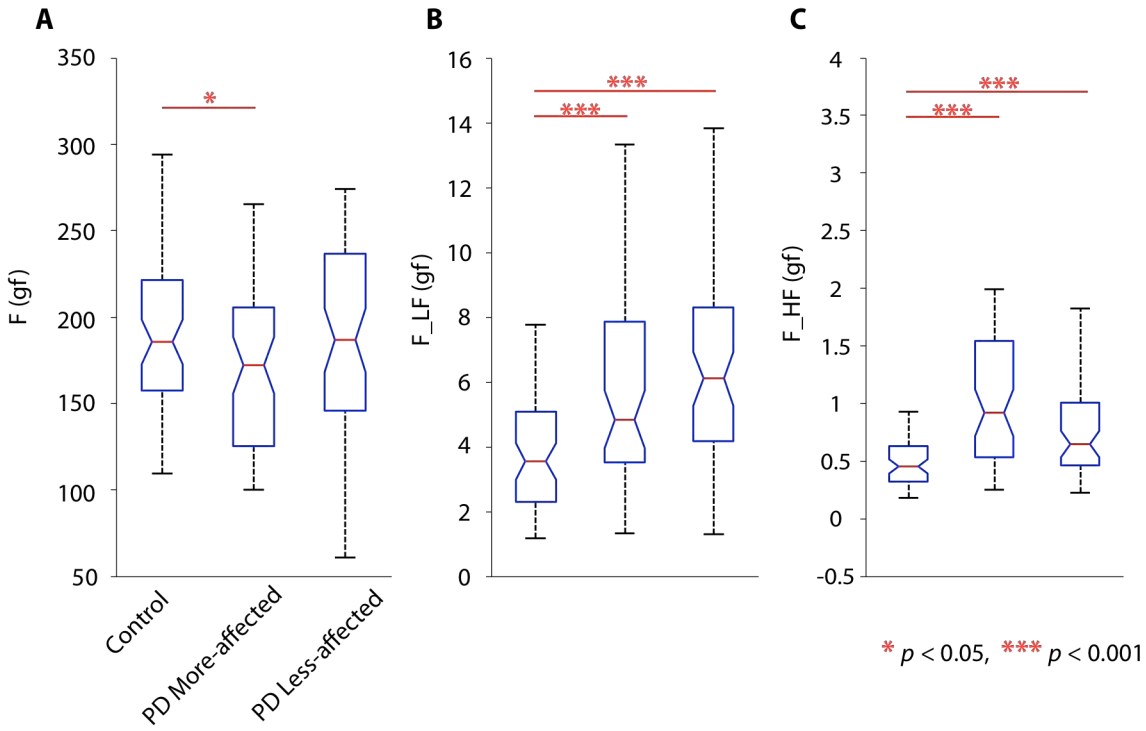

Figure 3.2 The boxplots of the median and interquartile ranges for the three S-D test measures. (A) Mean compression force. (B) Low frequency force variability, the standard deviation of force < 4 Hz. (C) High-frequency force variability, RMS of force at 4-12 Hz. The statistical comparisons were carried out using a 10,000-iteration permutation test on means. (gf: gram force).

Results

Force measures between PD and control groups

No differences were found in all force measures between the dominant and non-dominant hand in the control group. Figure 3.2 shows boxplots depicting the median and inter-quartile ranges for each S-D test measure. Data collected from both hands of the healthy participants have been pooled together as we saw no significant difference

between the two hands. The boxplot for the control group therefore includes 60 data points (10 individuals, two hands with three trials each), while the boxplots for the PD patients cover 60 data points (20 individuals, each hand with three trials). It is clear that force variability (F_LF and F_HF) was larger in PD participants compared with healthy controls, regardless of the hand recorded from. As previously described, individuals with PD did not show consistent differences between their more- and less-affected hands for any measure due to the heterogeneity of symptom severity in this particular PD group (Ko et al., 2015).

Percentile Rank

Figure 3.3 depicts the three S-D test measures ranked for each hand/individual with respect to the measures recorded from the healthy control group. The twenty individuals have been sorted so as to set the percentile ranks recorded from their more affected hand in ascending order from left to right. This allows an easy visual count of how many participants showed highly abnormal values (> 80^{th} percentile, marked by the horizontal dashed lines), but also shows if the S-D test measures in the more-affected hand generally follow the same trends as the less- affected hands.

It can be seen that for mean compression force (Fig. 3.3, panel A), values tended not to cluster above or below those expected for a healthy participant. For the F_LF (Fig. 3.3, panel B) measure, however, 9 of 20 more-affected hands and 13 of 20 less-affected hands showed ranks above the 80^{th} percentile. Six participants whose more-affected hand ranked below the 80^{th} percentile actually showed variability at the > 80^{th} percentile level in their less-affected hands. For the F_HF measure (Fig. 3.3, panel C), 14 of 20 participants showed >80^{th} percentile values for their more-affected hands and somewhat

fewer high values for their less-affected hands (10 of 20).

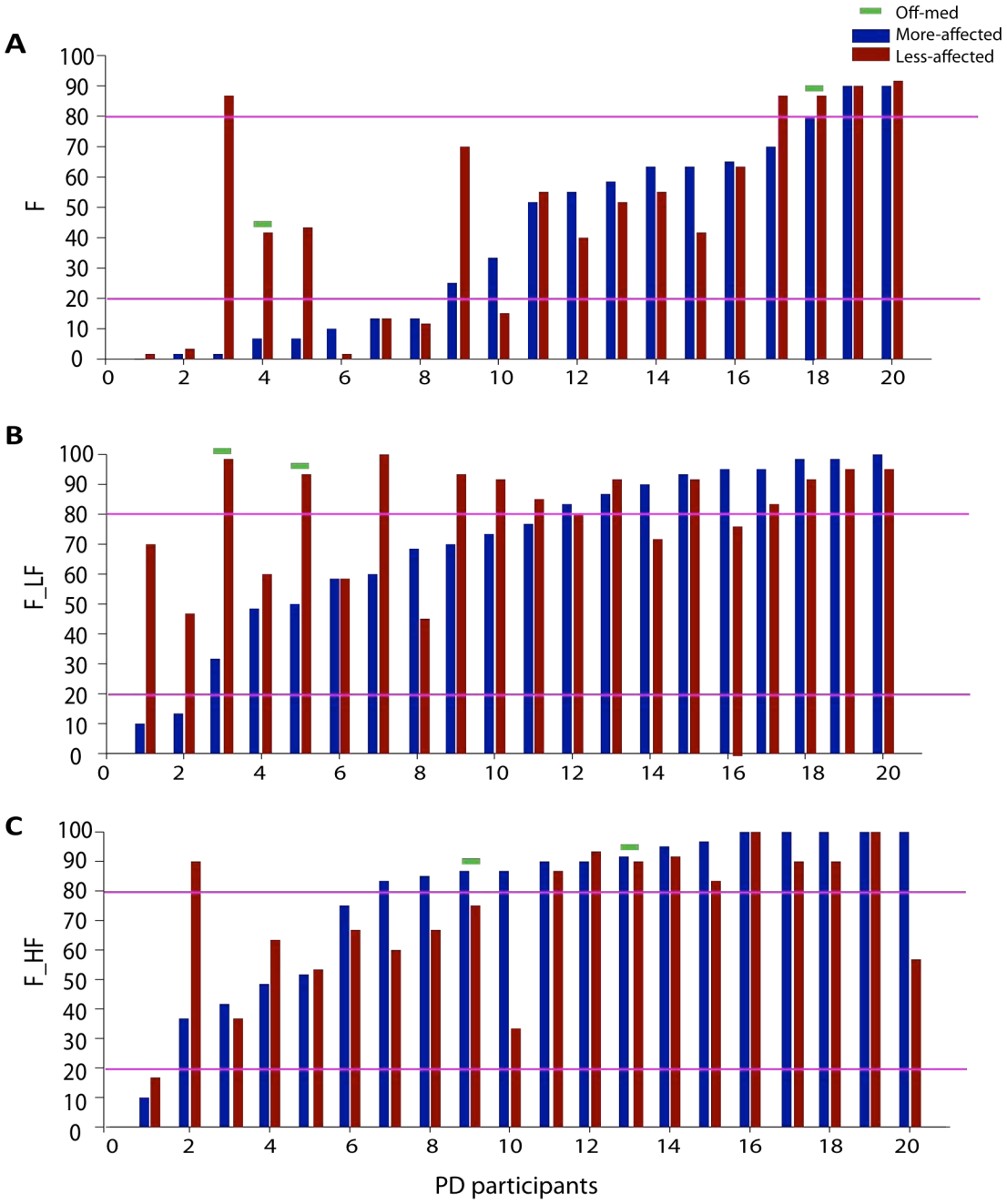

Figure 3.3 Percentile ranking of S-D test measures in participants with Parkinson's disease, as compared with healthy individuals. Panels A-C depict the mean compression force (A), force variability < 4 Hz (B), and force variability in the 4-12 Hz frequency range (C). The order of participants on along x-axis has been sorted such that the rankings of the more-affected hand increase from left to right. Horizontal lines (pink) mark the 80th and 20th percentiles. The green line indicates two individuals with off-medicine.

Within our set of PD participants, thirteen participants had been rated using the UPDRS motor examination. This allowed us to determine if the percentile rankings correspond (per hand) with symptom severity. Figure 3.4 shows the percentile rank vs. UPDRS motor scores (total motor, hand-only, and non hand motor scores, see Ko et al., (2015) for more details). In the first row, the three measures are plotted so as to compare percentile ranking with the hand-only motor score from the UPDRS. Each hand has its own UPDRS score, thus, each participant is represented by two marks (one for each hand), which may have different UPDRS scores.

In the second row, the percentile rankings for each hand are plotted against the total motor score. In this case, both hands from a given participant will share a single UPDRS score. The third row depicts the percentile rankings compared with the non-hand UPDRS motor scores, that is, the degree of motor impairment, which do not relate to hands (e.g. gait and balance). Again, each participant will show two marks (each hand) for their associated UPDRS scores. It is clear that both the F_LF and F_HF percentile rankings tended to cluster above the 80^{th} percentile, and that the particular UPDRS score associated with each hand had no visually-obvious influence on the ranking of force variability with respect to healthy participants.

ROC curves

Figure 5 shows the ROC curve constructed for each S-D test force measure. The mean compression force (black) lies on a nearly 45-degree angle and has an area under the curve of 0.46. Mean compression force has no potential as a diagnostic measure. In contrast, both the F_LF (red) and F_HF (blue) showed good performance (0.845 and 0.833 respectively). The areas were calculated using the trapezoid method of integration.

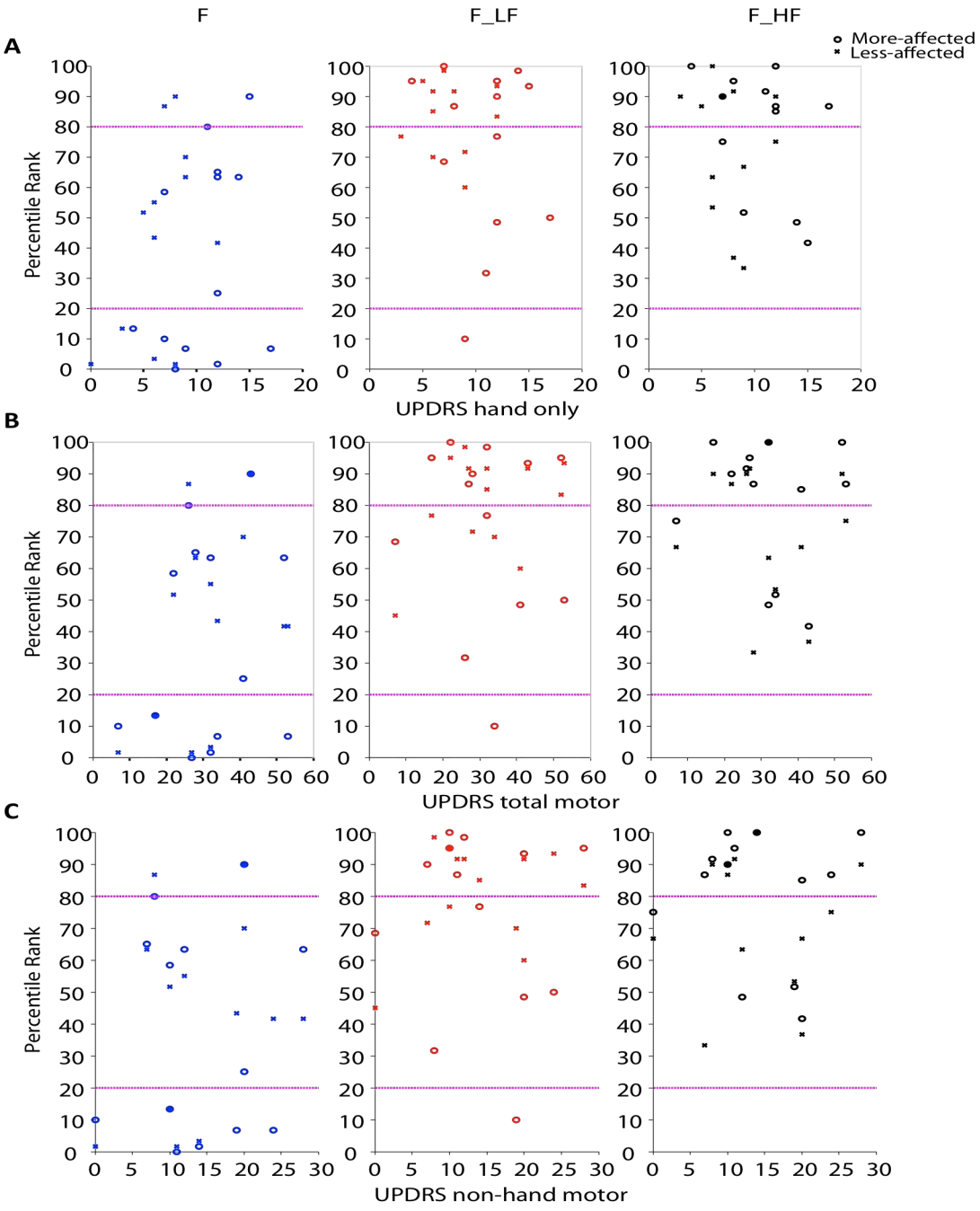

Figure 3.4 Percentile ranking of S-D test measures in relation to UPDRS scores. Rows A-C depict the percentile rankings vs. different UPDRS scores. (A) Rankings against the UPDRS motor score for each hand individually. (B) Rankings against the UPDRS total motor score. (C) Rankings against the non-hand UPDRS score. Horizontal lines (pink) mark the 20th and 80th percentile.

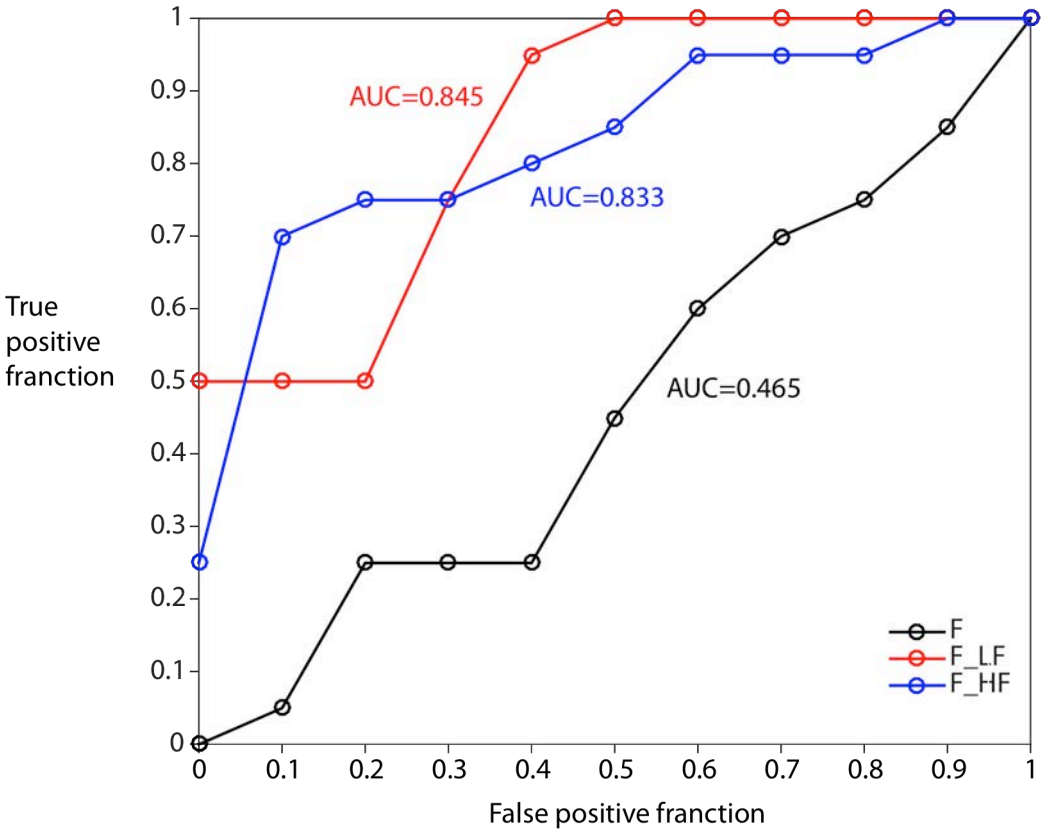

Figure 3.5 ROC curves for each S-D test measure. Depicted in this figure are ROC curves constructed for each of the three S-D test measures. Each curve shows the ability of a given measure to 'diagnose' the performance of a participant as either healthy or having Parkinson's disease. Both the F_LF and F_HF measures have good classification ability, with areas of 0.845 and 0.833 respectively. Mean compression force was found to have no ability to classify a hand as belonging to a healthy individual vs. one with PD.

Discussion

In this study, we compared S-D test performance between individuals with well-managed mild-moderate Parkinson's disease and a group of healthy older adults. Our results provide an important proof of principle that S-D test measures may have utility for

the detection of PD. In addition, we show that the influence of PD on force variability in this task is not only (or even primarily) determined by the overt presence of motor symptoms, and may reflect a more general disruption of sensorimotor integration or associated compensatory strategies.

Our first major finding relates to the maximal compression force that each individual was able to sustain without causing the spring to buckle. The majority of S-D test analysis in the past has focused on mean compression force, and indeed, the measure has been shown to be sensitive to age and even the effects of surgical interventions like pollicization (Dayanidhi, Hedberg, et al., 2013; Dayanidhi & Valero-Cuevas, 2014; Lightdale-Miric et al., 2015; Vollmer et al., 2010). Our results suggest that mean compression force was not a particularly sensitive measure for detecting the presence of PD, which is in line with the results of a previous investigation of this measure in a set of more advanced patients (Lawrence et al., 2014). In fact, our ROC analysis suggested that mean compression force is no better than random chance as a predictor of PD. These findings, along with the fact that mean compression force does not correlate with PD symptom severity (Ko et al., 2015), strongly suggest that the overall magnitude of spring compression is not an informative measure of PD-related motor dysfunction.

In contrast, the dynamics of force control, as measured by the variability of compression force overtime, was clearly sensitive to motor dysfunction in PD. Our previous study showed a negative correlation between F_LF and symptom severity as measured by the UPDRS scale (Ko et al., 2015). If F_LF were simply a measure of symptom severity, we might expect that the healthy subjects analyzed in this study, having no symptoms, would show the most low frequency variability. This was not the

case. In fact, the magnitude of low-frequency variability in the healthy participants was much less than that observed in those with PD, and the extent of this difference (as determined by the percentile rankings in figure 4) appears unrelated to UPDRS ratings. Essentially, the presence of PD increases F_LF, but as an individual's symptoms progress, F_LF decreases (Ko et al., 2015). One possible interpretation is that presence of the PD makes control of the spring more difficult, and thus participants must make larger or more frequent corrective actions compared with healthy controls. Then, as symptoms progress, an individual's ability to identify and execute appropriate corrective actions may diminish, leading to reduced force variability. There are numerous possible causes for abnormal force variability in PD patients. For example, people with PD might rely more heavily on visual information to detect and compensate for the bending of the spring, (Carlton, 1981; Gordon et al., 1997). In addition, motor symptoms such as increased stiffness, rigidity, and bradykinesia (Jankovic, 2008; Morris, 2000) would likely influence the execution of any corrective actions that are attempted. Such difficulties may favor a strategy of joint-stiffness through muscle co-contraction rather than execution of subtle corrective actions. Our present interpretation is that the majority of 'abnormal' force variability is a general feature of PD rather than a direct consequence of overt motor symptoms, since differences between the more- and less-affected hands in the PD group were relatively minor compared with the differences between the PD group and the control group.

In our previous study, F_HF was not a strong predictor of symptom severity, yet was clearly abnormal in the patient group as compared with healthy individuals. High frequency force variability during spring compression could potentially relate to action

tremor during force production. Such action tremor can be a feature of Parkinson's disease, (Hallett, 2012). The extent of abnormality in the F_HF measure, like F_LF, did not appear to relate to UPDRS motor scores, and showed the same diagnostic potential as F_LF in terms of the area under the ROC curve constructed for this measure.

Our findings are therefore in line with those, who showed high frequency action tremor (6-15 Hz) during pinching of an object was more common in PD patients than healthy controls (Raethjen et al., 2005). They also showed that "re-emergent" tremor in the 3.5-6.5 Hz range was very common in PD patients, and that this tremor, unlike the high-frequency tremor, was abolished when patients were medicated (Raethjen et al., 2005). The fact that high-frequency action tremor was unaffected by medication indicates a dopamine-independent mechanism, which nonetheless is sensitive to the presence of PD. It is likely that F_HF quantifies the same phenomenon, since it was abnormal compared with controls, yet does not correlate with symptom severity. It seems unlikely that the classical "re-emergent" tremor described by Raethjen et al., (2005) was the primary source of F_LF though, since the patients in our study were nearly all medicated. However, we cannot completely rule out the possibility that spring-compression somehow enhanced "re-emergent" tremor despite its known suppression by medication under less demanding conditions.

While neither the F_LF nor the F_HF measure could be considered an extremely strong predictor of PD (ROC area values of ~0.84), it is important to consider several limiting factors. For one, the modest number of individuals within our control group renders ROC and percentile measures fairly coarse. For an initial exploration, our sample size was sufficient to establish diagnostic potential and characterize the general features

of PD-related effects on S-D test performance, but larger numbers would certainly be required for producing normative performance values in the aging population. Another important consideration is that 18 of 20 PD patients in this study were medicated to reduce symptoms and optimize motor function. Because of this, we must consider two alternative interpretations for our results. First, it could be that S-D test measures are sensitive enough to detect subtle sensorimotor deficits present in PD, even when symptoms are minimal. In that scenario, the S-D test may be useful in detecting the condition before symptoms become severe enough to prompt clinical diagnosis/intervention. A second, less attractive possibility is that the S-D test measures are themselves somehow related to the medication and not the disease. We consider this possibility to be extremely unlikely, given the overall consistency of abnormal S-D test performance in PD patients despite the heterogeneity of our patient population in terms of clinical presentation and history. Further, it is not clear how a medication-related effect would cause abnormally-high force variability or tremor, which one might expect to be reduced, or at worst unaffected by medication. Although levodopa-induced-dyskinesia (LID) could influence F_LF measures (Wenzelburger et al., 2002), LID typically occurs in late-stage PD, which were not at all common in our patient group.

Overall, our study has shown a clear difference in S-D test performance between healthy participants and those with mild to moderate PD. The variability of force during the compression of an unstable spring is not only indicative of symptom progression within the PD population, but appears to be sensitive to the presence of the condition itself, regardless of symptom severity. Our results imply that symptom severity and the presence of PD influence S-D test performance in different ways, and thus, the test may

have potential for both early detection and symptom tracking. Our results further justify future study of S-D test measures in the PD population, particularly those whose symptoms are very mild, or who are not currently on medication.

Acknowledgements

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Conflict of Interest

FV-C holds US Patent No. 6,537,075 on some of the technology used in this study that is commercialized by Neuromuscular Dynamics, LLC.

Chapter 4

[In preparation for submission to *Journal of Neuroscience*]

Unimanual dexterous tasks facilitate the corticospinal excitability in the ipsilateral M1

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Abstract

Dexterous manipulation with the index finger and thumb (dynamic precision pinch) is vital to activities of daily living, and is disproportionally impaired by neurological disorders. While it is now recognized that dynamic precision pinch with the dominant hand engages neural networks in both hemispheres, we lack functional details of those interhemispheric interactions. We tested corticospinal excitability to assess changes in interhemispheric interactions with increasing dexterity demands of unimanual precision pinch tasks. Ten right-dominant healthy adults (29.5 ± 3.5yrs, 4M 6F) kept their left hand at rest while performing force-matched unimanual precision pinch tasks with the right hand using (i) a rigid dowel, (ii) a short (stable) spring, and (iii) a longer slender (unstable) spring prone to buckling, and (iv) a rest condition. During each task, we delivered single-pulse TMS over the right M1, and recorded motor evoked potentials (MEPs) from the left first dorsal interosseous (FDI) and ipsilateral silent periods (ISPs) from the right (i.e., engaged) FDI. We found that the average MEPs in the resting left FDI were highest during compression of the unstable spring (p<0.001), the most

dexterous task. Compression of the stable spring and rigid dowel elicited similar MEP amplitudes (p=0.79), but greater than in the rest condition (p<0.05). Mirror EMG activity in the left FDI was not different among three pinch tasks, and did not consistently correlate with MEP amplitudes. Importantly, there was no significant difference in ISPs in the right FDI among the four conditions. These results demonstrate that the dexterity requirements of unimanual tasks modulate the net excitability of the unengaged corticospinal tract. From a clinical perspective, recording MEPs in the resting hand during unimanual precision pinch serves as a practical means to interrogate and quantify task-dependent modes of functional lateralization. We discuss the consequences of these novel findings to neurorehabilitation of hemiparesis in, for example, stroke or cerebral palsy.

Key words: dynamic grip force; corticospinal excitability; interhemispheric inhibition; ipsilateral silent period; sensorimotor control

Introduction

Over the last few decades, neuroimaging and non-invasive brain stimulation studies have identified the neuroanatomical structures and networks involved in unimanual precision grip control. These areas include the cortico-cortical network of the ventral premotor cortex (PMv), anterior intraparietal area (AIP), primary motor cortex (M1), and subcortical areas such as the basal ganglia and cerebellum (Davare et al., 2011; Grafton, 2010; Johansson, 1996; Prodoehl et al., 2009). The contralateral M1 is typically

involved during unimanual grip tasks (Ehrsson, Fagergren, & Forssberg, 2001; Ehrsson et al., 2000; Kuhtz-Buschbeck et al., 2008; Kuhtz‐Buschbeck, Ehrsson, & Forssberg, 2001). The primary neural control of lateralization evident by neuroanatomical structures (Kuypers, 1960; Lemon, 2008; Lemon, Kirkwood, Maier, Nakajima, & Nathan, 2004; Martin, 2005) and the known clinical consequences of contralateral motor impairment after M1 damage (Lang & Schieber, 2003; Lindenberg et al., 2010) explain this contralateral M1 activity during unimanual tasks. However, bilateral (or ipsilateral) activation of M1, among other cortical and subcortical areas, has also been consistently noted during unimanual precision pinch tasks (Holmström et al., 2011; Mosier et al., 2011). But the neuroanatomical and functional interpretation of these findings in unimanual control is less clear.

Recently, however, studies have begun to propose functional interpretations for bilateral activation of M1. In particular, studies of unimanual dynamic pinch tasks suggest that broad bilateral neural networks are involved when stabilizing unstable objects (spring devices prone to buckling), which the brain activity level increased objects with greater instability (Holmström et al., 2011; Mosier et al., 2011). These tasks go beyond stable grip force control and finger movements, and require rapid dynamic control of fingertip force vectors, magnitudes and directions (Valero-Cuevas et al., 2003; Venkadesan et al., 2007). These findings suggest that the dexterity demands of dynamic unimanual tasks can modulate the functional interactions across hemispheres.

The slow time constants of blood-oxygen-level-dependent (BOLD) signals, however, make it difficult to elucidate the neurophysiological mechanisms for dynamic manipulation tasks (Foltys et al., 2003; Kobayashi et al., 2003). In response to this,

transcranial magnetic stimulation (TMS) has been the preferred method to examine the net excitability of corticospinal pathway with high temporal resolution, which reflects the physiological state of the motor system (Bestmann & Krakauer, 2015; Di Lazzaro et al., 2008; Hallett, 2007; Reis et al., 2008). This has made it possible to report functional interhemispheric interactions in M1 during unimanual tasks by corticospinal excitability in the M1 ipsilateral to the active hand (Ferbert et al., 1992; Liepert et al., 2001; Ziemann & Hallett, 2001) and ipsilateral silent period (ISP), a reduction in ongoing electromyography (EMG) signals in the task hand (Ferbert et al., 1992; Giovannelli et al., 2009; Reis et al., 2008), where the interhemispheric engagement can be task dependent (Giovannelli et al., 2009; Liepert et al., 2001).

Therefore, we tested how unimanual tasks with increasing dexterity demands modulated interhemispheric interactions. We hypothesize that the net corticospinal excitability in ipsilateral M1 and ISP in the task hand will be modulated by different degrees of dexterity demands—with the greatest increase in excitability and the smallest ISP during the most difficult dynamic unimanual pinch task.

Materials and Methods

Ten healthy adults (29.5±3.5 years, 4M, 6F) participated in the study. All participants were right-handed (self-reported). They had no history of neurological or musculoskeletal disorders and no ongoing pain in the thumb and index finger at the experimental session. All participants were screened for TMS safety using a questionnaire. This study was approved by the Institutional Review Board at the University Southern California.

Precision grip tasks

The participants performed three force-matched precision pinch tasks with the right dominant hand. For each task, the object being pinched had different mechanical properties: 1) an unstable spring, 2) a stable spring, and 3) a dowel (Fig. 4.1). A period of rest served as a control condition. The compression force level was set as 95% of the maximal compression force that each participant could achieve with the unstable spring. Visual feedback of compression force and a target was presented on a computer screen. Participants compressed each object for 1 second, maintained the force level for 7 seconds, and released the compression for 1 second. As many practice trials as needed were given until consistent compression of the unstable spring was observed. The order of grip tasks was randomized and counterbalanced across participants. Twenty trials for each condition were collected. Forces were acquired using a miniature load cell (ELB4-10, Measurement Specialties, Hampton, VA, USA) connected to a USB-data acquisition unit (National Instruments, Austin TX, USA). The visual feedback was provided using custom MATLAB (MathWorks, Natick, MA, USA) scripts.

The unstable and stable springs (Century Springs Corp., Los Angeles, CA, USA) were custom-designed with the same spring constant but with different lengths (Dayanidhi, Hedberg, et al., 2013; Valero-Cuevas et al., 2003). The unstable spring was prone to buckle and challenging to compress fully. The unstable spring task required the greatest dexterity demands of dynamic control of fingertip force vectors (magnitudes and directions) to stabilize high instability, while the stable spring was easy to compress to a desired force level and required relatively low dexterity demands to stabilize low instability. The wooden dowel was approximately the same dimension as the unstable

spring, and it served as a baseline of static grip force control with no control of instability. The effects of force control of low and high instability were compared to the dowel.

TMS protocols and EMG setup

To measure the corticospinal excitability of the ipsilateral M1 during the unimanual pinch tasks, single TMS pulse (Magstim 200; Magstim Company Ltd., Whitland, UK) was delivered over the right M1, the representational area of the left first dorsal interosseous (FDI) (Fig. 4.1), during the hold phase of each compression force. Participants sat comfortably with the right forearm supported with a foam cushion. Their left arm and hand rested comfortably and was supported by pillows. A Lycra cap with 1cm grids was used to determine appropriate and consistent placement of the coil to search motor hot spots. A figure of eight coil (70mm diameter) was placed tangentially with handle pointing backwards and laterally 45 degrees from the midline so that the magnetic current was perpendicular to the central sulcus (Mills, Boniface, & Schubert, 1992). The coil was initially placed 5cm laterally and 2cm anteriorly from the vertex, and moved by 1 cm increments while searching for the motor hot spot at which the greatest motor evoked potential (MEP) responses from the left FDI occurred at the lowest stimulus intensity. The resting motor threshold (RMT) was determined as the minimum intensity that induced a peak MEP greater than 50μV in the left FDI for 5 out of 10 trials. Finally, single pulses were delivered over the right M1 of the hot spot of the left FDI at 120% of the RMT when the participant was maintaining compression force. A total of 20 trials were collected per condition.

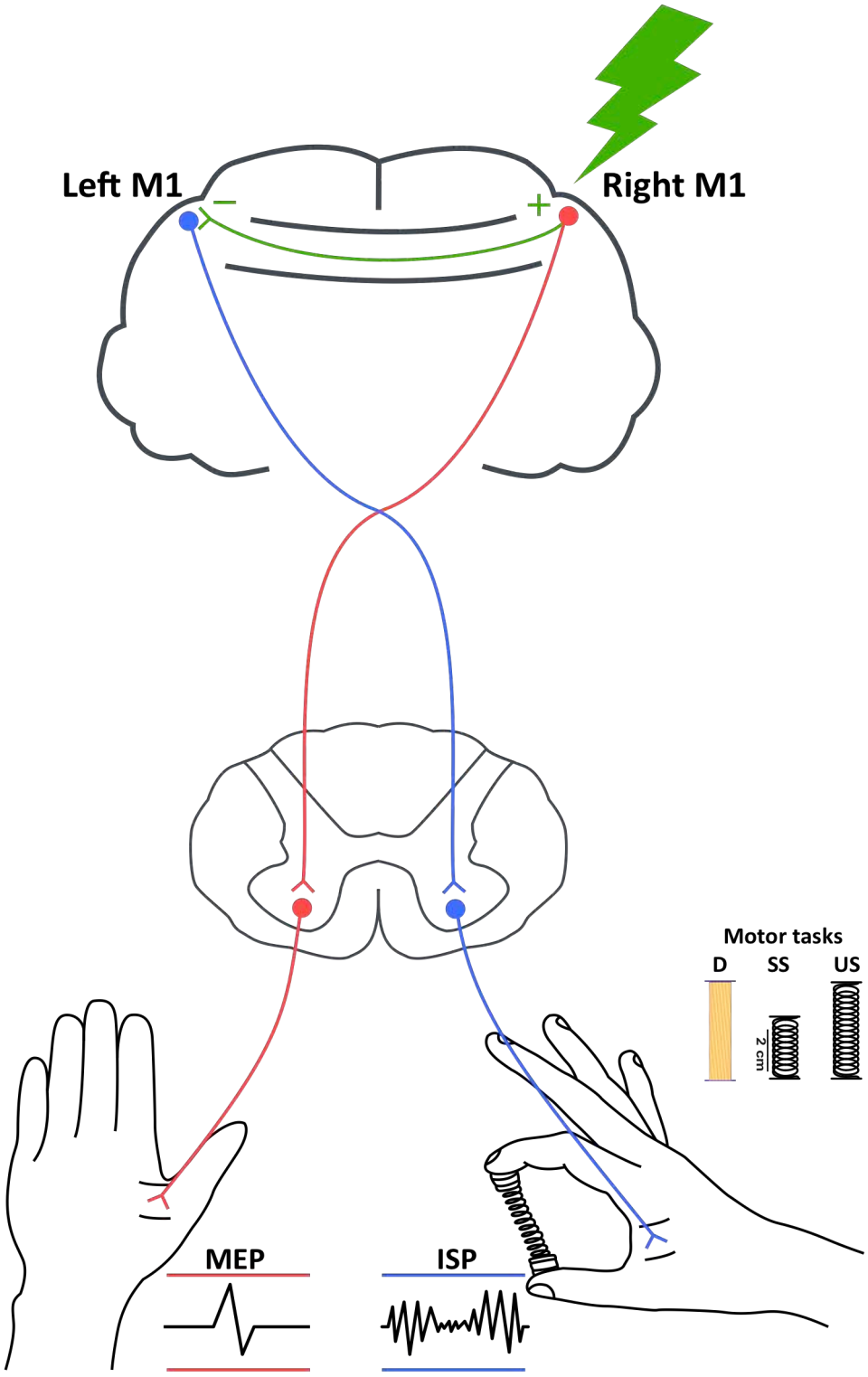

Figure 4.1. Experimental setup. Participants perform pinching tasks with three objects with the right hand while single TMS pulses are delivered over the right M1. MEPs are measured in the resting left FDI, and ISPs are measured in the right FDI. (MEP: motor evoked potential, ISP: ipsilateral silent period, D: dowel, SS: stable spring, US: unstable spring).

Active surface EMG sensors (Motion Lab Systems, Inc., Baton Rouge, LA, USA) amplified and band pass filtered the EMG signals at 15 to 3500Hz. The EMG data were acquired at 14993Hz and collected using the CED 1401 interface unit associated with the Signal 2 software (Cambridge Electronic Design, UK). The EMG electrodes recorded the EMG signals over the muscle belly of right and left FDI to record MEPs, EMG mirror activity in the left FDI, and ongoing EMG activity in the right FDI.

Data process and analysis

Peak-to-peak MEP in the left FDI. The mean peak-to-peak amplitude of each MEP in the resting left hand was quantified and averaged across trials for each participant. The mean peak-to-peak MEPs of all conditions were normalized per individual with respect to the amplitudes recorded during the dowel condition. The dowel condition was used as a baseline because the constant level of muscle contraction resulted in consistent motor responses with decreased signal variability compared with the inactive rest condition (Bestmann & Krakauer, 2015; Kiers, Cros, Chiappa, & Fang, 1993).

Mirror EMG activity in the left FDI. Mirror EMG activity in the resting hand can be induced in healthy adults during demanding unimanual tasks, and mirror EMG activity in the left FDI may associate with increased corticospinal excitability in the right M1 (Addamo, Farrow, Hoy, Bradshaw, & Georgiou-Karistianis, 2007; Cincotta & Ziemann, 2008; Hoy, Fitzgerald, Bradshaw, Armatas, & Georgiou-Karistianis, 2004). Therefore, we measured the amount of mirror EMG activity in the resting left FDI during precision pinch tasks. To measure mirror EMG activity in the left FDI while the right hand was performing the pinch tasks, we quantified the standard deviation (SD) of the

left muscle activity during the one-second period immediately preceding the pulse. The mean SD of muscle activity of all conditions was normalized to the dowel condition, as above.

EMG activity in the right FDI during motor tasks. High isometric contraction of finger muscles of one hand elicited greater MEPs in M1 ipsilateral to the hand (Liepert et al., 2001; Muellbacher, Facchini, Boroojerdi, & Hallett, 2000). Although force levels were low (<3N) and identical across the conditions per each subject, it is possible that the muscle activity levels might be varied by more of less co-contraction finger muscles required by each condition. Therefore, we quantified the SD of the right muscle activity during the one-second period immediately preceding the pulse. The mean SD of muscle activity of all conditions was normalized to the dowel condition.

Ipsilateral silent periods in the right FDI. To quantify the ipsilateral silent period associated with interhemispheric inhibition, we first rectified the EMG activity recorded from the right FDI during object compression and averaged these traces across trials. The average rectified EMG trace was then recast as z-scores with respect to the values observed in the one second time period immediately prior to pulse deliver. For each participant and condition, we were able to calculate the magnitude of any pulse-related reduction in EMG activity by sum of all z-score values falling below -1.65, 95% confidence level, within the time period of 20-70ms post stimulation. Values below the -1.65 threshold can be said to reflect a significant decrease with respect to the values observed in the baseline period (1s pre-pulse) We chose to test for EMG inhibition within 20 to 70ms post-pulse time period, because it is within this time span where ISPs of the FDI muscle are usually found (Ferbert et al., 1992; Meyer, Röricht, Von Einsiedel,

Kruggel, & Weindl, 1995) and a clear onset and offset of EMG inhibition during object compression at low force levels was difficult to observe.

Statistical analysis

Statistical analyses were carried out offline using custom- MATLAB (MathWorks, Natick, MA, USA) scripts. Because our data were not normally distributed (according to a Lilliefors test), we used non-parametric permutation tests (10,000 iterations) to compare means of peak-to-peak MEPs, mirror activity in the left FDI, and ISP during contraction of the right FDI between conditions. Spearman's rank correlation coefficient (rho) was used to test for any significant correlations between peak-to-peak MEP and mirror EMG activity in the left FDI as well as peak-to-peak MEP and ongoing EMG activity in the right FDI.

Results

Peak-to-peak Motor evoked potentials (MEPs) from the resting left FDI

The mean peak-to-peak MEP amplitude in the resting left FDI was significantly greater during compression of the unstable spring with the right hand as compared to compression of the stable spring, rigid dowel and at rest ($p < 0.001$). The average peak-to-peak MEP during the unstable spring compression was almost twofold of the dowel condition (1.95 ± 0.97, Fig. 4.2). The peak-to-peak MEPs for the stable spring and dowel were also significantly greater than rest ($p < 0.05$) (Fig. 4.2), however, no significant mean difference was found between these two conditions (stable spring to dowel, 1.12 ± 0.31, p=0.79). Eight of ten participants demonstrated greater mean peak-to-peak MEP amplitudes, one had a similar MEP amplitude, and one had a slightly smaller MEP

amplitude during unstable spring compression compared with the dowel condition (Fig. 4.3). For the stable spring condition, five participants demonstrated greater MEP amplitudes, three participants had similar MEP amplitudes, and only two participants had smaller MEP amplitudes as compared with the dowel condition (Fig. 4.3).

Mirror EMG activity in the left FDI

No significant mean difference in mirror EMG activity in the resting left FDI was found among compression tasks, however, mirror EMG activity was generally greater in all tasks as compared to the rest (Fig. 4.4, A).

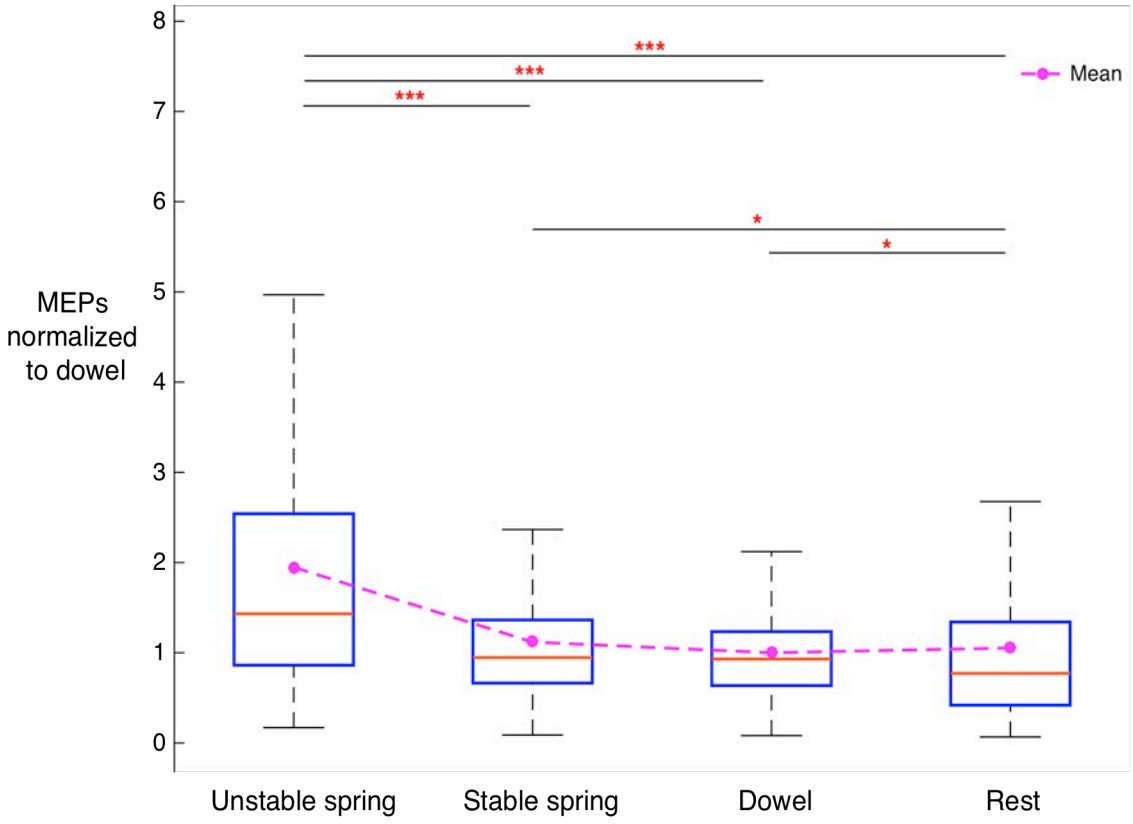

Figure 4.2. Peak to peak MEP from the resting left FDI. The boxplots represent medians and the first and third quartiles of all 200 trials of MEPs per task condition. Each dot represents mean values of all MEPs per task condition. (***$p < 0.001$, *$p < 0.05$, The statistical significant was determined by a 10,000 iteration permutation test.)

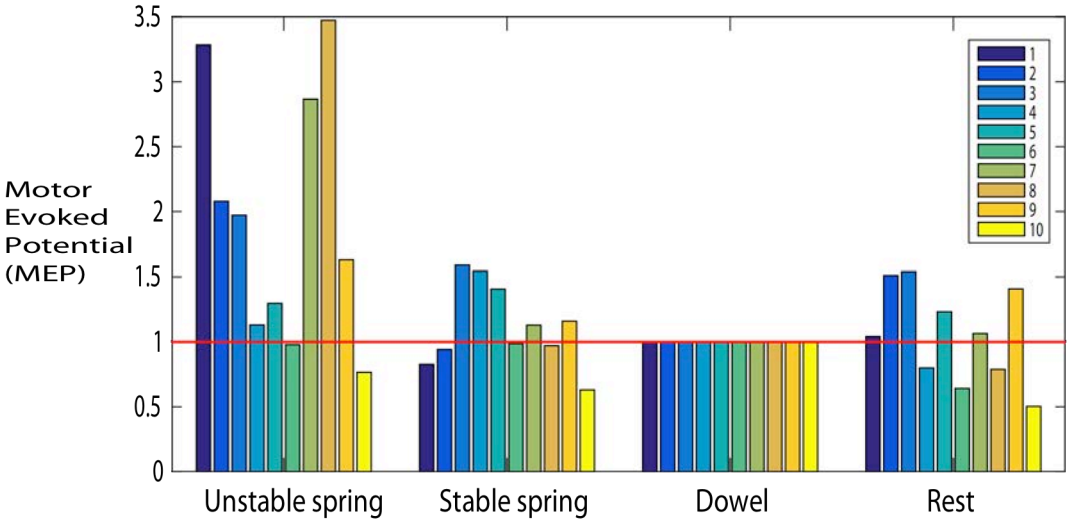

Figure 4.3. The mean peak-to-peak MEP for each individual. MEPs were normalized to the dowel condition. Each bar represents each participant (n=10).

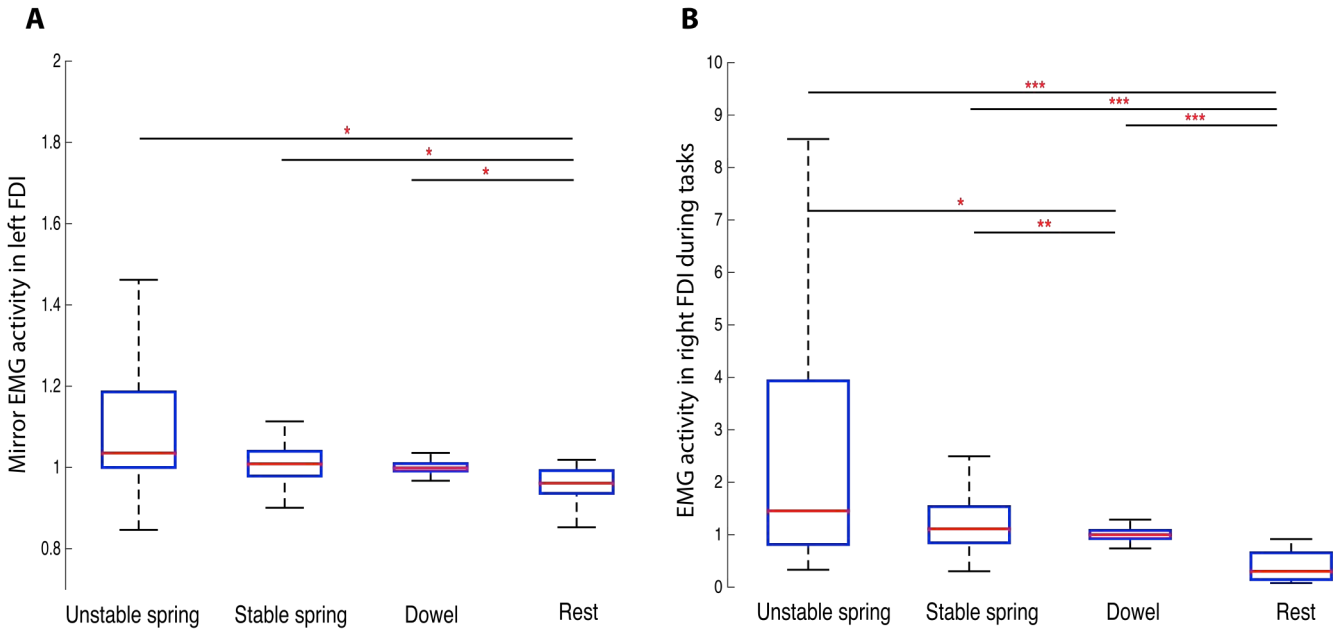

Figure 4.4. EMG activity levels in the left FDI and right FDI. (A) The boxplots of the median and interquartile ranges for the mirror EMG activity in the left FDI. No significant differences were found among tasks. (B) The boxplots of the median and interquartile ranges for the ongoing EMG activity in the right FDI during the motor tasks. No significant difference was found between the unstable and stable spring. The statistical significant was determined by a 10,000 iteration permutation test.
$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$

Muscle EMG activity in the right FDI

There was no significant mean difference in muscle activity in the active right FDI between stable and unstable spring compression (Fig 4.4, B). However, muscle activity during both stable and unstable spring compression was significantly greater compared with the dowel condition (unstable to dowel, p=0.041; stable to dowel, p=0.0022).

Correlations between MEPs and mirror EMG activity in the left FDI

Correlations between average peak-to-peak MEP and mirror EMG activity in the resting left FDI over all trials were very weak for all task conditions (Fig. 4.5) (unstable r^2=0.099, stable r^2=0.037, dowel r^2=0.017), and were inconsistent across individuals (Appendix B).

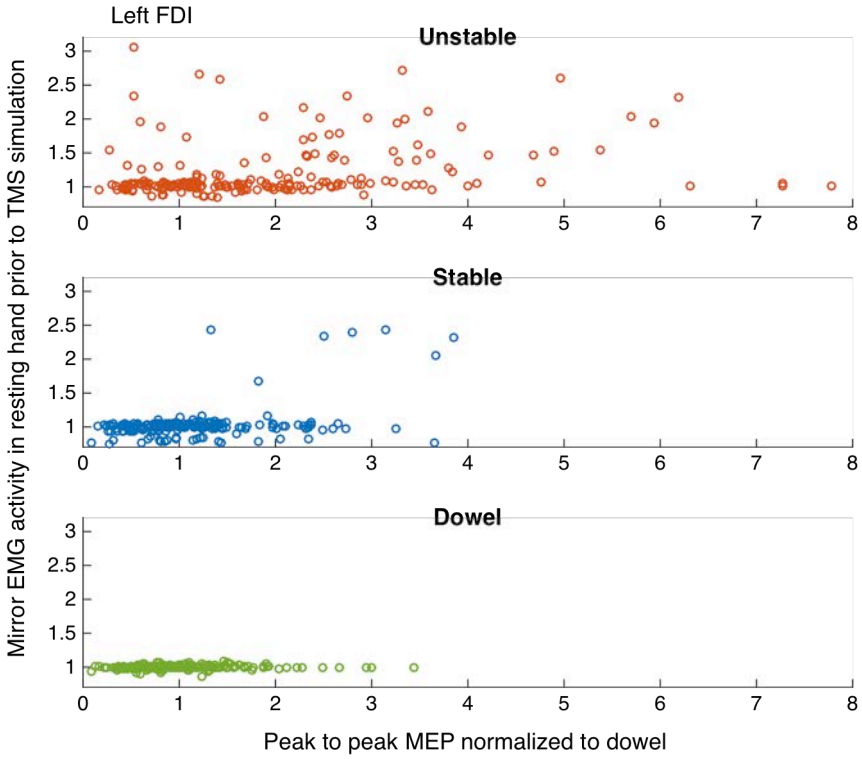

Figure 4.5. Correlations between MEPs and mirror EMG activity in the left FDI. All peak-to-peak MEPs and mirror EMG activity were normalized to dowel. The scatter plots show no strong correlations between MEPs and mirror EMG activity in all task conditions.

Correlations between MEPs and muscle EMG activity in the right FDI

Correlations between average peak-to-peak MEP and ongoing EMG activity in the right FDI over all trials were also very weak for all task conditions (unstable r^2=0.031, stable r^2=0.012, dowel r^2=0.030), and were inconsistent across individuals (Appendix B).

Ipsilateral silent periods (ISPs) in the right FDI

No significant between condition differences in ISP, normalized to the dowel condition, were observed (Fig. 4.6). No consistent changes in ISP among conditions were observed across individuals (Fig. 4.7).

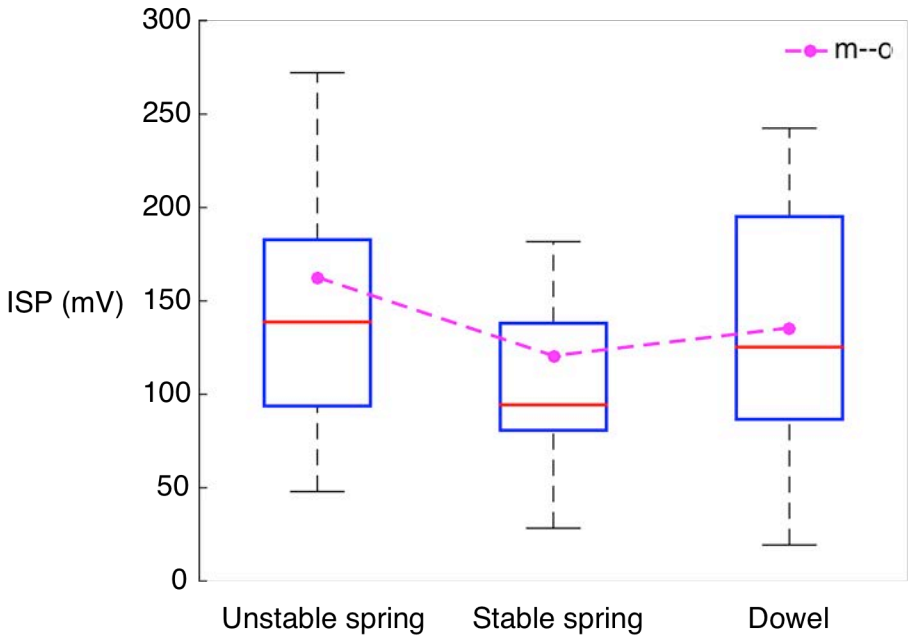

Figure 4.6. The boxplots of the ipsilateral silent periods (ISP). The boxplots show the median and interquartile ranges for ISP. No significant differences were found among three task conditions.

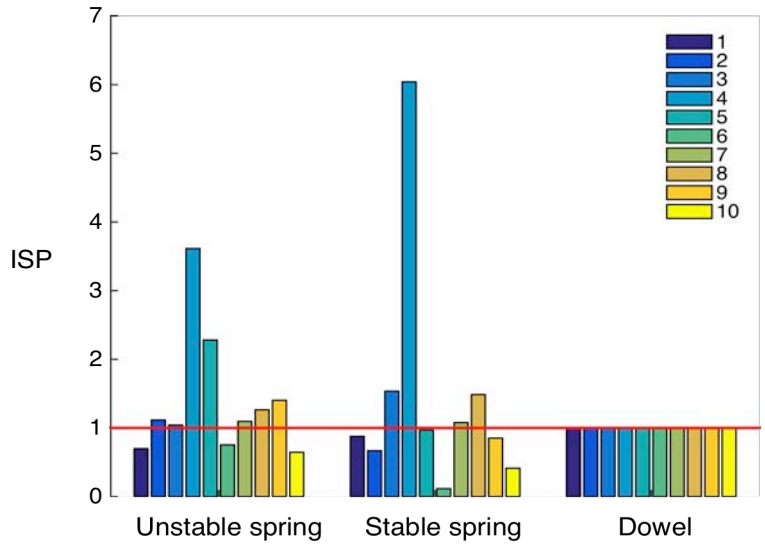

Figure 4.7. The individual data of ipsilateral silent periods (ISP). All ISPs were normalized to the dowel condition. Each color bar represents each participant (n=10). No consistent changes in ISP across individuals were found.

Discussion

The manipulation of an unstable object increased the corticospinal excitability in the ipsilateral M1 as suggested by prior fMRI findings (Holmström et al., 2011; Mosier et al., 2011) presumably due to increased interhemispheric interactions associated with such demanding task. This modulation of corticospinal excitability in the right M1 was not correlated with measures of interhemispheric inhibition (IHI). These findings provide detailed evidence of bilateral neurophysiological mechanisms for the control of dexterous manipulation of unstable objects that are distinct from control of isometric force or coordinated finger movements. We now discuss potential explanations of this task-dependent excitation or disinhibition of the unengaged right M1 by the ipsilateral left M1. We also discuss implications for the design of unimanual dexterous tasks with the less-involved side to promote bilateral recovery in hemiparesis.

Our main result is that using very low forces (<3N) to compress an unstable slender spring with the right hand, induced an almost twofold increase in MEP amplitudes in the resting left hand. This effect was not seen in force-matched compression of a stable slender spring, when compared to a stable rigid dowel. We have shown in the past that compressing the unstable spring is a task with greater dexterity demands; where we define dexterity as the ability to stabilize an unstable object by dynamically regulating the magnitude and direction of fingertip force vectors (Valero-Cuevas et al., 2003; Venkadesan et al., 2007), which is a practical means to asses the integrity of the sensorimotor system (Dayanidhi, Hedberg, et al., 2013). Performing these tasks at the edge of instability requires force corrections at short delays relying on somatosensory feedback but at the same time, the motor system has to plan continuously because the instability increases as the spring is compressed. This sensorimotor control is what distinct these tasks from other less neuromechanically demanding tasks such as finger movement or isometric force control tasks, which involves different cortical, subcortical and spinal networks during this dynamic precision pinch task (Dayanidhi, Kutch, & Valero-Cuevas, 2013; Holmström et al., 2011; Mosier et al., 2011). By probing intercortical interactions with high temporal resolution, these TMS results are the first to reveal that dynamic precision pinch of unstable objects involves distinct interhemispheric interactions.

Previous TMS studies with single pulse paradigm have used finger movement or isometric contractions to investigate changes in corticospinal excitability in the unengaged M1 with a unimanual task with different demands. Unimanual finger movement tasks also increased corticospinal excitability in the ipsilateral M1 to the task

hand, and the increase in excitability was greater with sequence tasks than simple opposition task (Ziemann & Hallett, 2001). Our unstable spring task also involves finger movement, however, the movement is subtle and involved more isolated and coordinated finger movements, maintaining finger posture. Other studies have used single muscle isometric contraction at different force levels (10-100% MVC),, and showed increased corticospinal excitability in the ipsilateral M1 with greater force levels (Ferbert et al., 1992; Hess, Mills, & Murray, 1986; Liang, Funase, Takahashi, Matsukawa, & Kasai, 2014; Liepert et al., 2001). However, our unstable spring task requires very low forces (< 3N), but still showed increased corticospinal excitability. Interestingly, however, a phasic precision pinch task with a stable object, as participants reached to low target forces (1 or 2% MVC), revealed the opposite result of decreased MEP amplitudes in the resting hand (Liepert et al., 2001). These ambiguous and conflicting findings suggest that our unstable spring task is unique, which requires synchronous control of finger movement and force at low forces as well as continuous and time-sensitive modulations of finger forces. The different demands of this uniqueness of the task might influence the modulation of corticospinal excitability in the less engaged M1 because we did not find a significant increase in MEP with the stable spring task of lower dexterity demands.

How does the current understanding of the neuroanatomical structures involved in unimanual precision grip tasks help us understand the increase in corticospinal excitability in the unengaged right M1? This work is in part motivated by our fMRI findings of a bilateral involvement of cortico-striatal-cerebellar network for precision pinch of unstable objects (Holmström et al., 2011; Mosier et al., 2011; E. L. Pavlova et al., 2015; Talati et al., 2005). This bilateral neural network during dynamic precision

pinch tasks would reflect high demands of sensorimotor control of dexterity that requires rapid regulation of dynamic force, because neuromechanically less demanding grip tasks, such as static precision grip tasks, never shown bilateral activity in M1 and seldom show bilateral involvement unless tasks were demanding, for example, gentle grip (requires more refine force control) vs. normal grip force control (Kuhtz‐Buschbeck et al., 2001). The high dexterity demands, especially at the edge of instability, therefore, would require great motor attention focused on the controlling hand. Studies have shown motor attention focused on a muscle and movement (Stefan, Wycislo, & Classen, 2004) and increased precision demands during grip force control (Bonnard, Galléa, De Graaf, & Pailhous, 2007) can increase corticospinal excitability. Further, the increased attention for more demanding tasks can modulate interhemispheric communication (Serrien, Ivry, & Swinnen, 2006). The unstable spring task, therefore, might increase the corticospinal excitability in the right M1 by the greater motor attention derived by great dexterity demands.

There is further evidence of anatomical and functional connections from ipsilaterally neighboring cortical and subcortical areas to M1 and corticospinal pathways in the same hemisphere, which might affect the corticospinal excitability of the unengaged right M1. Animal and human studies agree that M1 is connected to ipsilateral premotor areas, supplementary motor area (SMA), and cingulate motor area (CMA), (Dum & Strick, 2005; Koch & Rothwell, 2009; Matsumoto et al., 2007; Pandya & Kuypers, 1969; Picard & Strick, 1996, 2001) specifically for hand movement control (Dum & Strick, 2005). The posterior parietal cortex is also connected to the premotor areas (Dafotakis et al., 2008; Desmurget et al., 1999; Petrides & Pandya, 1984; Prodoehl

et al., 2009) for possible high-order somatosensory input (Petrides & Pandya, 1984). There is also evidence of transcallosal connections between the homotopical areas of premotor cortex and M1 receiving callosal input from the other side of hemisphere (Boussaoud, Tanné-Gariépy, Wannier, & Rouiller, 2005; O'Shea, Johansen-Berg, Trief, Göbel, & Rushworth, 2007). A combined study of fMRI and TMS also demonstrated potential transcallosal connections between parietal cortex to somatosensory cortex (Blankenburg et al., 2008). The interhemispheric connections among these cortical areas might function vigorously with great dexterity demanding tasks, eliciting bilateral involvement, which would increase the corticospinal excitability in the right M1. These motor areas and posterior parietal cortex directly project to the spinal cord for fine sensorimotor control (Dum & Strick, 1991; He, Dum, & Strick, 1993; Lemon, 2008). These direct projects to the spinal cord might influence excitability in corticospinal tract from the right M1 since there is evidence of subcortical contribution to corticospinal excitability (Gerloff et al., 1998). The basal ganglia, another important neural substrates for grip force control, are also connected to the M1, forming a sensorimotor cortico-striatal loop (Alexander et al., 1986; Prodoehl et al., 2009; Redgrave et al., 2010). These ipsilateral and transcallosal interconnections would easily activate precision grip networks in the right hemisphere, which resulted in increase in corticospinal excitability.

The control of unstable systems is very sensitive to time delays and noise (Milton, 2011; Sipahi, Niculescu, Abdallah, Michiels, & Gu, 2011). As we have argued before (Lawrence et al., 2014), the unavoidable delays and uncertainty that accompany trans-cortical, cortico-spinal or cortico-cortical neural processing must at some level compromise closed-loop control of dynamic precision pinch of unstable objects. This task

tightly coupled with setting the gains of sub-cortical or spinal circuits that produce corrections at shorter delays. There is ample evidence from fMRI, and now from this work, showing distinct modulation of cortical activity in response to instability in the task. Thus future work must seek a way to leverage these task-dependent neurophysiological mechanisms to disambiguate among peripheral, spinal and cortical mechanisms for dexterity.

The fact that we did not detect changes in two accepted metrics of interhemispheric inhibition further informs the distinct bilateral interactions seen during dynamic precision pinch of unstable objects. We saw no changes in mirror EMG activity in the left hand at rest (IHI, left M1 → right M1), or ISP in the EMG of the task right hand (IHI, right M1 → left M1) across pinch tasks. The increased corticospinal excitability in the right M1 indicates excitatory neural drives in the right M1, which there might be due to transcallosal facilitation, disinhibition of IHI or great influence of excitatory neural drive coming from neighboring cortical and subcortical areas from the right hemisphere via ipsilateral and transcallosal interconnections. Mirror movement (MM) is unintended movement in the resting hand during unimanual tasks, which appears to be suppressed by IHI from the active M1 to inactive M1 via transcallosal pathways (Addamo et al., 2007; Cincotta & Ziemann, 2008; Hoy et al., 2004). A positive correlation between MM and corticospinal excitability was reported in Parkinson's disease (Spagnolo et al., 2013), and MM increased with generating greater forces in healthy individuals (Armatas, Summers, & Bradshaw, 1996; Cernacek, 1961). Therefore, we expected to see the increased corticospinal excitability correlated with an increased mirror EMG activity. Interestingly, however, we found neither relative changes in the

mirror EMG activity among task conditions, nor strong positive correlations between mirror activity and MEP amplitudes for all conditions. MM is induced in effortful conditions in healthy adults, which increased with higher forces (Armatas et al., 1996; Cernacek, 1961). If high force levels are main cause of MM, our observations of no changes in mirror EMG activity among tasks seem reasonable because the low magnitude of the pinch forces were low (<3 N) and matched across tasks. Moreover, the lack of correlation between mirror EMG activity and MEP amplitudes in all tasks suggests that different degrees of dexterity demands are less likely influenced by IHI.

The lack of modulation of IHI across pinch tasks was further emphasized by the lack of significant differences in ISP among tasks. Previous studies measured ISP during single muscle isometric contractions at higher force levels (Ferbert et al., 1992; Giovannelli et al., 2009). If ISPs are mostly sensitive to high force contractions, the pinch force level in this study might be too low to detect subtle reduction of the EMG signals. Further, observations of ISP might be also more challenging during dynamic pinch tasks because of rapidly modulating muscle contraction accompanied by dynamic force control, as compared to isometric contraction. Our findings thus suggest that precision pinch at low forces is less influenced by interhemispheric inhibition, but possibly influenced by interhemispheric facilitation or disinhibition. Given that the intensity of the conditioning pulse preceding the test pulse can modulate the degrees of ISP (Ferbert et al., 1992), further investigation is needed to dissociate these mechanisms by, for example, using a TMS paired-pulse paradigm.

Lastly, challenging the sensorimotor system with unimanual precision pinch of unstable objects opens up potentially powerful clinical applications for rehabilitation of

hemiparesis by activating the entire neural network in the less-engaged hemisphere (i.e. "mirroring neural network overflows"). Neurorehabilitation for stroke or cerebral palsy often focuses on improving motor functions in the more affected side, for example, seen in constraint induced movement therapy (Gordon, Charles, & Wolf, 2005; Wolf et al., 2006). However, there is evidence of abnormal neurophysiological function in the intact M1 such as increased IHI in stroke, which is associated with poor motor performance with the paretic hand (Murase, Duque, Mazzocchio, & Cohen, 2004). As altered IHI is from intact M1 to lesion M1 might further hinder motor recovery in stroke (Murase et al., 2004), it is important to restore neurophysiological function in intact M1 as well as balance IHI between two hemispheres. Compressing an unstable spring with the noninvolved hand, for example, may be beneficial not only to maintain neural function of M1 intact side, but also stimulate or disinhibit the involved neural circuits. Non-invasive brain stimulations have been used to up-regulate the lesion M1 to improve motor function (Hummel & Cohen, 2006; Ward & Cohen, 2004), which seems to be effective, however, here we propose a simple pinch task could elicit similar effect, or even better, inducing the entire precision grip network. Additionally, priming the involved neural circuit with non-paretic hand can be used as an adjunct to regular physical rehabilitation to promote better outcomes of the paretic hand function.

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Conflict of Interest

FV-C holds US Patent No. 6,537,075 on some of the technology used in this study that is commercialized by Neuromuscular Dynamics, LLC.

Chapter 5

Conclusion and Future Work

People with PD experience impaired hand function, which affects their independence and quality of life. Dexterous manipulation requires the ability to control dynamic grip force against instability. The Strength-Dexterity (S-D) test, which requires compressing an unstable spring prone to buckling as much as possible, allowed us to measure continuous dynamic grip force control to understand the way in which individuals with PD perform this task.

Neuroanatomical and neurofunctional evidence suggests that the basal ganglia are important neural substrates for grip force control, and behavioral evidence supports this notion revealing deficits in static grip force control in PD. By using the S-D test, we pushed the PD motor system to its limit of performance to maximize expression of abnormal behaviors, with the aim of ultimately developing more sensitive clinical assessments, as there is a need for definitive diagnostic assessment for PD.

In this dissertation, we studied the way individuals with PD performed dynamic grip force control, interrogating differences in force variability between the two hands and its correlation with motor severity, measured by UPDRS motor examination. Further, we tested how sensitive these force measures were to distinguish PD from controls for a potential clinical use for a biomarker. Then, we studied neurophysiological changes in M1 ipsilateral to a manipulating hand with different dexterity demands in healthy individuals to expand our knowledge of abnormal behaviors of in PD during dynamic grip force control and to propose future studies.

Our results from the series of studies suggest that measures of force variability during dynamic grip force control, when stabilizing an unstable spring at the edge of instability, are useful and have potential for a clinical use as an adjunct to current standard clinical assessments. This unique unimanual task utilizing an unstable spring facilitates corticospinal excitability in M1 ipsilateral to the task hand. which is poorly explained by the effect of interhemispheric inhibition (IHI). There was no modulation in IHI among tasks with different dexterity demands, when measured by mirror EMG activity in the resting hand and ipsilateral silent period (ISP) in the task hand. This suggests that the neural mechanisms underlying dynamic grip force control might be different from those for simple finger movement or single muscle isometric contractions, as modulation of IHI was found with task difficulty during these tasks. This conflicting finding prompts us to discuss and suggest future studies.

The increased force variability during dynamic grip force control in PD might be influenced by altered neurophysiological function, especially in M1 because it is the final cortical output for descending pathways to generate movement. Multiple studies suggest that there is a general decrease in inhibition in PD and imbalanced IHI between the more- and less-affected hands (Cantello et al., 1991; Cantello et al., 2007; Ridding et al., 1995; Spagnolo et al., 2013). Decreased cortical inhibition was also associated with motor severity or presence of mirror movement (Cantello et al., 2007; Li et al., 2007; Spagnolo et al., 2013). Using the same protocols of our previous study (chapter 4), we can examine 1) if there is modulation of neurophysiological function with different dexterity demands: dynamic grip force control with a dowel, stable spring, or unstable spring and 2) differences in corticospinal excitability in ipsilateral M1 between more-affected and less-

affected hand performance. In addition, if we measure this ipsilateral M1 corticospinal excitability during the unstable spring task at 95% of maximal instability, abnormal neurophysiological changes would be maximized, which means that abnormal changes are more likely to be detectable. The measured MEPs can be further correlated with force variability (F_LF and F_HF), mirror EMG activity in the resting hand, and motor severity measured by UPDRS motor scores, to examine if the neurophysiological changes can reflect motor deficits. If we find a positive correlation between force variability and MEPs, it would support the hypothesis, which increased force variability is due to altered neurophysiological function.

As we suggested in chapter 4, a paired-pulse TMS paradigm would be necessary to further investigate if the increased MEP with the unstable spring task was due to reduction in interhemispheric inhibition or interhemispheric facilitation. These mechanisms are dissociable by varying inter-stimulus intervals and stimulation intensity between conditioning and testing pulses (Ferbert et al., 1992; Hanajima et al., 2001; Ugawa, Hanajima, & Kanazawa, 1993). With the same grip tasks, we can measure corticospinal excitability in M1 ipsilateral to the task hand with paired pulse TMS. Furthermore, we speculated that no dexterity-dependent modulation in ipsilateral silent period in the task hand was seen because of low compression force levels (<3N) of grip tasks. Instead of stimulating the right M1 to measure ISP in the task right hand, we can stimulate the left M1 to measure ISP in the left hand with maximal voluntary contraction while performing the task with the right hand. This will allow us to measure changes in IHI coming from the left M1 to right M1, which is influenced by the dexterity demands of the task. This protocol has been used in a previous study (Giovannelli et al., 2009), and

it may be a more practical ways to measure ISP during dynamic and isolated muscle control at low forces.

In conclusion, the paradigm of pushing the motor system to its limit of performance might be useful both clinically and scientifically. We have shown how potentially useful the measures of force variability during dynamic grip force control might be for a clinical assessment and biomarker. We have also expanded current knowledge of the neurophysiological mechanisms underlying dexterous manipulation, which have not been studied before. The findings from the TMS study also suggested the usefulness of this paradigm, pushing the motor system to its limit, for neurorehabilitation for bilateral recovery in hemiparesis such as stroke and cerebral palsy, by increasing corticospinal excitability in the more involved M1 with the non-involved hand.

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Appendix A

Chapter 2. Multiple Regression Analysis

Methods

Multiple linear regressions were performed considering age, gender, equal hand side for handedness and motor symptoms, and hand and non-hand motor severity measured by the UPDRS to predict dynamic fingertip force control for the affected hand in PD. Table A.1 summarized all independent and dependent variables (only for the affected hand). Dummy variables of male and female were generated for gender as well as same and different hand side for handedness and motor symptoms. The statistical significant was set at $p < 0.05$, and the best model for each dependent variable (F, F_LF, and F_HF) was selected based on BIC values. The SPSS version 22 (IBM, Armonk, NY, USA) was used to perform multiple regression analyses.

Results

Mean compression force (F). Different independent variables were selected for each dependent variable to predict the best model. Table A.2 summarized the unstandardized coefficients and significances of three models with three independent variables: age, female, and UPDRS hand motor score, to predict sustained compression force for the affected hand. The model 1 predicted F best based on BIC values, in which only age had a significant main effect on the sustained compression force. The model predicted that the compression force was more likely to increase by 2.56gram force with every year of aging in PD (Fig. A.1).

Standard deviation of force fluctuations <4Hz (F_LF). To predict F_LF (voluntary force fluctuations), only age, UPDRS hand motor score and UPDRS non-hand

motor score were included. Table A.3 summarized the unstandardized coefficients and significances of three models that tested with three independent variables. The model 2 was the best model to predict F_LF, and only UPDRS hand motor score showed a significant main effect. The model predicted that voluntary force fluctuations were likely to decrease by 0.36gf with increase of UPDRS hand motor score (increase of motor impairment), controlling other factors constant (Fig. A.2).

RMS of force at 4-12Hz (F_HF). F_HF was best predicted with UPDRS hand motor and non-hand motor scores. The model 2 was the best model (Table A.4), which predicted that fast and involuntary fluctuations more likely decreased by 0.055 with increase in each score of UPDRS non-hand motor (increase in motor impairment, $p = 0.012$), controlling UPDRS hand score constant (Fig. A.3). Then, the interaction term of hand x non-hand motor score was included as an independent variable since there was an interaction between hand and non-hand motor scores. Interestingly, the main effect of UPDRS non-hand motor score was no longer significant, while UPDRS hand-motor score became significant. When both hand and non-hand motor scores were considered with the model 2, F_HF was increased with increase of both hand and non-hand motor impairment (Fig. A.4).

Table A.1. Descriptions of all variables for multiple regression analysis

Independent variable name	Description	Metric	Mean/frequency	SD	Percent distribution
Age	Participants' age	Numeric (years)	70.0	6.2	----
Gender	Gender of participants	Male = 0 Female = 1	Male (n) = 18 Female (n) = 21	----	Male, 46.2% Female, 53.8%
Same hand side	Whether dominant hand and affected hand are equal or not	Same = 0 Different = 1	Same (n) = 27 Different (n) = 12	----	Same = 69.2% Different = 30.8%
UPDRS hand score	UPDRS motor scores for hand related items	Numeric	10.77 (range: 4-17)	3.53	----
UPDRS non-hand score	UPDRS motor scores for non-hand related items	Numeric	14.98 (range: 0-28)	7.53	----
Dependent variable name	**Description**	**Metric**	**Means**	**SD**	**Percent distribution**
F	Three maximal compression force	Numeric (gram force)	180.00	47.23	----
F_LF	Standard deviation of force at low frequency (<4Hz) during a hold	Numeric (gf)	5.15	3.08	----
F_HF	Root mean square of force at high frequency band (4-12Hz) during a hold	Numeric (gf)	1.14	0.85	----

Table A.2. Unstandardized coefficients and significances for the multiple regression models on sustained compression force (F) in the affected hand.

	Model 1		**Model 2**		**Model 3**	
Constant	.262		-31.473		2.631	
Age	2.562	*	2.832	*	2.814	*
Female	----		23.725		22.419	
UPDRS hand	----		----		-2.981	
R^2	0.10		0.17		0.22	
df	1		2		3	
BIC	-0.59		0.23		1.50	

N=39, *$p < 0.05$

Figure A.1. Estimated sustained compression force (F) with aging in the affected hand.

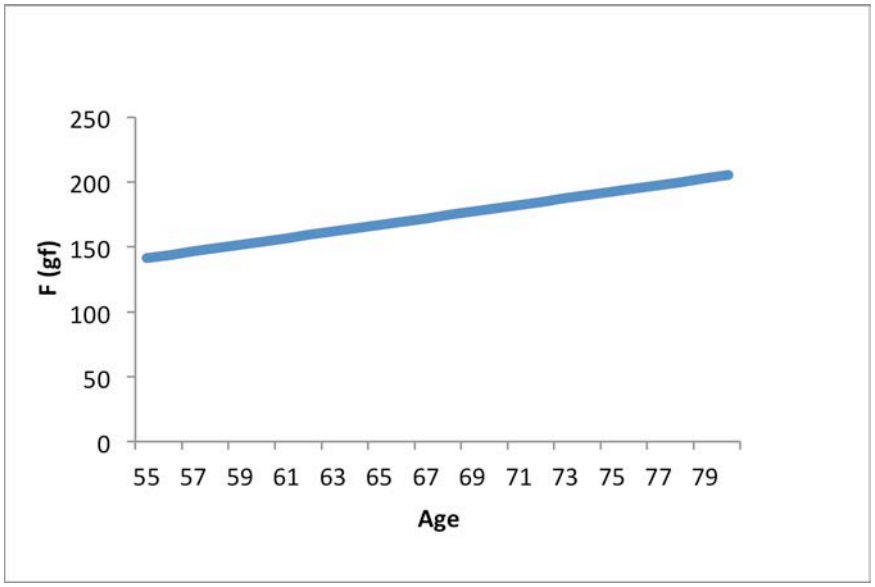


Table A.3. Unstandardized coefficients and significances for the multiple regression models on voluntary force fluctuations (F_LF) in the affected hand.

	Model 1		**Model 2**		**Model 3**	
Constant	5.519		9.443		9.338	
Age	-.005		-.006		-.004	
UPDRS hand	----		-.362	*	-.353	*
UPDRS non-hand	----		----		-.007	
R^2	0.00		0.17		0.17	
df	1		2		3	
BIC	3.66		-.061		3.59	

N=39, *$p < 0.05$

Figure A.2. Estimated voluntary force fluctuations (F_LF) by UPDRS hand score in the affected hand.

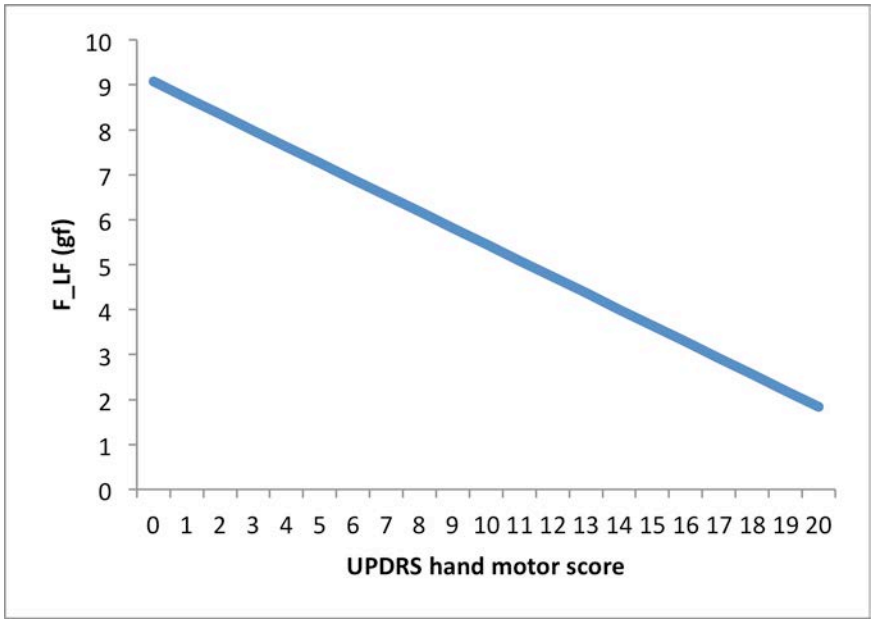


Table A.4. Unstandardized coefficients and significances for the multiple regression models on involuntary force fluctuations (F_HF) in the affected hand.

	Model 1		**Model 2**		**Model 3**	
Constant	1.067		1.129		-.162	
UPDRS hand	.006		.073		.203	*
UPDRS non-hand	----		-.055	*	.046	
UPDRS hand*non-hand	----		----		-.009	
R^2	0.001		0.16		0.22	
df	1		2		3	
BIC	3.64		0.33		1.26	

N=39, *$p < 0.05$

Figure A.3. Estimated involuntary force fluctuations (F_HF) by UPDRS non-hand motor score in the affected hand.

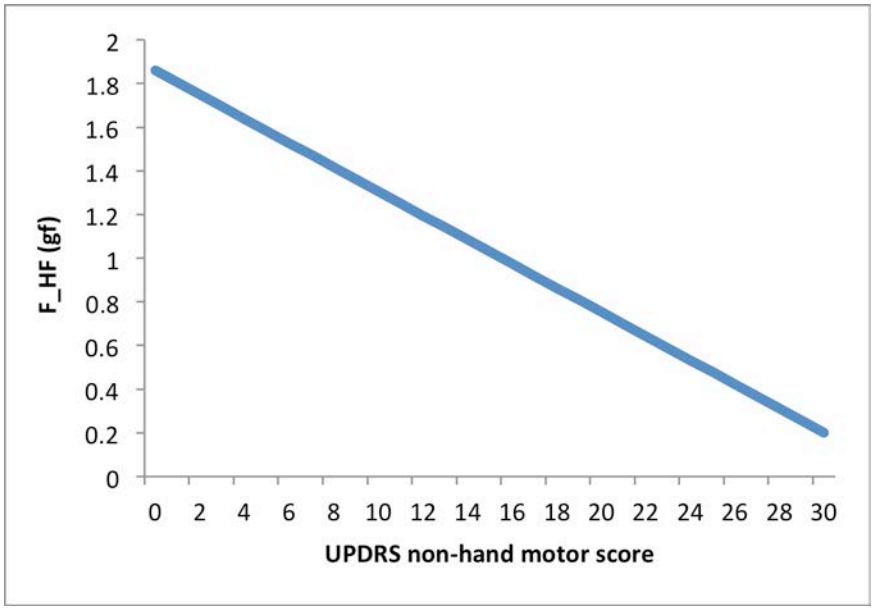
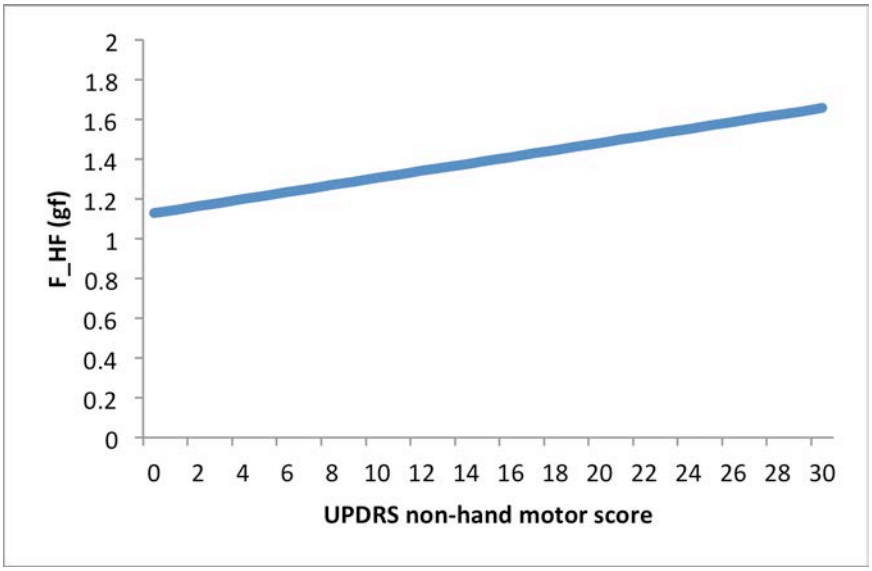


Figure A.4. Estimated involuntary force fluctuations (F_HF) by both UPDRS hand motor and non-hand motor scores in the affected hand.



Appendix B

Chapter 4. Additional figures

Figure B.1. Spearman's rank correlation coefficients (rho) between the MEPs and left mirror EMG activity of each individual. Red lines indicate the individuals with a significant rho. The figure shows inconsistent correlations across participants and among tasks within participants.

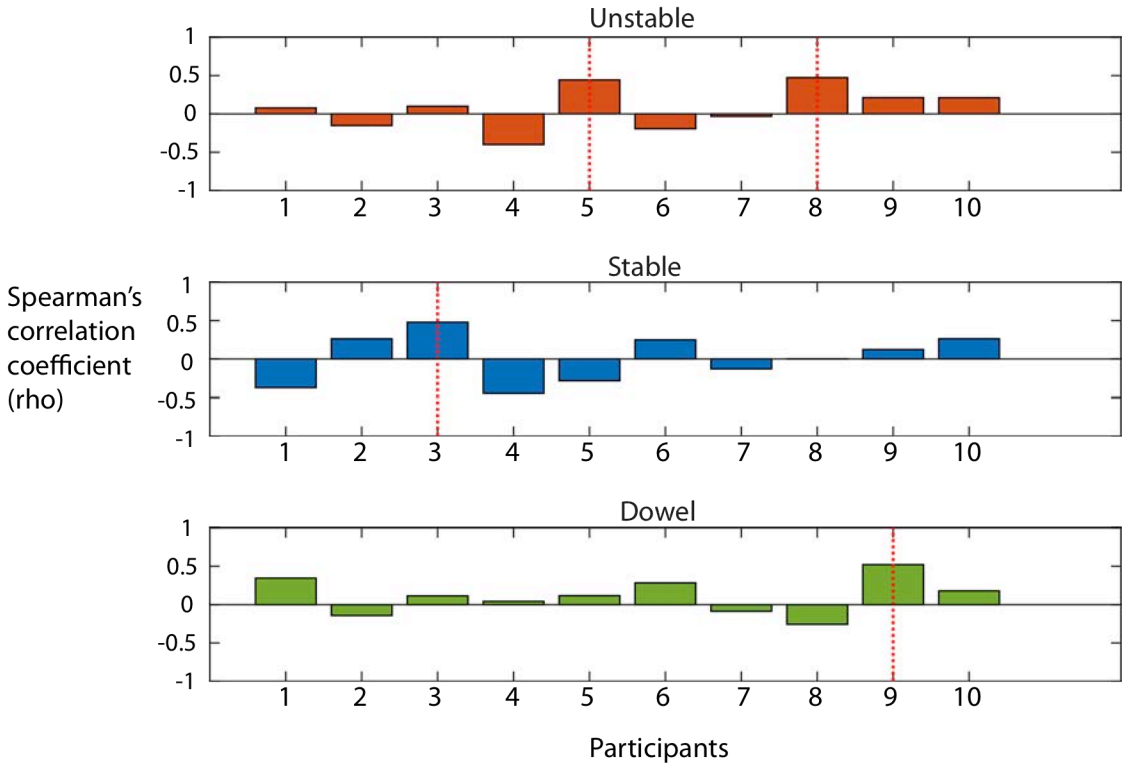


Figure B.2. Correlations between MEPs and ongoing EMG activity in the right FDI. All peak-to-peak MEPs and mirror EMG activity were normalized to dowel. The scatter plots show no strong correlations between MEPs and ongoing EMG activity during all tasks.

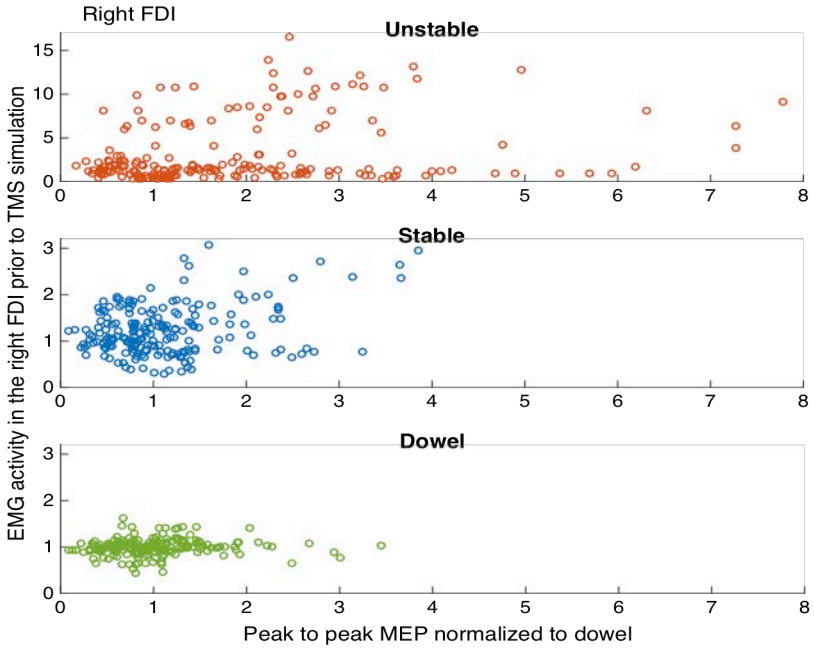
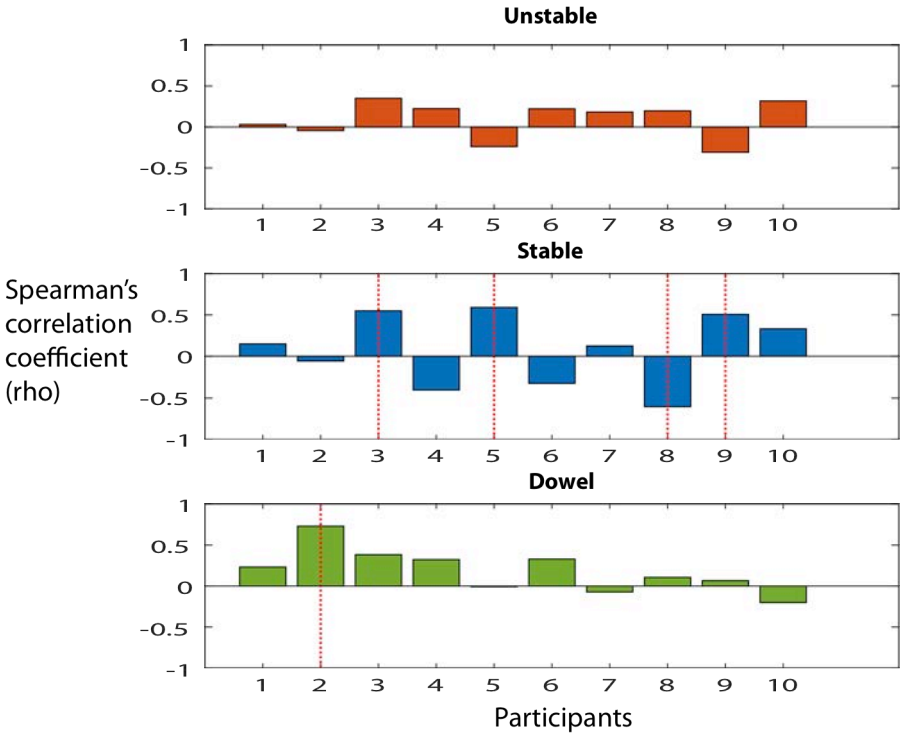


Figure B.3. Spearman's rank correlation coefficients (rho) between the MEPs and right EMG activity of each individual. Red lines indicate the individuals with a significant rho. The figure shows inconsistent correlations across participants and among tasks within participants.



Appendix C

Paper published in *Frontiers in Aging Neuroscience*

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ORIGINAL RESEARCH
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Force variability during dexterous manipulation in individuals with mild to moderate Parkinson's disease

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Parkinson's disease (PD) is a progressive neurodegenerative disease affecting about 1–2% of the population over the age of 65. Individuals with PD experience gradual deterioration of dexterous manipulation for activities of daily living; however, current clinical evaluations are mostly subjective and do not quantify changes in dynamic control of fingertip force that is critical for manual dexterity. Thus, there is a need to develop clinical measures to quantify those changes with aging and disease progression. We investigated the dynamic control of fingertip forces in both hands of 20 individuals with PD (69.0 ± 7.4 years) using the Strength–Dexterity test. The test requires low forces (<3 N) to compress a compliant and slender spring prone to buckling. A maximal level of sustained compression is informative of the greatest instability the person can control, and thus is indicative of the integrity of the neuromuscular system for dexterous manipulation. Miniature sensors recorded fingertip force (F) during maximal sustained compressions. The force variability during sustained compression was quantified in two frequency bands: low (<4 Hz, F_LF) and high (4–12 Hz, F_HF). F_LF characterizes variability in voluntary fluctuations, while F_HF characterizes variability in involuntary fluctuations including tremor. The more-affected hand exhibited significantly lower F and lower F_LF than those in the less-affected hand. The more-affected hand showed significant negative correlations between F_LF and the Unified Parkinson's Disease Rating Scale motor scores for both total and hand-only, suggesting that greater force variability in the voluntary range was associated with less clinical motor impairment. We conclude the nature of force variability in the voluntary range during this dynamic and dexterous task may be a biomarker of greater motor capability/flexibility/adaptability in PD. This approach may provide a more quantitative clinical assessment of changes of sensorimotor control in individuals with PD.

Keywords: Parkinson's disease, sensorimotor control, fingers, dexterity, dynamic force control, force variability, clinical evaluations

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Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease in the United States, affecting about 1–2% of the population over age of 65 (Guttmacher et al., 2003; de Lau and Breteler, 2006; Weintraub et al., 2008). Loss of hand dexterity and impaired sensorimotor control of grip force have been reported in PD (Gordon et al., 1997; Ingvarsson et al., 1997; Fellows et al., 1998; Gordon, 1998; Nowak and Hermsdörfer, 2006; Lawrence et al., 2014; Lukos et al., 2014).

The gradual impairment of dexterous manipulation leads to difficulties in daily activities, such as buttoning, eating, extracting money from a wallet, or signing a check (Lukos et al., 2014). Loss of these abilities will negatively impact qualify of life (Lukos et al., 2014).

The Unified Parkinson's Disease Rating Scale (UPDRS) is the most well-established and accepted assessment in PD (Ramaker et al., 2002; Goetz et al., 2008). The motor examination portion of the UPDRS (part III) provides a global motor severity score, but does not measure force control. The ability to dynamically regulate both the magnitude and direction of fingertip force vectors is fundamental for dexterous manipulation (Cole and Abbs, 1988; Valero-Cuevas et al., 1998, 2003), and can be revealing of sensorimotor processing capability in older adults (Dayanidhi and Valero-Cuevas, 2014; Lawrence et al., 2015). This ability progressively deteriorates with the progression of PD, but the physiology of this process is not well understood. Therefore, it is critical to develop a sensitive measure of the neural control of fingertip force vectors in PD. Such a measure would add an informative and currently missing component to the current set of clinical assessment tools used for PD.

In the past, quantification of dynamic dexterous manipulation ability in PD has been difficult because of lack of appropriate techniques (Lukos et al., 2014). The Strength–Dexterity test was developed to quantify dynamic dexterous manipulation in general, and has been used to measure finger dexterity in healthy individuals (4–89 years) and those suffering from pathological conditions, such as carpometacarpal osteoarthritis, PD, and children with pollicized hands (Vollmer et al., 2010; Dayanidhi et al., 2013; Dayanidhi and Valero-Cuevas, 2014; Lawrence et al., 2014; Lightdale-Miric et al., 2015). The previous study of dynamic dexterous manipulation in PD, however, did not consider different degrees of motor symptoms between the hands (Lawrence et al., 2014) despite the fact that lateralized motor impairment is common in PD (Lukos et al., 2014). Differences in dynamic force control between the more- and less-affected hands could be highly informative, given that motor symptoms likely affect dynamic dexterous manipulation.

Measures of dynamic force control during the Strength–Dexterity test might reveal sensorimotor impairment in PD. fMRI studies have shown that the basal ganglia are active during the sustained spring compressions of the Strength–Dexterity test (Mosier et al., 2011; Pavlova et al., 2015) (in press). In addition, the blood–oxygen-level dependent (BOLD) signals in the putamen increased as the spring became more unstable (Mosier et al., 2011). Given that disruption of the basal ganglia result in motor impairment in PD, and that the basal ganglia are known to be involved in the spring task, it is likely that measuring the dynamic control of fingertip forces during performance of the Strength–Dexterity test may provide a sensitive index of manual sensorimotor control in PD.

Therefore, the purpose of this study was to explore differences in dynamic control of fingertip forces between the more-affected and less-affected hands in individuals with PD. If such differences exist, it would indicate that measures of force during the spring task hold a potential as markers of symptom severity that may not be evident with traditional clinical testing. As a further evaluation of this potential, spring force measures were correlated with the well-established clinical assessment of motor impairment, the UPDRS. Thus, we respond to the goal of this Research Topic to develop clinical measures to enable future studies of the mechanisms of declining motor control in aging and disease.

Materials and Methods

Participants

A total of 20 individuals with PD (69.0 ± 7.4 years, 11 M, 9 F) participated in the study. Given the observational, cross-sectional nature of this study, we included patients with a diagnosis of PD who were functionally independent (regardless of their medication status) and demonstrated intact cognitive functions and excluded patients with musculoskeletal symptoms including pain and fatigue as well as a history of other neurological disorders and surgical procedures affecting the thumb and index finger. The study was approved by the Institutional Review Board at the University of Southern California. Informed consent was obtained from all participants. The average disease duration for 20 individuals with PD was 6.0 years ($\pm$4.1 years), and all participants were physically independent and Hoehn and Yahr stages 1–3. Eighteen participants were on PD medications while two participants did not take PD medications. We included participants both on- and off-medication because our study represents a cross-sectional and exploratory investigation of dynamic fingertip force control in the general population of functionally independent patients with PD. The more-affected side was determined by UPDRS motor examination and self-report from patients asked, "*which hand has been giving you more trouble in daily activities?*" UPDRS motor scores were only obtained from a subset of 13 patients. Thus, the more-affected side was self-reported from seven patients whose UPDRS scores were not available and also from two patients whose UPDRS scores were the same for both hands. Handedness was also measured by the Edinburgh Handedness Inventory at the screening. However, a subsequent multiple regression analysis revealed handedness did not influence dynamic fingertip force control. This is in line with findings reported for the healthy population (Lawrence et al., 2014).

Instrumentation for Dynamic Fingertip Force Measurement

The Strength–Dexterity test was used to measure dynamic sensorimotor control of fingertip force from the thumb and index finger. The test required compressing a slender spring with the thumb and index fingers without allowing it to buckle (**Figure 1**) (Valero-Cuevas et al., 2003; Dayanidhi et al., 2013). The specifications of the custom spring (Century Springs Corp., Los Angeles, CA, USA) were the following: (1) free length = 3.96 cm, (2) solid length = 0.69 cm, (3) force range = 0–2.84 N, (4) stiffness = 0.86 N/cm, and (5) the diameter of end caps were 0.95 cm (**Figure 1**) (Dayanidhi et al., 2013). The spring was designed to be impossible to compress fully, and thus the maximal compression participants could achieve was less than 3N (Dayanidhi et al., 2013). As the spring is compressed, it becomes increasingly unstable in a non-linear way (Venkadesan et al., 2007), making it unpredictable and also making the particular dynamics of each

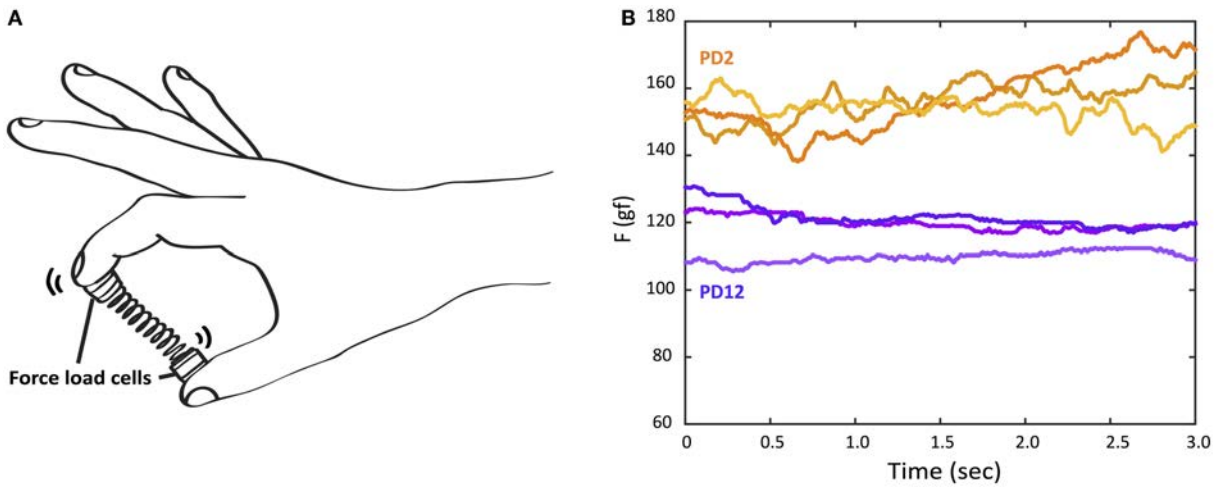

FIGURE 1 | The Strength–Dexterity test and raw force data examples of three trials from the more-affected hand of two PD participants with different UPDRS hand motor scores. **(A)** Participants compress a slender spring prone to buckling as much as they can to its solid length, sustain the compression for 5 s, and release the compression. The force data were recorded from miniature load cells at the tips of spring. **(B)** *Orange lines:* the top three force traces during a hold phase from PD2 with UPDRS (more-affected) hand motor score, 7. *Purple lines:* the top three force traces during a hold phase from PD12 with UPDRS (more-affected) hand motor score, 15.

sustained compression unique. The maximal level of compression that is sustained reflects the integrity of the sensorimotor system, which controls fingertip force and direction during object manipulation (Dayanidhi et al., 2013; Dayanidhi and Valero-Cuevas, 2014; Lawrence et al., 2014).

Experimental Procedure

The participants were seated comfortably with their forearm supported by a foam pad. They were asked to pick up the spring with the thumb and index finger and familiarize themselves with the properties of the spring. As in our prior studies, the number of trials was varied among patients as needed in order to make them familiar with the test and produce relatively consistent performance with each attempt. They were asked to either open or curl the other three fingers so as not to touch or assist the index finger. The instruction given to the participants was "*compress the spring as much as possible without buckling, hold the compression for 5 s, and release the compression*." We measured both affected and less-affected hands. All participants were tested with their less-affected hand first to ensure that they fully understood the task before testing with the more-affected hand. Since the task requires dynamic control of an unpredictable object, it is unlikely that the testing order would influence performance. Only hold periods where force was held stable for at least 3 s were used for further analysis. The goal of the experiment was to obtain the highest compression force possible. The three trials with the highest compression forces (per hand) were used for further analysis. We chose to analyze only the three best trials per subject to minimize potential sources of variance related to learning, task-familiarization, and sub-maximal (overly cautious) efforts.

Data Collection and Analysis

Customized miniature load cells (ELB4–10, Measurement Specialties, Hampton, VA, USA) at the end caps were used to measure fingertip force in the compression direction. The load cells were connected to a signal conditioner and USB-DAQ (National Instruments, Austin, TX, USA). The signals were sampled at 400 Hz with a custom-written MATLAB (MathWorks, Natick, MA, USA) program.

For a particular sustained compression period to be used in further analysis, the compression force was required to remain within 1 SD of mean force recorded during the attempt (Dayanidhi et al., 2013).

In addition to measuring the maximal mean sustained compression force for each trial, force variability was analyzed at two frequency bands to distinguish slow voluntary force fluctuations (<4 Hz) from fast involuntary force fluctuations (4–12 Hz) that include tremor, a well-known symptom in PD. The first was aimed at quantifying voluntary fluctuations in force, produced as the subjects attempted to control the buckling of the spring by dynamically altering the magnitude and direction of their fingertip forces. These voluntary fluctuations occur at low frequencies (<4 Hz) (Miall et al., 1993; Slifkin et al., 2000; Vaillancourt et al., 2001). We quantified them simply as the SD of the sustained compression force after applying a 4 Hz low-pass filter (zero-phase, fourth order Butterworth) to the force. SD is a commonly reported measure because of its simplicity, compatibility with prior literature on force control in PD (Slifkin and Newell, 1999; Vaillancourt et al., 2001, 2002), and lack of dependence on the duration of the hold period or the mean value of the signal. We did remove any linear trend for each sustained compression prior to calculation of SD to prevent it potential inflation by such slow trends. This measure of low-frequency force dynamics is referred to herein as F_LF.

The second measure of force dynamics was aimed at quantifying faster, involuntary fluctuations, which include tremor oscillations and noise from the motor system. For this analysis, the force signal during each sustained compression was band-pass filtered

between 4 and 12 Hz (zero-phase, fourth order Butterworth) and the RMS of the resulting signal was calculated. The RMS of the band-pass filtered force trace gives a value, which is directly comparable and mathematically related to the signal power in the frequencies present. The most common way to quantify "tremor-band" activity is by a measure of spectral power (McAuley and Marsden, 2000; Vaillancourt et al., 2001), thus, our analysis is in keeping with standard methodology while taking advantage of the simplicity and robustness of time-domain calculations of signal variance. This measure of high frequency force dynamics is referred to herein as F_HF.

Statistical Analysis

To quantify differences in each measure of force between the more- and less-affected hands, we first checked all distributions for normality using a Lilliefors test. Force measures that showed non-normal and skewed distributions were normalized using a log transformation before testing for differences of means. To test for differences in means, we used a 10,000 iteration permutation test on paired-differences (Hooton, 1991; Ludbrook, 1994). This test directly determines the probability that the mean paired-difference between two data sets could have occurred by chance (i.e., after randomly changing the sign of each paired-difference). We chose this non-parametric test over a repeated measures ANOVA design for its robustness and lack of assumptions regarding the distribution of variances across subjects and trials. The method directly tests the null hypothesis that hand designation, such as more-affected vs. less-affected, had no effect on the force measurement.

Where differences were found between hands at the group level, we determined the directional consistency of the effect at the subject level by calculating an average difference in each force measure per subject. If significantly more than 50% of subjects showed a directional difference across hands according to a binomial test, we considered the effect to be generalizable at the subject level. If not, we can assume that a subset (e.g., those with more severe symptoms) were primarily responsible for the group effect.

Finally, we tested all force measures – and the magnitude of their differences across hands – for correlation with the UPDRS motor scores obtained for a subset of 13 participants out of the original 20. In particular, we tested for correlation to (i) the entire UPDRS motor score, (ii) the UPDRS hand-only score for the more-affected and the less-affected hands, and finally (iii) the UPDRS motor score excluding all hand scores (non-hand motor score). Given that UPDRS tremor scores have received recent attention as potentially descriptive for PD classification (Stebbins et al., 2013), we also tested our force measures for correlation with UPDRS hand-tremor scores. These were calculated as the sum of the postural tremor, kinetic tremor, and rest tremor amplitude evaluations within the UPDRS. To be conservative, we used the non-parametric Spearman's rho rank correlation, with the significance of each coefficient determined by a permutation test. This test calculated the correlation between force measures and UPDRS scores before and after shuffling the UPDRS score assignments across subjects, replacing the scores from one subject with the scores from another. The probability that the correlation coefficient obtained could have occurred by chance was thus directly calculated from 10,000 sets of shuffled data. This permutation process allowed all 3 trial replicates for the 13 subjects to be used, rather than reducing the data set to 13 mean values. This allowed us to test for the significance of correlations in a conservative and assumption-free way.

In this study, we calculate a large number of correlations. Because each test is deemed significant at the 95% confidence level, we can expect that 5% of independent tests might show significance by chance. This is important if we interpret the occurrence of a single significant result to imply clinical utility for the Strength–Dexterity test. We do not specifically make this claim; nonetheless, we used a binomial test to determine if the number of significant correlations observed could have occurred by chance given the number of statistical tests. The approach directly addresses the problem of multiple comparisons without requiring the global adjustment of confidence levels.

Results

Force Measures

We found significant group differences in dynamic fingertip force control between the more- and less-affected hands during the Strength–Dexterity test. The basic group-level differences in F, F_LF, and F_HF are as follows.

Mean Compression Force (F)

The mean compression force measured from the more-affected hand was significantly lower (i.e., worse) than that of the less-affected hand ($p = 0.019$). Interestingly, although the difference was significant at the group level, 60% of individual participants showed greater (i.e., better) F in the less-affected hand. For 20 participants, 60% is essentially chance-level according to a binomial test, thus, a difference between hands in compression force was not, on average, directionally consistent across PD patients.

SD of Force Fluctuations <4 Hz (F_LF)

The mean of F_LF was significantly lower in the more-affected hand ($p = 0.042$) than in the less-affected hand at the group level. Only 50% of tested individuals displayed greater mean F_LF in the less-affected hand than in the more-affected hand, indicating a subgroup-driven effect rather than a general feature of PD.

Root Mean Square of Force at 4–12 Hz (F_HF)

No significant mean difference was found for F_HF between hands.

The heterogeneity of symptom severity among individuals may have influenced these results and is further explored below at the individual level.

UPDRS Motor Scores and Force Measures

The MDS-UPDRS (the revised version by the movement disorder society) motor examination scores were obtained from 13 of the 20 participants by a trained and certified clinician. Twelve participants were on medication while one participant (PD1) in the early stage of disease voluntarily delayed drug therapy. The total motor scores ranged from 7 to 53 among the 13 participants (**Table 1**). The lower the UPDRS motor scores, the lesser the motor impairment.

TABLE 1 | Clinical characteristics of 13 patients with Parkinson's disease.

PD no.	Age	Sex	Disease duration (years)	Affected hand	H and Y stage	UPDRS motor score			Medication
						Total	More-affected hand	Less-affected hand	
1	70	F	2	R	1	32	12	6	Off
2	70	M	0.4	R	1	7	7	0	On
3	55	F	3	R	1	32	14	6	On
4	66	M	0.33	L	2	26	11	7	On
5	73	F	7	L	2	17	4	3	On
6	76	F	8.75	R	2	27	8	8	On
7	65	F	8	L	2	22	7	5	On
8	72	F	3.75	R	2	53	17	12	On
9	71	M	3	L	2	41	12	9	On
10	68	M	4	R	2	34	9	6	On
11	71	M	4	L	3	52	12	12	On
12	80	M	2.5	R	2	43	15	8	On
13	75	F	7	R	2	28	12	9	On

TABLE 2 | Spearman's rho coefficients (ρ) and *p*-values between UPDRS motor scores and force measures.

UPDRS	More-affected hand						Less-affected hand					
	Total motor		Hand only		Non-hand		Total motor		Hand only		Non-hand	
	ρ	*p*-value	ρ	*p*-value	ρ	*p*-value	ρ	*p*-value	ρ	*p*-value	ρ	*p*-value
F	−0.11	0.35	−0.22	0.23	−0.20	0.25	−0.006	0.49	0.096	0.37	−0.16	0.29
F_LF	−0.44	0.04*	−0.52	0.016*	−0.39	0.062	−0.024	0.46	−0.16	0.24	0.05	0.43
F_HF	−0.26	0.16	−0.14	0.30	−0.42	0.060	0.18	0.25	0.067	0.41	0.16	0.28

Only low-frequency force fluctuation was significantly correlated with the UPDRS total motor and hand-only motor scores.
**p < 0.05, statistical significance was determined by a 10,000 iteration permutation test.*

Correlations Between the UPDRS Total Motor Score and Force Measures (F, F_LF, and F_HF)

Table 2 summarizes Spearman's rho rank correlation coefficients and *p*-values between the UPDRS total motor scores and force measures between two hands at the group level. Only F_LF showed a significant correlation in the more-affected hand ($\rho = -0.44$, $p = 0.04$).

Correlations Between the UPDRS Hand-Only Motor Score and Force Measures

For the UPDRS hand-only motor score, we considered a set of seven hand-related items from the full assessment list: rigidity, finger tapping, hand movements, pronation/supination, postural tremor, kinetic tremor, and resting tremor amplitude. The UPDRS hand-only motor score for the more-affected hands ranged from 4 to 17, and from 0 to 12 for the less-affected hand. Once again, only F_LF ($\rho = -0.52$, $p = 0.016$) showed a significant correlation in the more-affected hand (**Figure 2**). That is, greater variability of voluntary force fluctuations was associated with less motor impairment measured by UPDRS total and hand-only motor scores.

Correlations Between the UPDRS Non-Hand Motor Score and Force Measures

To quantify the general, non-hand related, motor impairment, such as gait and balance, the hand-only motor score for both hands was subtracted from the UPDRS total motor score. The UPDRS motor score without the hand scores negatively correlated with both F_LF ($\rho = -0.39$, $p = 0.062$) and F_HF ($\rho = -0.42$, $p = 0.06$) for the more-affected hand, although these correlations fell just short of statistical significance. Interestingly, these correlations were not found in the less-affected hand (**Table 2**).

Correlations Between the UPDRS Tremor Score and Force Measures

We derived a tremor score per each hand by summing scores from three UPDRS tremor-related items: postural tremor, kinetic tremor, and rest tremor amplitude. The tremor scores ranged from 1 to 7 for the more-affected hand, and 0 to 4 for the less-affected hand. We found no significant correlations between tremor scores and any of our force measures.

Correlations Between the UPDRS Total Motor Score and Between-Hand Difference in F, F_LF, and F_HF

Because only a subset of all participants influenced the group differences in F and F_LF (60 and 50%, respectively), due to heterogeneity of symptom severity among participants, we tested if the between-hand differences in force and force variability for each individual were correlated with overall motor impairment level. **Table 3** summarized Spearman's rho rank correlation coefficients and *p*-values between the UPDRS motor scores and between-hand difference in force measures at the individual level. The between-hand differences in force measures were calculated as the more-affected minus the less-affected hand in magnitude.

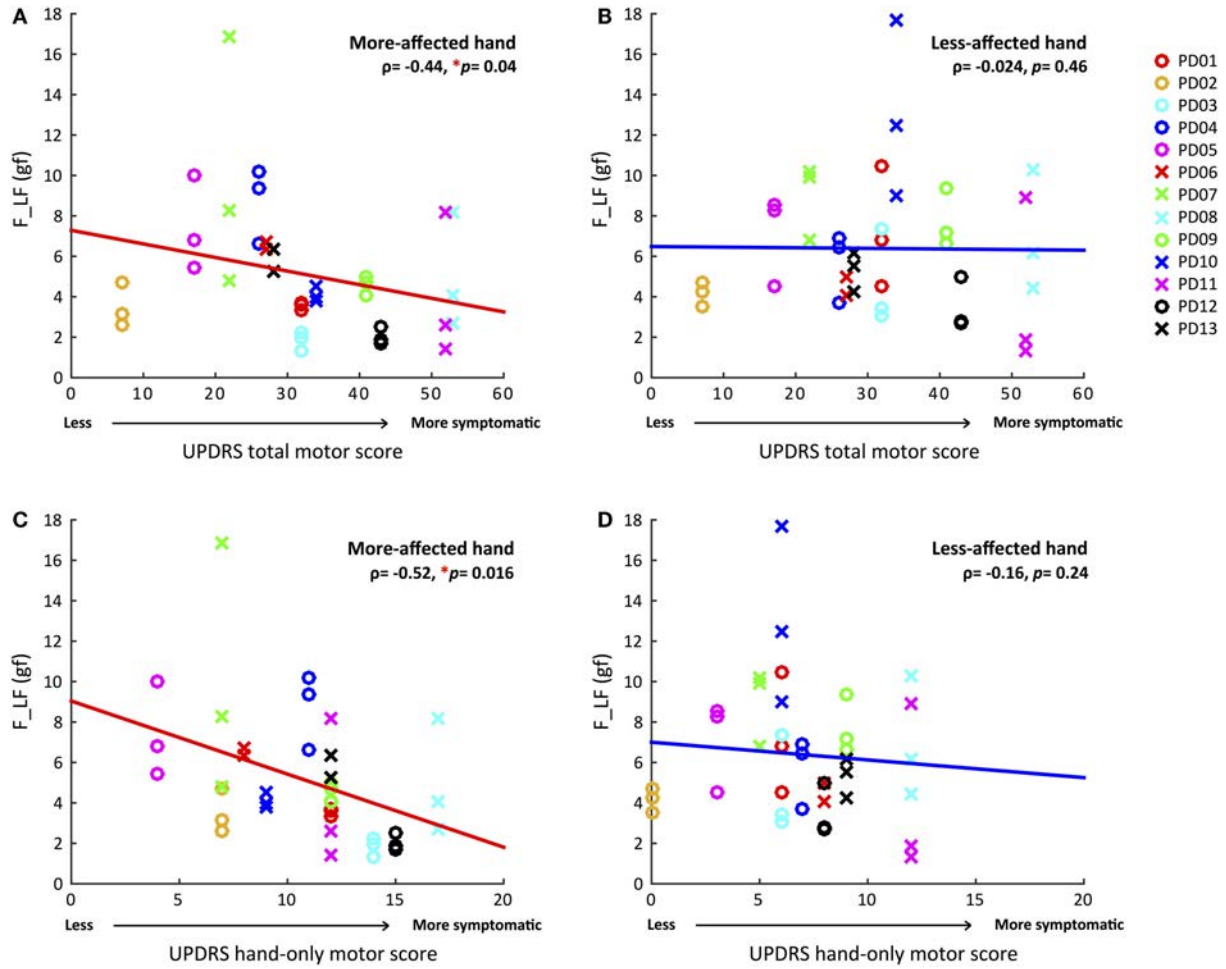

FIGURE 2 | Correlations between magnitudes of voluntary force fluctuations and UPDRS total and hand-only motor scores for both hands. **(A)** Greater voluntary force fluctuations correlated with less total motor impairment in the more-affected hand. **(B)** No significant correlation between voluntary force fluctuations and UPDRS total motor score in the less-affected hand. **(C)** Greater voluntary force fluctuations associated with less hand-related motor impairment in the more-affected hand. **(D)** No significant correlation between voluntary force fluctuations and UPDRS hand-only motor score in the less-affected hand. (*$p < 0.05$, Statistical significance of each Spearman's coefficient was determined by a 10,000 iteration permutation test. The linear fit was only for visual representations.)

A significantly negative correlation was again found only between the overall UPDRS motor score and ΔF_LF ($\rho = -0.46, p = 0.039$) (**Figure 3**). Less difference in F_LF between hands was associated with increased overall motor impairment.

Correlations Between the UPDRS Non-Hand Motor Score and Between-Hand Difference in F, F_LF, and F_HF

We determined if the magnitude of difference in force measures between the two hands were correlated with the more systemic and non-hand-related motor symptoms covered by the UPDRS motor examination. A significantly negative correlation was found for ΔF_LF ($\rho = -0.47$, $p = 0.032$) (**Figure 3**) once again, indicating that decrease in differences between hands corresponded to greater non-hand motor symptom severity, such as impairment of balance and gait. But additionally, ΔF_HF now showed a significant negative correlation ($\rho = -0.48, p = 0.039$) (**Table 3**) with UPDRS, indicating that larger differences between hands in involuntary force fluctuations corresponded to less systemic motor impairment.

TABLE 3 | Spearman's rho coefficients (ρ) and *p*-values between UPDRS motor scores and between-hand difference in force measures.

UPDRS	Total motor		Non-hand motor	
	ρ	*p*-Value	ρ	*p*-Value
ΔF	−0.083	0.38	−0.009	0.49
ΔF_LF	−0.46	0.04*	−0.47	0.032*
ΔF_HF	−0.39	0.076	−0.48	0.039*

*$p < 0.05$, statistical significance was determined by a 10,000 iteration permutation test.

Because a large number of correlations were tested for statistical significance, we used a binomial test (Dodge, 2008) to determine if the overall proportion of correlations exceeding the 95% confidence level was greater than would be expected given the number of tests executed. Many of our tests are not independent,

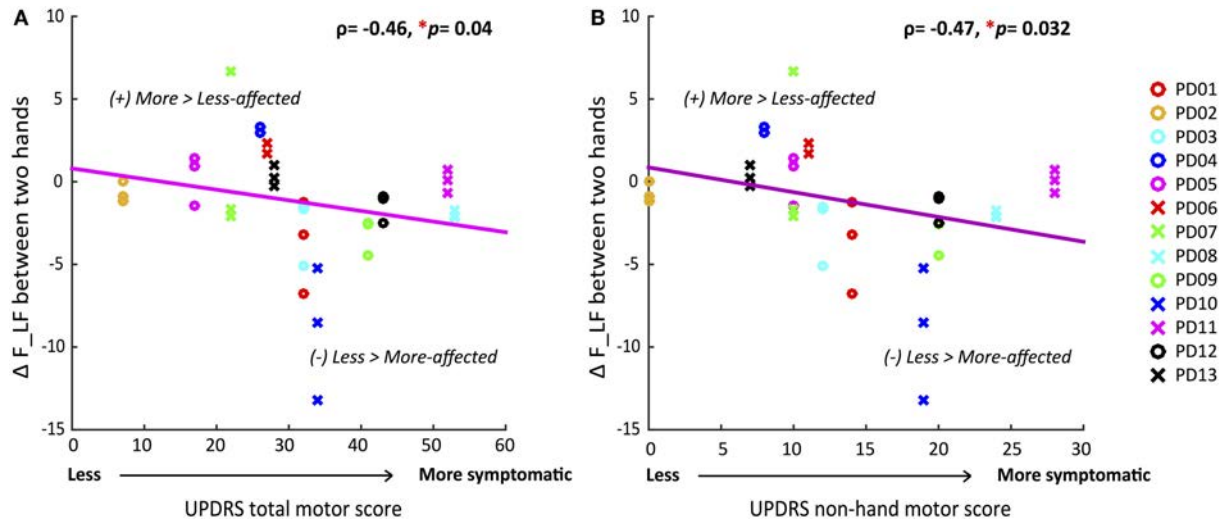

FIGURE 3 | Correlations between differences in voluntary force fluctuations between the more-affected and less-affected hands and UPDRS motor scores. **(A)** Decrease of between-hand difference in AF_LF was significantly correlated with greater total motor impairment. **(B)** Decrease of between-hand difference in AFLF was significantly correlated with greater non-hand motor impairment. (*$p < 0.05$, statistical significance of each Spearman's coefficient was determined by a 10,000 iteration permutation test. The linear fit was only for visual representations.)

however, to be extremely conservative, we assumed 24 independent tests (every test in **Tables 2** and **3**). The binomial probability that we would have obtained five significant results by chance is $p = 0.00019$. Of course, reducing the number of independent tests can only strengthen our results.

Discussions and Conclusion

Measures of dynamic force control during the Strength–Dexterity test, an inherently dynamical and dexterous task, revealed characteristic differences between the more- and less-affected hands in PD, an aging population with progressively declining hand function. The purpose of the paper was to explore force control strategies during a dynamic and dexterous task. Measurements of dynamic finger force may begin to fill the need for more objective and sensitive measures of sensorimotor function to better chart the progression of disease and gage treatment. Note: although we speak of maximal sustained compression forces and variability therein, these maximal forces are all <3 N (<10% maximal static pinch force). The Strength–Dexterity test is predicated on the notion that studying precision manipulation with the fingertips at low force magnitudes while pushing the motor system to a limit of dynamical performance (i.e., the edge of instability) is informative of the integrity and deficits in the neuromuscular mechanisms for sensorimotor control in manipulation (Venkadesan et al., 2007; Dayanidhi et al., 2013; Dayanidhi and Valero-Cuevas, 2014; Lawrence et al., 2014, 2015; Duff et al., 2015).

The main finding of the study concerns the force fluctuations at low frequencies (in the voluntary range <4 Hz, F_LF) seen during the maximal level of sustained compression. We found lower variability at these frequencies was associated with greater severity of motor impairment measured by the UPDRS total and hand-only motor scores. Thus, measures of force variability during the performance of the Strength–Dexterity test hold potential as objective clinical assessment tool in PD, and may be a useful addition to current clinical assessments for characterizing and tracking the severity of both hand and general motor impairment.

Many individuals with PD naturally show greater motor impairment in one hand compared with the other (Jankovic, 2008; Lukos et al., 2014). Because of this, we sought to identify group differences in dynamic force control between the more- and less-affected hands. We found that the more-affected hand compressed the unstable spring with less force and with reduced low-frequency force fluctuations (<4 Hz) compared with the less-affected hand. Slow fluctuations in force relate mostly to active and voluntary strategies and adjustments to stabilize the unstable object. Since the instability of the spring increases with compression force, our finding of decreased compression force in the more-affected hand implies reduced ability to control instability (Venkadesan et al., 2007). This reduced control of instability appears to influence both compression force and force variability. However, our data suggest that compression force and low-frequency force variability may reflect relatively independent aspects of stability control in PD because a subsequent analysis showed no significant correlation between compression force and low-frequency force variability (more-affected side: $\rho = 0.32$, $p = 0.11$, less-affected side: $\rho = 0.25$, $p = 0.2$). Interestingly, force fluctuations at higher frequencies (4–12 Hz), which includes tremor (Vaillancourt et al., 2001; Jankovic, 2008), a well-known symptom in PD, were not different between the two hands. PD may also be classified into tremor dominant and postural instability/gait difficulty groups with UPDRS measures (Stebbins et al., 2013). Given the potential importance of tremor for disease categorization, we also explored the relationship between UPDRS tremors scores and force measures. We found no significant correlations indicating that our measures are not directly affected by tremor symptoms measured in the UPDRS. These findings suggest that force variability during the Strength–Dexterity test is

most sensitive to impairment of voluntary rather than reflexive and involuntary aspects of sensorimotor control.

We examined if the force measures (F, F_LF, and F_HF) reflected hand-specific motor symptom severity. We found that the F_LF, low-frequency force fluctuations significantly negatively correlate with UPDRS measures only in the more-affected hand. This indicates that greater low-frequency fluctuations during the Strength–Dexterity task are associated with less impairment level of the more-affected hand. The same significant correlation was found for the UPDRS total motor score. The UPDRS non-hand motor score showed this same trend, albeit at a non-significant level.

The inevitable diversity of symptom severity in our participants may have affected our group comparisons. Therefore, we analyzed differences in force dynamics between hands. This within-subject analysis showed that it was mostly the participants with greater impairment that exhibited decreased F_LF in the more-affected hand relative to the less-affected hand. This was also the case for the UPDRS non-hand motor score. The latter finding is particularly interesting, because it suggests that ΔF_LF between hands may be indicative of systemic and general motor dysfunction.

Furthermore, the difference in high frequency force fluctuations (ΔF_HF) between hands correlated only with the UPDRS non-hand motor score. It may be that high frequency force fluctuations could reflect mostly systemic and general motor impairment. The magnitude of maximal sustained compression force, F, although different across hands on average, did not correlate well with any UPDRS measure. Thus, force fluctuations during the sustained compressions are likely more informative of neural control capabilities than the level of compression itself.

Given that low-frequency force fluctuations were smaller in hands with greater levels of motor impairment, it is reasonable to speculate that the reduced variability represents a loss of compensatory mechanisms employed by PD patients to control instabilities with the more-affected hand. Previous research showed greater variability in various force generation tasks in PD patients relative to controls (Sheridan et al., 1987; Stelmach et al., 1989; Vaillancourt et al., 2002). While increased force variability in PD might indicate impairment under some conditions, the within-subject design of the present study compels an alternative interpretation of force variability. In some contexts, motor variability may reflect flexibility or adaptability of motor systems (Vereijken, 2010). Variability in a physiological process is thought to be necessary to adapt to unpredictable environmental changes, and this capability decreases with aging (Lipsitz and Goldberger, 1992). In the present task of controlling an unstable compliant object, the correlation between increased clinical motor impairment and reduced force variability may represent a progressive failure of the PD motor system to employ flexible/adaptive strategies for stabilizing the spring. Thus, our findings have important consequences to our understanding of variability and motor impairment in PD because it shows that not all variability is detrimental. We suggest, therefore, that such changes in variability with disease progression during a highly dynamical and complex stabilization task (i.e., as the system is pushed to some limit of performance) are informative of motor impairment in PD.

It is also possible that individuals with PD employ a fundamentally different motor strategy when using their more-affected hand relative to their less-affected hand. The Strength–Dexterity task requires mainly online somatosensory feedback to control the unstable spring. It is reported that in general, individuals with PD rely more heavily on visual feedback to guide motor actions (Cooke et al., 1978; Gordon et al., 1997; Redgrave et al., 2010). We, however, have seen reliance on slower and less effective visuomotor corrections only when tactile sensation is removed in healthy individuals (Venkadesan et al., 2007). Greater reliance on visual feedback could enhance force variability (Shadmehr et al., 2010); however, the advantages and disadvantages of visual strategies in the context of our study are unknown. Thus, it could be that the reduced force variability in the more-affected hand reflects a compensatory adaptation to impaired tactile and proprioceptive control.

The reflexive/reactive/low-level component of dexterous manipulation, however, is relatively preserved in PD. Reactive force control by a perturbation during in-hand manipulation takes about 70 ms (Cole and Abbs, 1988; Johansson and Cole, 1992), and continuous updating of somatosensory information and motor response may even shorten to about 40–50 ms (Johansson et al., 1992). The PD motor system seems to preserve intact neural control for early reflexive responses to the perturbation (Ingvarsson et al., 1997; Fellows et al., 1998). Furthermore, the short latency reflex is intact in PD (Rothwell et al., 1983; Cody et al., 1986). In our study, high frequency force fluctuations, which may reflect this reflexive/reactive/low-level component of task performance, were not different between the more and less-affected hands. Only the difference in this measure between hands was significantly correlated with UPDRS non-hand motor score. This would seem to support the idea that PD influences the active/voluntary/high-level aspects of dexterous manipulation more so than reflexive/reactive/low-level of control aspects.

Interestingly, both ΔF_LF and ΔF_HF between the two hands showed a significant negative correlation with non-hand-related motor scores [i.e., systemic and gross motor function (Lawrence et al., 2014)]. These findings suggest that dynamic fingertip forces measured within the context of a voluntary task may still provide information about the degree of systemic motor impairments, such as alteration of posture, gait, and balance, suggesting some commonality of neural circuitry in the system. Motor impairment in posture, gait, and balance is common in individuals with PD (Jankovic and Kapadia, 2001; Jankovic, 2008; Weintraub et al., 2008). The potential for the Strength–Dexterity test to provide information about systemic and gross motor control is attested to by the findings, in which dexterity measures tended to be correlated between the fingers and legs of an individual (Lawrence et al., 2014).

Measures of dynamic force control within the Strength–Dexterity test reflect the degree of hand motor impairment in individuals with PD, potentially fulfilling the need for more objective measures of sensorimotor function. Measuring force variability when the motor system is pushed to a limit of performance (as in the Strength–Dexterity test) may represent a valuable strategy in assessing motor control in both

health and disease. Our measures appear to be informative of symptom severity in PD; however, further research is required to determine the effects of disease progression and medication level on performance of the Strength–Dexterity test. We also hope to enable future studies of its underlying mechanisms by developing measurements of force variability or other measures of performance during well-defined tasks. Such measures may prove valuable for monitoring changes in motor impairment, determining dosages for medication, appropriate parameters for deep brain stimulation, or even for early detection of PD. What is more, such dynamical tasks may also be used for rehabilitation to improve sensorimotor function in dexterous manipulation in clinical populations by challenging the motor system at the edge of instability.

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