

DEMOGRAPHIC AND CLINICAL COVARIATES OF
SENSORIMOTOR PROCESSING

by

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Epigraph

“We are lucky to be in an age where we are still making discoveries.”

Richard Feynman

Dedication

To my parents for their love and support

Acknowledgements

It is an understatement to say “it takes a village” to be successful during doctoral research. It is a time in one’s life filled with both opportunities and challenges, neither of which are achieved or overcome without the help, support, and guidance of many people. While this dissertation presents my doctoral research, there are a several people who have helped me achieve personal and professional successes behind the scenes. I am honored to have them in my life and would like to take the opportunity to acknowledge them now.

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Abstract

This dissertation focuses on the low force dexterous manipulation capabilities of the fingers and legs and the effects of age, sex, and clinical condition. The Strength-Dexterity (SD) paradigm, based one's ability to compress a slender spring prone to buckling at low forces, allowed us to quantify dexterity in over 300 participants from 15-93 years of age. We find dexterous manipulation capabilities improve significantly during young adulthood, followed by gradual, but significant, declines from the middle age. Interestingly, we find sex differences in both upper and lower extremity dexterity across the lifespan. We also find that clinical conditions (i.e., Parkinson's disease (PD), and thumb osteoarthritis) affect finger dexterity.

Traditional linear analyses (i.e., mean compression force, root mean square of the time series variability, the time derivatives of the force traces, and frequency analyses) can quantify dexterity and have shown limited successes quantifying differences among populations. However, the nonlinear nature of the SD paradigm dictates that nonlinear dynamical analyses must be also considered, particularly when exploring between group differences. Therefore, we incorporate the delayed embedding theorem to reconstruct the attractors from time series data collected

during the SD paradigm. We find that while linear techniques are certainly informative, nonlinear dynamical analyses are much more suitable to discern differences between contributors to dexterous ability (e.g., age, sex, and clinical condition) and among populations (e.g., skilled versus non-skilled athletes and healthy versus pathologic participants).

Chapter 1

Introduction

1.1 Background

1.1.1 Statement of the Problem

The use of the hands and legs and the associated neural control have evolved over millions of years. It began with quadruped ambulation and slowly and systematically there has been a shift to biped locomotion with the hind limbs coupled with more dexterous fore limbs used to manipulate and grasp objects as seen in early man and primates (Johanson, Johanson & Edgar 1994). While the evolution of these features has been well-documented by many groups (Johanson et al. 1994, Young 2003, Tuttle 1967), the underlying neural control strategies and their evolution is less understood. Therefore, it is of interest to understand how such a mechanism can control both the upper and lower extremities, despite their obvious evolutionary, anatomical, and functional differences.

Sensorimotor processing for low force manipulation of both the fingers and legs is an essential component of everyday activities. When considering dexterous manipulation, attention is naturally focused on upper extremity function, however, one must also extend that consideration to the lower extremity (e.g., the ability to appropriately respond to ground reaction forces during ambulation or static and dynamic balance tasks). It is also important to understand the effects of demographic and clinical covariates for sensorimotor processing. It is well-known that neural control strategies for dexterous manipulation, as with many learned skills, are affected by development and aging (Dayanidhi, Hedberg, Valero-Cuevas & Forssberg 2013, Dayanidhi & Valero-Cuevas 2014). Typically developing children begin grasping objects around two to three months (Forssberg, Eliasson, Kinoshita, Johansson & Westling 1991) and walking between one to two years of age (Sutherland, Olshen, Cooper & Woo 1980). On the other end of the age spectrum, declines in hand and leg function are often reported beginning at six decades of life and continue throughout older adulthood (Hackel, Wolfe, Bang & Canfield 1992, Lockhart, Woldstad & Smith 2003, Dayanidhi & Valero-Cuevas 2014, Steffen, Hacker & Mollinger 2002, Woollacott & Tang 1997, Seidler, Bernard, Burutolu, Fling, Gordon, Gwin, Kwak & Lipps 2010).

It is not only important to understand the timeline for development and decline of these abilities, but also the effects of sex and clinical conditions as they

significantly impact performance and exist naturally across the lifespan. For example, there are many reports of sex differences in both upper and lower extremity functional performance. Contributing factors are known to include differences in strength, anatomical structure and function, and hormonal levels (Smith 1994, Lissek, Hausmann, Knossalla, Peters, Nicolas, Güntürkün & Tegenthoff 2007, Wolfson, Whipple, Derby, Amerman & Nashner 1994, Granata, Padua & Wilson 2002, Granata, Wilson & Padua 2002, Franzoi & Shields 1984). However, there are many unanswered questions when considering sex differences in sensorimotor processing ability. The same can be said for the effects of clinical conditions on neural control of the extremities. The functional outcomes are typically investigated, while the underlying neural control strategies are less studied (Hurley, Scott, Rees & Newham 1997, Jankovic 2008, Buck-Gramcko 1971, Kopin 1993, Parks, Geha, Baliki, Katz, Schnitzer & Apkarian 2011).

1.1.2 Research Motivation

1.1.2.1 Aging

Motor performance deficits due to anatomical changes and dysfunction of the central and peripheral nervous systems and the neuromuscular system are commonly associated with healthy aging. One of the most reported physiological changes is sarcopenia, or a reduction of muscle tissue (Lauretani, Russo, Bandinelli,

Bartali, Cavazzini, Di Iorio, Corsi, Rantanen, Guralnik & Ferrucci 2003). However, there are many other age-related alterations in muscle physiology including the enlargement of motor units, distribution of muscle fiber types, variations in muscle synergies, and changes in muscle contractile properties (Woollacott & Tang 1997, Larsson & Ansved 1995, Doherty & Brown 1997). In terms of changes to the nervous systems, there are reports of reduced reflex sensitivity and nerve conduction and changes in neural commands to motoneuronal pools, brain structure, and volume (Seidler et al. 2010, Sowell, Peterson, Thompson, Welcome, Henkenius & Toga 2003, Ge, Grossman, Babb, Rabin, Mannon & Kolson 2002, Dorfman & Bosley 1979). There are also numerous reports of age-related changes in sensory mechanisms (e.g., visual acuity, auditory acuity, proprioception, and cognition) (Li & Lindenberger 2002). These age-related physiological changes typically result in reduced functional performance of both the upper and lower extremities including activities of daily living (ADLs), hand function (i.e., dexterous manipulation), gait, balance, and responses to perturbations (Seidler et al. 2010, Sowell et al. 2003, Dayanidhi & Valero-Cuevas 2014, Woollacott & Tang 1997).

1.1.2.2 Sex Differences

Sex differences in anatomical features and motor control occur at the cortical, subcortical, and peripheral levels in both human and non-human models (Becker,

Snyder, Miller, Westgate & Jenuwine 1987, Beatty 1979, Smith 1994, Zimmerman & Parlee 1973, Lissek et al. 2007). At the brain level, differences in brain structure and connectivity have been investigated with numerous imaging techniques. There are reports of sex differences in activation patterns during motor tasks (Lissek et al. 2007), interhemispheric connectivity (e.g., corpus callosum) (Ardekani, Figarsky & Sidtis 2012), and cortical organization for hand movements (Amunts, Jäncke, Mohlberg, Steinmetz & Zilles 2000). Differences in hormonal levels are responsible for multiple instances of sex differences in motor skills during non reproductive behavior including locomotor activity, hurdle negotiation, and balance beam walking in rats (Becker et al. 1987, Beatty 1979) and arm-hand steadiness (Zimmerman & Parlee 1973) and fine motor control tasks (Hampson & Kimura 1988) in humans. Biomechanical and anatomical differences are also responsible for sexual dimorphism of motor skills and are most often considered in postural stability, balance, or landing tasks (Lephart, Ferris, Riemann, Myers & Fu 2002, Sigward & Powers 2006, Ford, Myer, Toms & Hewett 2005). Despite the well-known sex differences in motor skills and the sexual dimorphism of the motor cortex in humans and non-humans, we find that sex differences in sensorimotor processing in humans are less reported perhaps due in part to i) the inherent complexity of the human sensorimotor system, ii) the confounds of physiological and anatomical based differences (i.e., ligament laxity, hormonal levels, strength, joint angles, etc.), and iii) their restricted access.

1.1.2.3 Clinical Conditions

The effects clinical conditions (e.g., orthopedic and neurological) must be considered when assessing overall quality of life. Many of them are progressive in nature and present during development and in aging. Therefore, is particularly important to consider them separately from effects of age and sex in order to better understand their effects on sensorimotor ability and functional performance. Osteoarthritis of the carpometacarpal joint at the base of the thumb (CMC OA) causes inflammation and anatomical deformity and reduced joint range of motion, strength, motoneuron excitability, and proprioceptive ability (Hurley et al. 1997). More recently, the prolonged exposure to pain due to CMC OA is associated with changes in brain structure including decreases in cortical and subcortical grey matter (Rodriguez-Raecke, Niemeier, Ihle, Ruether & May 2009, Wartolowska, Hough, Jenkinson, Andersson, Wordsworth & Tracey 2012). These physiological effects result in decreased ability to perform ADLs, sensorimotor ability, and in the case of lower extremity OA, postural stability (Hurley et al. 1997, Valero-Cuevas, Smaby, Venkadesan, Peterson & Wright 2003). Progressive neurodegenerative conditions such as Parkinson's disease (PD) are characterized by rigidity, tremor, and bradykinesia due to the degeneration of dopamine-producing cells in basal ganglia (Kopin 1993, Jankovic 2008). As with those with OA, patients with PD typically experience reductions in functional performance and postural stability (Kopin 1993, Jankovic 2008).

1.1.3 Description of Outcome Measures

There are many outcome measures for hand and leg function currently available in both the research and clinical settings. Here the outcome measures considered in this research are described for succinctness as they are repeated throughout this dissertation.

1.1.3.1 Upper Extremity Outcome Measures

Outcome Measure Abbreviations:

- Grip: Grip strength
- Key: Key pinch strength
- Precision: Precision (tip-to-tip) pinch strength
- BBT: Box and Blocks test
- NHPT: Nine Hole Peg test
- SD: Strength Dexterity test

Grip/key pinch/precision pinch strengths:

Hand and finger strength is often used as a measure of function in the upper extremity (Light, Chappell, Kyberd & Ellis 1999). Grip, key, and precision (tip-to-tip) pinch strengths are measured using standard techniques (patient sitting with the upper arm by the side, elbow flexed to 90 degrees, and forearm in neutral

rotation) with calibrated grip and pinch meters (Jamar, Jackson, MO) (Mathiowetz, Kashman, Volland, Weber, Dowe & Rogers 1985). Participants complete three trials for each measure and the dependent variables are the highest value from the three trials. Participant performances are compared to age-matched published normative data (Mathiowetz, Kashman, Volland, Weber, Dowe & Rogers 1985, Mathiowetz, Volland, Kashman & Weber 1985, Oxford Grice, Vogel, Le, Mitchell, Muniz & Vollmer 2003, Poole, Burtner, Torres, McMullen, Markham, Marcum, Anderson & Qualls 2005, Dayanidhi, Hedberg, Valero-Cuevas & Forssberg 2013, Lee-Valkov, Aaron, Eladoumikdachi, Thornby & Netscher 2003, Jongbloed-Pereboom, Nijhuis-van der Sanden & Steenbergen 2013, Hager-Ross & Rosblad 2002). The strength tests are illustrated below in Figure 1.1.



Figure 1.1: Measures of Hand Strength. Grip strength was measured by the dynamometer shown to the left and key (center) and precision (right) pinch strengths were measured as shown with a pinch meter.

Box and Blocks test:

The BBT is a measure of coordinated upper extremity function (Trombly 2002) that has been validated and used to assess numerous clinical conditions (Cromwell

1976, Mathiowetz, Volland, Kashman & Weber 1985). Participants are asked to use one hand to move blocks, one at a time, from one compartment of a box to another that is separated by a divider (Figure 1.2). The dependent variable is the number of blocks transported in one minute.



Figure 1.2: Box and Blocks test.

Nine-Hole Peg test:

The NHPT is a test of fine motor control featuring an emphasis on finger dexterity (Oxford Grice et al. 2003). For the NHPT, participants are asked to take narrow pegs from a shallow trough, one by one, and place them into the holes on the board, then remove the pegs from the holes, one by one and return them to the trough as quickly as possible (Figure 1.3). The time to complete the task, the dependent variable, is recorded with a stopwatch.

Strength-Dexterity test

The SD test is well described elsewhere (Valero-Cuevas et al. 2003, Talati, Valero-Cuevas & Hirsch 2005, Venkadesan & Valero-Cuevas 2008, Vollmer, Holmstrom, Forsman, Krumlinde-Sundholm, Valero-Cuevas, Forssberg & Ullen 2010,



Figure 1.3: Nine Hole Peg test.

Holmstrom, Manzano, Vollmer, Forsman, Valero-Cuevas, Ullen & Forssberg 2011, Mosier, Lau, Wang, Venkadesan & Valero-Cuevas 2011, Dayanidhi, Hedberg, Valero-Cuevas & Forssberg 2013, Dayanidhi, Kutch & Valero-Cuevas 2013, Fassola, Lawrence, Dayanidhi, Ko, Leclercq & Valero-Cuevas 2013, Lawrence, Fassola, Dayanidhi, Leclercq & Valero-Cuevas 2013). Briefly, it involves using the fingertips to compress as far as possible a slender spring, prone to buckling. This requires control of fingertip motions and force vectors at very low force levels (Figure 1.4, left). It is conducted with a custom spring (Century Springs Corp., Los Angeles, CA) outfitted with two compression miniature load cells (ELFF-10, Measurement Specialties, Hampton, VA). The load cells are connected to a signal-conditioning box and USB-DAQ (National Instruments, Austin, TX), collected using custom Matlab (v2015 b, The Mathworks, Natick, MA) software, and calibrated with a deadweight procedure. Four different springs of equal stiffness (0.86 N/cm) and diameter (0.9

cm) but varying lengths (2.9 to 4.0 cm) are used to accommodate hands with different sizes and abilities (Dayanidhi, Hedberg, Valero-Cuevas & Forssberg 2013). Each participant uses the shortest spring that he or she is not able to fully compress. SD performance is calculated based on the mean steady state force over 3 maximal trials (Dayanidhi, Hedberg, Valero-Cuevas & Forssberg 2013). Participants are asked to compress the spring in a controlled way at their own pace to the point of maximal instability they can sustain (i.e., beyond which they felt it would slip out of their hand), and maintain that compression at a steady level for at least five seconds (Figure 1.4, right) (Dayanidhi, Hedberg, Valero-Cuevas & Forssberg 2013, Dayanidhi & Valero-Cuevas 2014). They are then to release in a controlled way at their own pace.

After familiarization, at least 10 trials are performed for each test limb and the compression force (F_f) was defined as the mean of the three maximal trials. Phase portraits of force vs. force velocity (\dot{F}_f , first derivative) vs. force acceleration (\ddot{F}_f , second derivative) are produced and characterized using mean Euclidean distance (ED), which represents the mean distance of the cloud of points from the origin per unit time. A greater Euclidean distance indicates larger dynamical dispersion and suggests weaker corrective actions by the neuromuscular controller enforcing the sustained compression (Dayanidhi, Hedberg, Valero-Cuevas & Forssberg 2013, Lawrence, Fassola, Werner, Leclercq & Valero-Cuevas 2014). The compression dynamics are also characterized in terms of the root mean square

(RMS_f) of the compression force, which indicates the level of deviation from maintaining a completely stable force. Participants are allowed as many practice trials as needed to obtain steady state compression for the minimum required compression time of three seconds.

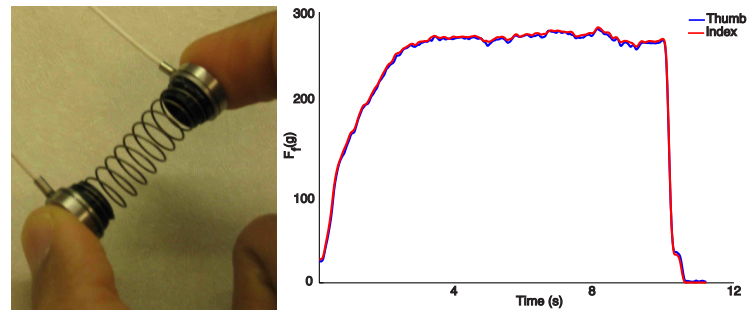


Figure 1.4: The SD test (left) consists of compressing a compliant, slender spring prone to buckling, and sustaining the maximal level of compression for >3 s. The pulps of the thumb and index finger press against miniature load cells. Sample data from spring compression are shown to the right. The forces from the thumb and index finger, in grams force, are averaged to calculate the maximal compression force.

1.1.3.2 Lower Extremity Outcome Measures

Outcome Measure Abbreviations:

- VJ: Vertical Jump test
- YBT: Y-balance test
- SLHB: Single Limb Hop and Balance test
- SLB: Single Limb Balance test
- LED: Lower Extremity Dexterity test

Vertical Jump test:

Participants are instructed to stand adjacent to a Vertec Jump Measurement device (Sports Imports, Hilliard, OH) (positioned on the same side of their self-reported dominant hand) with their feet on the force plate shoulder width apart. After squatting to a comfortable position they are instructed to perform a maximal vertical jump (Figure 1.5). Participants are allowed to use their arms to augment performance and they are asked to use the dominant hand to displace the highest possible horizontal swivel vane to encourage maximum jump height. Power is calculated as the product of the vertical ground reaction force and the vertical velocity of the reflective marker placed over their sacrum using BTS SMART-Analyzer software (BTS Bioengineering, Milan, Italy). The outcome measure, peak power (W/kg; normalized to body mass (BM)), is identified for each trial and averaged across three trials for analysis.



Figure 1.5: Vertical Jump test.

Y-Balance test:

The YBT, a simplified version of the Star Excursion Balance Test, is a reliable measure of dynamic balance featuring the anterior, posterior-medial (PM), and posterior-lateral (PL) components (Plisky, Gorman, Butler, Kiesel, Underwood & Elkins 2009). The anterior direction is defined as directly in front of the participant and the PM and PL directions are located 135 degrees from the anterior direction, separated by 45 degrees, making the "Y" shape described in the name [3]. Participants are asked to stand and maintain balance on their dominant leg and reach as far as possible with the free limb in each direction initiating from the start position (Figure 1.6). Participants perform three trials in each direction with 40 seconds of rest between reach directions. Trials are terminated early if a participant 1) fails to maintain single-leg balance, 2) uses the free limb for stance support, or 3) fails

to return to the start position. Participants are provided a visual demonstration prior to testing and are tested in the following order: anterior then PL then PM. The outcome measures, average distances reached in each direction as a percent of leg length (LL), are considered dependent variables for analysis (YBT_A , YBT_{PL} , YBT_{PM} , respectively). LL is measured while standing with a tape measure from the left greater trochanter to the floor.



Figure 1.6: Y-Balance test. The PM and PL directions are shown in the upper and lower left figures, respectively, and the anterior direction is shown to the right.

Single limb hop and balance test:

During the SLHB, upon verbal command, participants perform a single limb forward hop of a distance (normalized to their LL) with their dominant leg while their arms were folded across their chest (Figure 1.7). Upon landing, they are instructed to maintain single limb standing balance with arms still folded across their chest. In accordance with several groups (Wikstrom, Tillman, Chmielewski & Borsa 2006, Myer, Ford, Brent & Hewett 2006), the outcome measures center of pressure (COP) variability in the medial-lateral (ML) and anterior-posterior (AP) directions, COP_{ML} and COP_{AP} , respectively are considered dependent variables for analysis. COP excursion measurements are representative of body sway and provide information about the ability motor system to control the center of mass (COM). While all humans exhibit some level of body sway as measured by COP variability, greater COP variability has been linked to instability and falls (Gribble, Tucker & White 2007, Horak, Henry & Shumway-Cook 1997). As with the previous tests, the average across three trials is used to indicate performance level.



Figure 1.7: Single limb hop and balance test.

Single limb balance test:

During the SLB, participants maintain balance on their dominant leg with their arms folded across their chest and eyes closed for a total of 15 seconds. Participants are positioned on a force plate and upon verbal command, asked to lift their non-dominant foot off the floor (knee bent at approximately 60 degrees) and close their eyes 1.8. Trials are terminated early upon ground contact with the non-dominant limb or when participants open their eyes. As with the SLHB, the mean of the three trials are reported and the outcome measures of COP variability in the ML and AP directions are considered dependent variables for analysis.



Figure 1.8: Single limb balance test.

Lower Extremity Dexterity test

Similar to the SD paradigm, the Lower Extremity Dexterity (LED) test is a single leg dynamic contact control task that is based on the ability of participants to compress a slender spring (Lyle, Valero-Cuevas, Gregor & Powers 2013a, Lyle, Valero-Cuevas, Gregor & Powers 2013b, Lyle, Valero-Cuevas, Gregor & Powers 2014). The LED test device consists of a helical compression spring mounted on a single-axis force sensor (Transducer Techniques, Temecula, CA) affixed to a stable base with a 15 x 30 cm platform affixed to the free end (Figure 1.9, left). Participants are positioned in an upright partially seated posture on a bicycle saddle intended to stabilize the body and minimize the extraneous use of the contralateral limb and upper extremities during testing. A computer monitor provides visual force feedback of the vertical force (Lyle et al. 2013a, Lyle et al. 2013b, Lyle et al. 2014). Similar to the SD test, participants are instructed to slowly compress

the spring with their foot with the goal to raise the force feedback line as high as possible and maintain that compression for at least ten seconds (Figure 1.9, right). Participants are allowed as many practice trials as needed to obtain steady state compression for the minimum required compression time of ten seconds. After familiarization, between 10 and 20 trials are performed for each test limb (Lyle et al. 2013a, Lyle et al. 2013b, Lyle et al. 2014). The outcome variables, mean compression force (F_1) and a measure of force variability defined by the RMS of the force signal during the steady-state hold (RMS_1), are processed using custom Matlab software (v2013b, The Mathworks, Natick, MA) and are considered dependent variables for analysis.

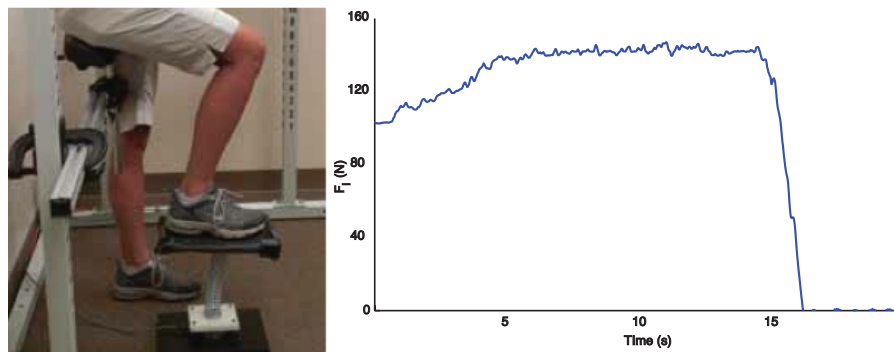


Figure 1.9: The LED test (left) consists of pressing an appropriately scaled-up spring with the foot against the ground. Compression forces, in N, are quantified with a load cell located under the spring. Sample data from spring compression are shown to the right.

1.2 Previous Work

Successful use of the hands and legs have traditionally been assessed with outcome measures of strength or function and over the last several decades an extensive library has been developed. While these outcome measures provide important information about endpoint hand and leg function the underlying sensorimotor processes required for such abilities are not captured. To address this need, the SD test, an informative measure of sensorimotor processing for low force finger function (i.e., dexterity), was introduced over a decade ago (Valero-Cuevas et al. 2003). More recently, an appropriately modified version for the legs, the LED test was developed (Lyle et al. 2013*b*).

The SD paradigm is desirable as a clinical assessment both in healthy and pathologic populations because it is designed to provide a quantitative method of evaluating dexterity in the isolated finger and leg at low forces and independently of strength. Moreover, it i) provides the benefit of both linear and non-linear time series analyses unlike discrete performance scores offered by traditional functional tests, ii) allows for the unique opportunity to evaluate both the upper and lower extremities with a single paradigm, and iii) is easily coupled with other technology including, but not limited to, electromyography (EMG), electroencephalography (EEG), functional magnetic resonance imaging (fMRI), measures of corticospinal excitability, and even gaming platforms.

The SD test has successfully quantified sensorimotor ability for finger dexterity throughout the lifespan in over 240 healthy volunteers and shows an increase in ability well into adolescence and decline beginning in the fourth decade of life (Dayanidhi, Hedberg, Valero-Cuevas & Forssberg 2013, Dayanidhi & Valero-Cuevas 2014). Measures of finger strength (pinch strength), whole arm pick and place ability (BBT), and the SD test were shown have a combination of unique and shared contributions in a study on pediatric hand function (Vollmer et al. 2010). While no significant sex differences in mean SD test compression are reported in any of these studies, a linear regression of SD test performance with age demonstrated a significantly steeper slope in male children compared to females (Vollmer et al. 2010). In clinical populations, the SD test is also able to distinguish between patients diagnosed with CMC OA and asymptomatic older adults, although pinch meter readings did not (Valero-Cuevas et al. 2003). In terms of lower extremity sensorimotor ability, findings from a recent study with the LED test indicate that it is predictive of agility level in adolescent soccer athletes and may have implications for sports performance, injury risk, and rehabilitation (Lyle et al. 2013*a*). Moreover, a follow-up study indicates that female adolescents exhibit reduced dexterity as per the LED test and higher limb stiffness during landing, which may provide important information about the disproportionate number of anterior cruciate ligament (ACL) tears in females (Lyle et al. 2014).

The mean compression force during the hold phases of the SD paradigm is the standard linear method of calculating test performance and shown successes quantifying sensorimotor ability (Valero-Cuevas et al. 2003, Vollmer et al. 2010, Dayanidhi, Hedberg, Valero-Cuevas & Forssberg 2013, Dayanidhi & Valero-Cuevas 2014, Lyle et al. 2013*a*, Lyle et al. 2013*b*, Lyle et al. 2014). However, dynamic sensorimotor behavior, as captured by the SD paradigm, is complex, nonlinear, and high-dimensional, and a nonlinear approach is best suited for analysis. Non-linear analysis techniques were first investigated in a study that modeled SD test performance as a subcritical pitchfork bifurcation of the endcap angle of the spring (Venkadesan & Valero-Cuevas 2008). The results indicate that a low-order normal form equation from bifurcation theory produces dynamics similar to experimental measurements of SD test compression (Venkadesan & Valero-Cuevas 2008). A series of publications then characterized the dynamic nature during sustained SD test compression by plotting the phase portraits of the compression force versus the first and second time derivatives (force velocity and acceleration, respectively) (Dayanidhi, Hedberg, Valero-Cuevas & Forssberg 2013, Dayanidhi & Valero-Cuevas 2014). This work shows that the points making up the phase portrait have a larger Euclidean distance from the attractor during development and in aging and suggest weaker corrective actions by the neuromuscular controller in children and older adults (Dayanidhi, Hedberg, Valero-Cuevas & Forssberg 2013, Dayanidhi & Valero-Cuevas 2014).

1.3 Significance of Research

A primary goal of this dissertation is to expand on previous work from this group and investigate and quantify the changes in dexterous ability of both the upper and lower extremities quantify the effects of age, sex, and clinical condition. It is anticipated that the results from this work will significantly advance the current state of knowledge particularly when considering sex differences in low force manipulation and will aid in understanding how sensorimotor processing is affected by various clinical conditions. These innovative results support prior knowledge that the SD paradigm is an ideal system for challenging neuromuscular system to quantify dexterous manipulation both in the upper and lower extremities. Moreover, we show that sensorimotor processing is a latent domain of both hand and leg function that is independent of strength or limb coordination. This has important implications for the development of preventative countermeasures and rehabilitation regimens designed to specifically target each latent domain.

1.4 Dissertation outline

1.4.1 Chapter 2

This chapter focuses on quantifying the effects of age, sex, and certain clinical conditions (i.e., CMC OA and PD) on low force dexterous ability of the upper and lower extremities. It was made possible by collaborations with the Institut de la

Main in Paris, France and the University of Innsbruck in Innsbruck, Austria. Professor Valero-Cuevas guided this research with the help of Dr. Caroline Leclerc, Dr. Isabella Fassola, and Professor Inge Werner. Parts of this work have been presented in 2011 at the Neural Control of Movement Conference and the International Thumb Osteoarthritis Workshop and in 2015 at the annual meeting for the Organization for the Study of Sex Differences. This research was published in 2014 in the Movement Disorders topic of *Frontiers in Neurology* in 2014.

1.4.2 Chapter 3

This chapter uses Principal Components Analysis (PCA) to examine the latent domains of hand function in healthy older adults and in those diagnosed with CMC OA. We find the three domains are strength, limb coordination, and sensorimotor processing. This was done as part of the Rehabilitation Engineering Research Center (RERC) on Technologies for Successful Aging with Disability at USC and Rancho Los Amigos National Rehabilitation Center under the guidance of Professors Valero-Cuevas, Winstein, and Requejo. Drs. Leclerc and Fassola spearheaded the data collection in participants with CMC OA and Sudarshan Dayanidhi was responsible for the majority of the data collection in healthy older adults. This work was presented at the annual meeting of the American Society of Biomechanics in 2015 and was published in *Frontiers in Aging Neuroscience*.

1.4.3 Chapter 4

This chapter extends the work in Chapter 4 by using PCA to examine the latent domains of leg function for balance ability in healthy young adults. We find that the same three latent domains in the hand are represented in the lower extremity. This research was guided by Professors Sigward and Valero-Cuevas with contributions from Guilherme Cesar, Martha Bromfield, and Richard Peterson. This work was presented at the annual meeting of the American Society of Biomechanics in 2015 and was published in BioMed Research International the same year.

1.4.4 Chapter 5

This chapter uses attractor reconstruction to examine differences in neural control strategies leg dexterity in young adults both with and without athletic training. We find that the phase portraits of skilled athletes are distinctly different from non-skilled athletes and indicate an advanced neural control strategy. We further find that sex differences in sensorimotor processing are present in non-skilled athletes, but not in skilled athletes. The data were collected in collaboration with Professor Werner at the University of Innsbruck in Innsbruck, Austria under the guidance of Professor Valero-Cuevas with analysis assistance from Lorenzo Peppoloni. This work will be presented at the 2016 annual meeting of the Organization for the Study of Sex Differences and is in preparation to submit to *Frontiers in Computational Neuroscience*.

Chapter 2

Quantification of Dexterity as the Dynamical Regulation of Instabilities: Comparisons across Sex, Age, and Disease

2.1 Abstract

Dexterous manipulation depends on using the fingertips to stabilize unstable objects. The Strength-Dexterity paradigm consists of asking subjects to compress a slender and compliant spring prone to buckling. The maximal level of compression [requiring low fingertip forces ≤ 300 grams force (gf)] quantifies the neural control capability to dynamically regulate fingertip force vectors and motions for a dynamic manipulation task. We found that finger dexterity is significantly affected by age ($p = 0.017$) and gender ($p = 0.021$) in 147 healthy individuals (66F, 81M, 20-88 years). We then measured finger dexterity in 42 hands of patients following treatment for osteoarthritis of the base of the thumb (CMC OA, 33F, 65.8 ± 9.7 years), and

31 hands from patients being treated for Parkinson’s disease (PD, 6F, 10M, 67.68 \pm 8.5 years). Importantly, we found no differences in finger compression force among patients or controls. However, we did find stronger age-related declines in performance in the patients with PD (slope -2.7 gf/year, $p = 0.002$) than in those with CMC OA (slope -1.4 gf/year, $p = 0.015$), than in controls (slope -0.86 gf/year). In addition, the temporal variability of forces during spring compression shows clearly different dynamics in the clinical populations compared to the controls ($p < 0.001$). Lastly, we compared dexterity across extremities. We found stronger age ($p = 0.005$) and gender ($p = 0.002$) effects of leg compression force in 188 healthy subjects who compressed a larger spring with the foot of an isolated leg (73F, 115M, 14-92 years). In 81 subjects who performed the tests with all four limbs separately, we found finger and leg compression force to be significantly correlated (females $\rho = 0.529$, $p = 0.004$; males $\rho = 0.403$, $p = 0.003$; 28F, 53M, 20-85 years), but surprisingly found no differences between dominant and non-dominant limbs. These results have important clinical implications, and suggest the existence—and compel the investigation—of systemic versus limb-specific mechanisms for dexterity.

2.2 Introduction

Dynamic upper extremity function in general, and of the fingertips in particular, is essential for ADLs and quality of life (Backman, Gibson & Parsons 1992, Hackel

et al. 1992). While there are multiple measures of hand function, we have historically lacked a means to quantify the dynamical interaction of the fingertips with objects without the confounds of strength, functional adaptations, whole-arm coordination, visual acuity, etc. We have proposed the SD paradigm as a versatile, repeatable, and informative paradigm to quantify finger dexterity across the lifespan in some clinical populations. We define dexterity as the sensorimotor capability to dynamically regulate fingertip force vectors and motions to stabilize an unstable object (Valero-Cuevas et al. 2003, Talati et al. 2005, Venkadesan & Valero-Cuevas 2008, Vollmer et al. 2010, Holmstrom et al. 2011, Mosier et al. 2011, Dayanidhi, Hedberg, Valero-Cuevas & Forssberg 2013, Dayanidhi, Kutch & Valero-Cuevas 2013, Dayanidhi & Valero-Cuevas 2014, Fassola et al. 2013, Lawrence et al. 2013). This paradigm consists of testing the extent to which people can compress a slender spring prone to buckling. The spring naturally becomes unstable as it is compressed; thus the maximal level of compression is indicative of the maximal sensorimotor capability to control the fingertips. The springs are designed to require very low forces to reflect the nature of ADLs. Moreover, fMRI studies show the SD paradigm can systematically interrogate brain function for dexterous manipulation, which exhibits differential activity across cortical networks depending on the level of difficulty and behavioral goals of the task (Talati et al. 2005, Holmstrom et al. 2011, Mosier et al. 2011).

Given that we have previously established the reliability and utility of this approach to dexterity (Valero-Cuevas et al. 2003, Talati et al. 2005, Venkadesan & Valero-Cuevas 2008, Vollmer et al. 2010, Holmstrom et al. 2011, Mosier et al. 2011, Dayanidhi, Hedberg, Valero-Cuevas & Forssberg 2013, Dayanidhi, Kutch & Valero-Cuevas 2013, Dayanidhi & Valero-Cuevas 2014, Fassola et al. 2013, Lawrence et al. 2013), the purpose of this work is to understand the effects of sex, age and disease on this sensorimotor ability to control instabilities. The effect of age on motor function in general, and hand function in particular, is well-known (Hackel et al. 1992, Shiffman 1992, Michimata, Kondo, Suzukamo, Chiba & Izumi 2008, Dayanidhi & Valero-Cuevas 2014). However, recent studies using the SD paradigm have demonstrated its ability to detect previously unknown changes in dexterity lasting into late adolescence in typical development (Vollmer et al. 2010, Dayanidhi, Hedberg, Valero-Cuevas & Forssberg 2013, Dayanidhi, Kutch & Valero-Cuevas 2013), or starting in middle age in healthy older adults (Dayanidhi & Valero-Cuevas 2014). One goal of this work is to expand upon those findings by including larger numbers of participants, and including those individuals suffering from clinical conditions. While the effect of sex on muscle strength is well-known, its effects on sensorimotor function are less clear. There continues to be keen clinical interest given the greater incidence of some musculoskeletal pathologies and injuries in women, such as osteoarthritis (Armstrong, Hunter & Davis 1994) and non-contact ligament tears (Sigward, Pollard & Powers 2012).

The literature contains contradictory reports (Shinohara, Li, Kang, Zatsiorsky & Latash 2003, Michimata et al. 2008) that feed continued debate on the issue. Our own work using the SD paradigm has hinted at sex differences in dexterity in typical development (Vollmer et al. 2010, Dayanidhi, Hedberg, Valero-Cuevas & Forssberg 2013), but these remain to be explored in detail.

Lastly, our more recent work has extended the concept of finger dexterity to limbs in general. By simply scaling up the physical size of our test system, we have introduced the concept of limb dexterity (Lyle et al. 2013*b*). The LED test has been shown to be a valid and repeatable metric of dynamic leg function (Lyle et al. 2013*b*). Importantly, our report of strong differences in leg dexterity between men and women has begun to provide a neuromuscular explanation for sex differences in agility, and the much higher incidence of non-contact ligament tears in women athletes (Lyle et al. 2013*a*, Lyle et al. 2013*b*). We are therefore compelled to explore the nature of systemic versus limb-specific dexterity as it relates to age and sex. This is necessary to further our understanding of the neural mechanisms for dynamical function in health and disease.

2.3 Methods

All participants gave their informed consent to the experimental protocol, which was approved by the Health Sciences Campus Institutional Review Board at the

University of Southern California in Los Angeles, and/or the relevant ethics committees at the Institut de la Main-Clinique Jouvenet in Paris, and the Institute of Sports Science in Innsbruck.

2.3.1 Control Participants

We measured finger dexterity in 147 healthy volunteers (66F, 81M, 52.7 ± 21.6 years) between 20 and 88 years of age. Similarly, we measured single leg dexterity in 188 healthy volunteers (73F, 115M, 42.7 ± 23.6 years) between the ages of 14 and 92 years. Of these, 81 volunteers from 20-85 years of age (28F, 53M, 47 ± 22.8 years) completed both the finger and leg dexterity protocols in order to evaluate dexterity systemically. Participants were excluded if they had pathology of the hand or a history of injury that prevented unrestricted use of their fingers or legs. All participants gave their informed consent to the experimental protocol, which was approved by the Health Sciences Campus Institutional Review Board at the University of Southern California in Los Angeles, and the Institute of Sports Science in Innsbruck.

2.3.2 Clinical Populations

We used a sample of convenience from two clinical conditions known to affect hand function as a first exploration of the clinical utility of this paradigm. Our goal was not to diagnose or evaluate treatment, but simply collect cross-sectional data

from patients suffering from these conditions. For these clinical groups, participants were excluded if they were undergoing treatment for injury or surgery and had not been released by their surgeon or physical/occupational therapist to participate in everyday activities of daily living, had a concurrent injury or pathologic condition that caused pain or discomfort in the tested limb during physical activity and/or at rest, had clinical, surgical, physical, cognitive or other conditions that may have prevented their ability to perform the tasks proposed in this study, including the clinical restriction decided by the surgeon or therapist, or were unable to complete the protocol. We then compared performance on the SD test (\dot{F}_f , \ddot{F}_f , and RMS_f) between clinical patients diagnosed with either CMC OA or PD and a subset from our dataset of 29 healthy, age-matched volunteers (10M, 19F; 65.6 ± 9.7 years, 48 hands) with no history of hand injury or disease or neurological disorder.

The first clinical group, defined as patients treated for CMC OA, consisted of 33 female participants (65.81 ± 9.72 years, 42 hands) evaluated at an average of 40 months after treatment at Institut de la Main. The same surgeon performed the treatments on all the patients. The CMC OA patients underwent one of four treatment types: ligament reconstruction with tendon interposition (LRTI) arthroplasty (Burton & Pellegrini 1986), trapeziectomy (TS) (Froimson 1970), non-surgical medical treatment (i.e., rehabilitation), and no treatment. The second clinical group, defined as patients treated for PD, consisted of 14 volunteers (10M, 4F; 67.68 ± 8.5 years, 27 hands). All patients were treated at the USC Keck School of Medicine,

Department of Neurology in the Parkinson's Disease and other Movement Disorders Clinic.

2.3.3 Data Analysis and Variable Descriptions

The dependent variables for the SD and LED paradigms are defined in Table 2.1. Linear regressions, two-tailed t-tests, and analysis of variance (ANOVA) were applied to the data set, as appropriate, to identify and quantify the relationships between test performance, age, sex, and dominance. Significance was set at $p < 0.05$ for all analyses. Matlab and SPSS version 22 (IBM, Armonk, NY) were used for these analyses.

Table 2.1: Definition of variables used in analyses.

Note that force magnitudes for the finger and leg tasks (cf. Figures 1.4 and 1.9) are two orders of magnitude apart. Therefore, we use the SI units of grams force and N, respectively, to accommodate those differences.)

Variable	Symbol	Description
Finger Compression Force	F_f	Mean compression force during the hold phase of the SD test (units: gf)
Finger Force Velocity	\dot{F}_f	Mean of the absolute value of the first time derivate of compression force during the hold phase of the SD test (units: gf/s)
Finger Force Acceleration	\ddot{F}_f	Mean of the absolute value of the second time derivate of compression force during the hold phase of the SD test (units: gf/s ²)
Finger Force RMS	RMS_f	Magnitude of the mean of the force dispersions during the hold phase of the SD test (units: gf)
Leg Compression Force	F_1	Mean compression force during the hold phase of the LED test (units: N)
Leg Force Velocity	\dot{F}_1	Mean of the absolute value of the first time derivate of compression force during the hold phase of the LED test (units: N/s)
Leg Force Acceleration	\ddot{F}_1	Mean of the absolute value of the second time derivate of compression force during the hold phase of the LED test (units: N/s ²)
Leg Force RMS	RMS_1	Magnitude of the mean of the force dispersions during the hold phase of the LED test (units: N)

2.4 Results

2.4.1 Overview

The ANOVA results are summarized in Table 2.2 and discussed in detail in this section. We report strong age and gender effects in leg and finger compression force in healthy participants. Furthermore, we report strong effects of clinical condition (both CMC OA and PD) on the force velocity, acceleration, and RMS of the SD test. Interestingly, we report no differences in any variable between the dominant and non-dominant sides of control participants, patients diagnosed with CMC OA, and between self-reported affected and unaffected sides of patients diagnosed with PD.

Table 2.2: Summary of multifactor ANOVA results. (^T indicates transformed data set)

Variable	Age	Sex	Side	Clinical Condition
Finger Compression Force (F_f)	*p=0.017 ^T	*p=0.021 ^T	p=0.461 ^T	p=0.081
Finger Force Velocity (\dot{F}_f)	*p=0.048 ^T	p=0.542 ^T	p=0.408 ^T	*p<0.001
Finger Force Acceleration (\ddot{F}_f)	p=0.061 ^T	p=0.158 ^T	p=0.672 ^T	*p<0.001
Finger Force RMS (RMS _f)	p=0.880 ^T	p=0.989 ^T	p=0.183 ^T	*p<0.001
Leg Compression Force (F_l)	*p=0.005 ^T	*p=0.002 ^T	p=0.295 ^T	-
Leg Force Velocity (\dot{F}_l)	p=0.595 ^T	p=0.536 ^T	p=0.945 ^T	-
Leg Force Acceleration (\ddot{F}_l)	p=0.519 ^T	p=0.441 ^T	p=0.872 ^T	-
Leg Force RMS (RMS _l)	p=0.532 ^T	p=0.135 ^T	p=0.237 ^T	-

The results from the linear regression analyses of compression force with respect to age are summarized in Table 2.3. We report significant increases in compression force in both the finger and leg in healthy participants under the age of 40, and vice versa for those over the age of 40 years-but as clarified in the Discussion, this effect is not always seen when separating subjects by sex.

Table 2.3: Summary of linear regressions of compression force with age results.

Variable	Adults < 40 years			Adults > 40 years			Clinical Conditions	
	Males	Females	All	Males	Females	All	CMC OA	PD
Finger Compression Force	p=0.328	p=0.316	*p=0.019	p=0.09	*p=0.008	*p=0.002	*p<0.001	*p<0.001
Leg Com- pression Force	*p=0.001	p=0.09	*p<0.001	p=0.055	p=0.076	*p=0.007	-	-

2.4.2 Finger SD Test with Control Subjects in the Self-Reported Dominant Hand

We tested for the effects of age and sex on finger dexterity in the self-reported dominant hand of 147 healthy individuals between the ages of 20 and 88 years. We note the variables were transformed using the natural logarithm function to meet the assumptions of normality required for parametric statistics. As shown in Table 2.2, an ANOVA with finger compression force as the dependent variable and age and sex as factors performed on the transformed data revealed a significant effect by both age ($p=0.017$) and sex ($p=0.021$). Furthermore, we report no sex effects on the compression dynamics (\dot{F}_f , \ddot{F}_f , and RMS_f) and no age effects on

force accelerations and RMS, but age does affect the finger force velocity ($p=0.048$) (Table 2.2). Interestingly, we report no differences in any variable between the dominant and non-dominant sides of participants.

A linear regression of finger compression force with respect to age, grouped by sex, is shown in Figure 2.1. Without accounting for sex, adults under the age of 40 years have an increase in finger compression force with age ($p=0.019$) while adults over 40 have a decrease in force with age ($p=0.002$). When the groups are separated by sex, however, the increases in compression force in younger males and females and decreases in older males are no longer significant (Table 2.3). Note the offset in regression lines, which agrees with the significant on the sex effect on compression force as per the ANOVA

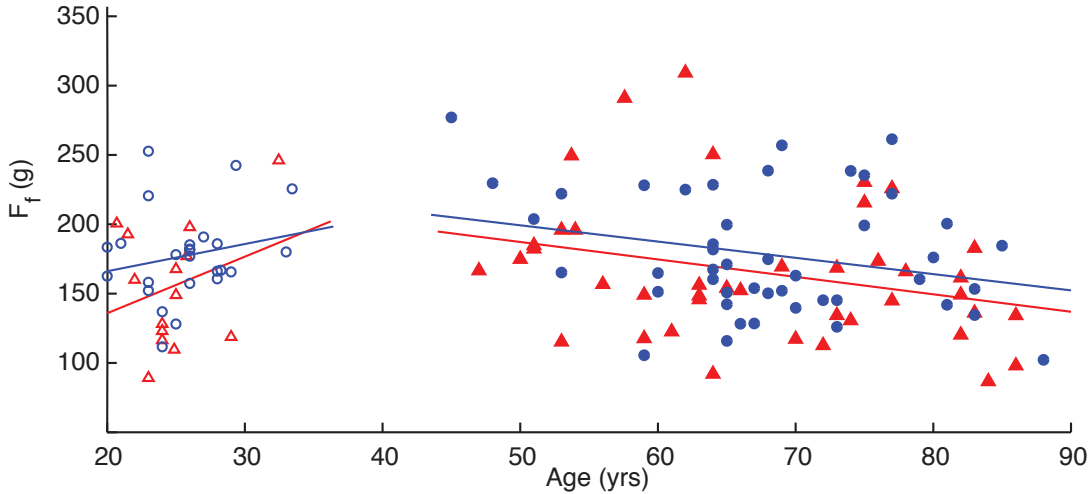


Figure 2.1: Linear regression of finger compression force with respect to age. Younger adults (empty symbols) tended to show an increase in compression force while older adults (filled symbols) showed a decrease. Male participants (blue circles) tended to have greater values than females (red triangles) as indicated by the position of the fit lines. See Table 2.3.

2.4.3 Finger SD Test with Clinical Subjects

We compared performance on the SD test (F_f , \dot{F}_f , \ddot{F}_f , and RMS_f) between clinical patients diagnosed with either CMC OA or PD and a subset from our dataset of 29 healthy, age-matched volunteers (10M, 19F; 65.6 ± 9.7 years, 48 hands) with no history of hand injury or disease or neurological disorder. Interestingly, we found no significant differences in finger compression force among groups, but we found differences between the clinical and control groups in compression dynamics (\dot{F}_f , \ddot{F}_f , and RMS_f) during the sustained compression as illustrated in Figure 2.2. We also found no differences in compression dynamics between the PD and CMC OA groups; however, both groups showed significant differences from the control participants ($p < 0.001$), indicating distinctly different dynamical behavior during manipulation in these clinical populations. Additionally, as in (Dayanidhi, Hedberg, Valero-Cuevas & Forssberg 2013, Dayanidhi & Valero-Cuevas 2014), we characterized the force dynamics during the sustained compression by plotting the phase portraits of F_f , \dot{F}_f , and \ddot{F}_f (Figure 2.3). The character of the phase portrait was quantified by the mean ED from the origin per unit time (Dayanidhi, Hedberg, Valero-Cuevas & Forssberg 2013, Dayanidhi & Valero-Cuevas 2014). A greater ED is suggestive of weaker corrective actions by the neuromuscular controller enforcing the sustained compression (Dayanidhi, Hedberg, Valero-Cuevas & Forssberg 2013, Dayanidhi & Valero-Cuevas 2014). There are clear differences in

the phase portraits of the control and clinical participants, with greater dispersion associated with the clinical groups.

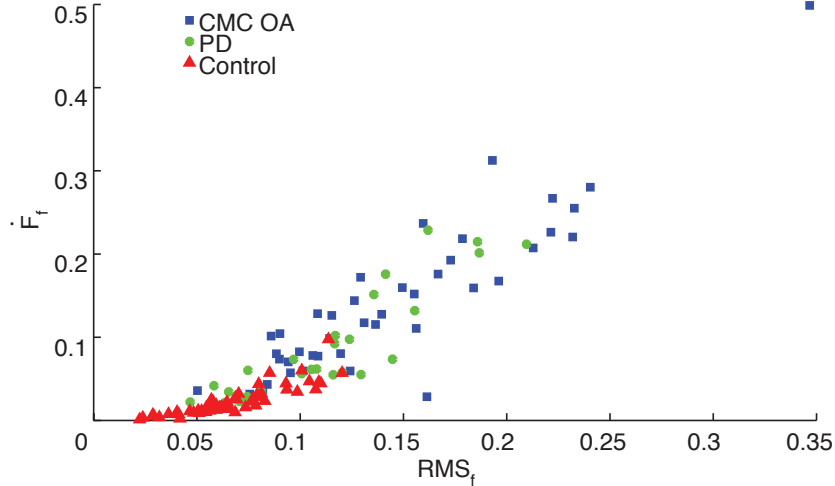


Figure 2.2: Dynamic characteristics of the SD test. Control participants (red triangles) had significantly greater stability during SD compression compared to patients with CMC OA (blue squares) and PD (green circles).

We also performed linear regressions of finger compression force versus age in these three populations, which revealed that individuals with CMC OA and PD showed greater rates of decline compared to control subjects ($p < 0.001$), Figure 2.4. Patients with CMC OA and PD had average rates of decline of -1.4 gf/yr and -2.7 gf/yr, respectively, compared to -0.86 gf/yr in control participants. To further expand the analysis and investigate the effect of laterality, we compared performance on the self-reported affected hand to the unaffected hand in a subset) of the PD ($n=8$) and CMC OA ($n=17$) groups. While we don't show the results for succinctness, ANOVA revealed no effect of side in any variables F_f , \dot{F}_f , and \ddot{F}_f , RMS_f , in either group.

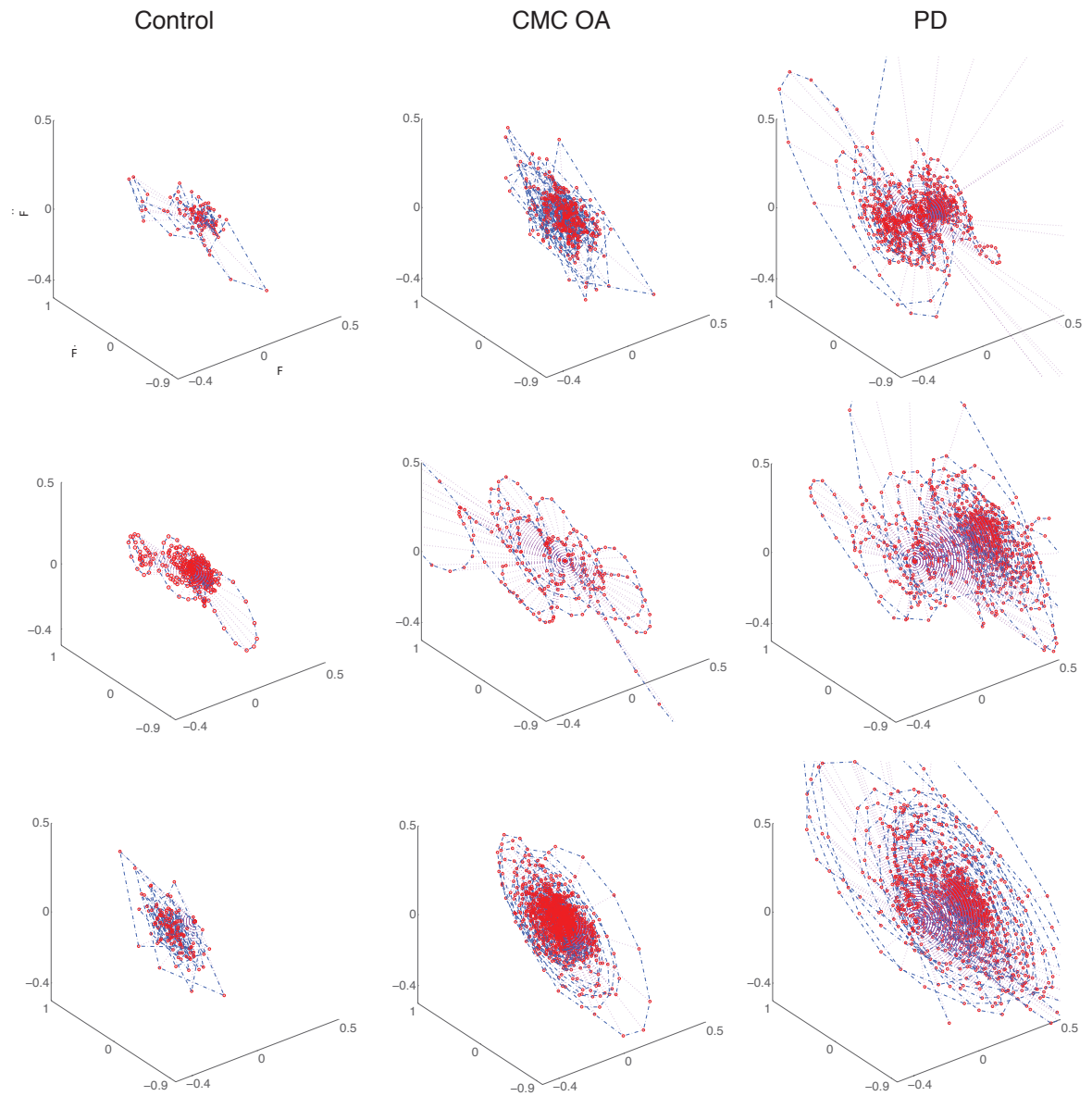


Figure 2.3: Representative phase portraits of three participants from each group (ages between 70-75 years): healthy control subjects (1st column), participants diagnosed with CMC OA (2nd column), and participants diagnosed with PD (3rd column). The clinical subjects exhibit greater dispersion in the phase portrait than the control subjects.

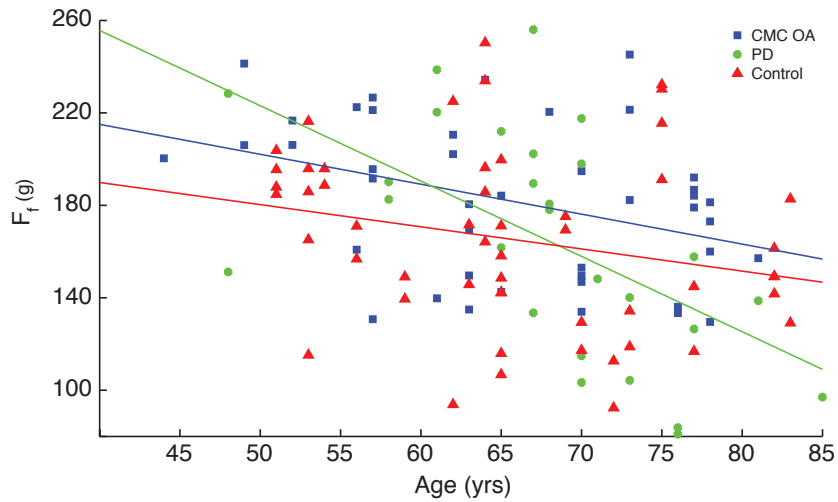


Figure 2.4: Comparison of rate of decline between clinical and control populations. Finger compression force was plotted against age and revealed that the clinical groups (PD and CMC OA, green circles and blue squares, respectively) had a greater rate of decline of with age than control participants (red triangles).

2.4.4 Leg LED Test with Control Subjects in the Right Leg

Mirroring the work on hand dexterity, we also tested for effects of age, sex, and dominance on leg dexterity in the right leg of 188 healthy individuals from 14-92 years. In order to account for the age and sex effects on body weight, which may influence leg compression force, we included body mass index (BMI) in the analysis. The data were normally distributed, and an ANOVA with leg compression force as dependent variable and age and sex as factors and BMI as a covariate showed that compression force is strongly affected by both age ($p=0.005$) and sex ($p=0.002$, Table 2.2), but not by BMI ($p=0.198$). Furthermore, ANOVA on the force dynamics (\dot{F}_1 , \ddot{F}_1 , and RMS_1) during sustained compression showed no effect of sex, age, or BMI.

Linear regressions of leg compression force versus age revealed significant increases in force in adults under the age of 40 ($p < 0.001$) and decreases in participants over 40 years ($p = 0.007$). However, when separated by sex, increase in compression force in young females and decreases in older males and females are no longer significant (Table 2.3). As with the hand, there are increases in compression force with respect to age in younger adults, and decreases in older adults; and the regression lines of male participants are slightly shifted above those of females, corroborating the ANOVA results that compression forces for male participants tended to be greater on average than that of female participants when using age as a factor (Figure 2.5). Note that in these subjects we only tested one leg, the right leg, for expediency because the effect of leg dominance was explored in a different subset of subjects (see below).

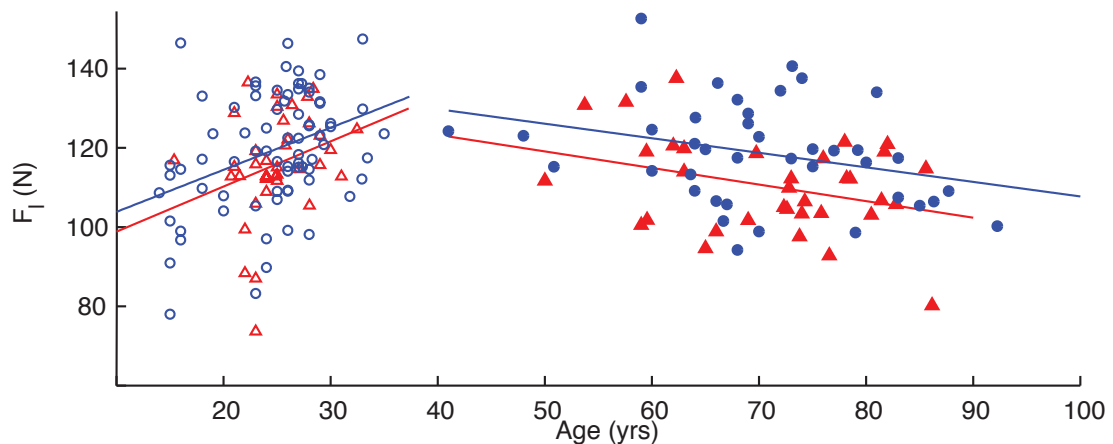


Figure 2.5: Age- and sex-related changes in leg compression force. Regressions against age indicated an increase in younger adults (empty symbols) and a decrease in older adults (filled symbols). Male participants (blue circles) tended to have greater values than females (red triangles) as indicated by the position of the fit lines.

2.4.5 Dexterity Across Both Fingers and Legs

Finally, we explored dexterity across the upper and lower extremities by comparing SD and LED performance in both hands and legs of 81 healthy volunteers between the ages of 20 and 85, each labeled as self-reported dominant or non-dominant (Figure 2.6). Surprisingly, ANOVA (in this case a repeated measures ANOVA given that we collected finger and leg data in the same subjects) revealed no effects of laterality (i.e., dominant versus non-dominant) for any variable, when controlling for sex and age in these participants (Table 2.2). However, we found statistically significant ($p < 0.001$) Pearson's product-moment correlation of $\rho = 0.458$ between finger and leg compression forces in all subjects. When separating them by sex, the correlation was higher in females ($\rho = 0.529$, $p = 0.004$, $n = 28$) than in males ($\rho = 0.403$, $p = 0.003$, $n = 53$).

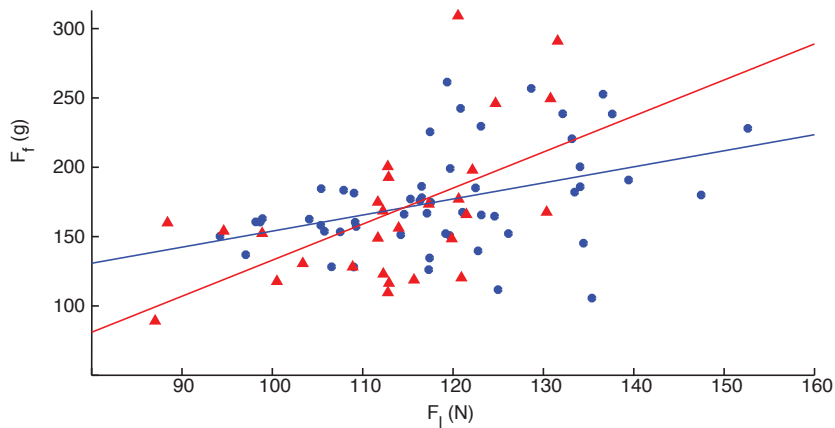


Figure 2.6: Correlation of finger and leg dexterity. Both male (blue circles) and female (red triangles) participants showed significant association between finger and leg compression force in the self-reported dominant limb, with females exhibiting higher correlation than males, $\rho = 0.529$ and 0.403 , respectively.

2.5 Discussion

There are multiple definitions for, and connotations of, the concept of dexterity. In a series of recent publications using the SD paradigm, we have argued that quantifying the sensorimotor ability to stabilize objects with the fingertips is a valid definition of one aspect of finger dexterity (Valero-Cuevas et al. 2003, Talati et al. 2005, Venkadesan & Valero-Cuevas 2008, Vollmer et al. 2010, Holmstrom et al. 2011, Mosier et al. 2011, Dayanidhi, Hedberg, Valero-Cuevas & Forssberg 2013, Dayanidhi, Kutch & Valero-Cuevas 2013). By focusing on how the fingertips act on an object by dynamically regulating the magnitude and direction of fingertip forces, we can quantify important features of using precision pinch (or tip-to-tip, or pincer grasp) to manipulate objects. Therefore, the purpose of this comparative cross-sectional study was to quantify how these features of dexterous manipulation are affected by age, sex and disease. We have previously attributed the sensitivity of the SD test to detect functional changes among both healthy and clinical populations across the life span to its ability to focus on the sensorimotor function of the isolated CNS-limb system without the confounds of visual acuity, whole arm function, or finger strength (Valero-Cuevas et al. 2003, Talati et al. 2005, Venkadesan & Valero-Cuevas 2008, Vollmer et al. 2010, Holmstrom et al. 2011, Mosier et al. 2011, Dayanidhi, Hedberg, Valero-Cuevas & Forssberg 2013, Dayanidhi, Kutch & Valero-Cuevas 2013, Fassola et al. 2013, Lawrence et al. 2013). Furthermore, it has allowed the detection and identification of specific and context-sensitive

brain circuits for dynamic control of the fingers (Talati et al. 2005, Holmstrom et al. 2011, Mosier et al. 2011). Those prior findings inform our interpretation of our important results now quantifying the effects of sex, age and disease.

2.5.1 Effect of Age

Our results corroborate the effect of age we have reported for finger dexterity in young children and adolescents (Dayanidhi, Hedberg, Valero-Cuevas & Forssberg 2013), and older adults (Dayanidhi & Valero-Cuevas 2014). However, we extend those results in crucial ways. It is important to note that our prior work (Dayanidhi, Hedberg, Valero-Cuevas & Forssberg 2013, Dayanidhi & Valero-Cuevas 2014) revealed no significant changes in dexterous manipulation in middle age and therefore, we used samples of convenience (college-aged students and older control subjects for comparison to clinical populations of interest), which resulted in an undersampling of subjects between 35-50 years of age, but does not affect the results we report. First, we emphasize our study of adults starting at 20 years of age, where we continue to see an improvement in young adulthood. In an earlier study, we report the strong association between improvements in finger compression force and compression dynamics with maturation of the brain in children and adolescents (Dayanidhi, Hedberg, Valero-Cuevas & Forssberg 2013). To our knowledge, this is the first report of continual improvement of dexterity into young adulthood after the age of 20. The continual behavioral improvements we see here are, therefore,

credibly associated—at least in part—with such neural maturation and have important clinical implications for the rehabilitation. For example, traumatic injuries (such as spinal cord injury in males (van den Berg, Castellote, Mahillo-Fernandez & de Pedro-Cuesta 2010) and anterior cruciate ligament tears in females (Sigward et al. 2012)) are most prevalent in young adults. Our results indicating the present of motor learning and neural plasticity in early adulthood suggest that these individuals would naturally have a propensity to respond to therapy better than older adults. Similarly, our results now come from 147 adults from 20 to 88 years of age. These include 108 subjects not previously analyzed, and 39 from our previous reported pool of 98 subjects (Dayanidhi & Valero-Cuevas 2014). This was critical to reveal the sex effect in finger compression not previously significant (see below and Table 2.2), and now confirm what was a near significant effect of age on finger force dynamics hinted at in our previous work (Vollmer et al. 2010, Dayanidhi, Hedberg, Valero-Cuevas & Forssberg 2013, Dayanidhi & Valero-Cuevas 2014), Table 2.2.

In our prior work (Dayanidhi, Hedberg, Valero-Cuevas & Forssberg 2013) we have noted that, in parallel with the development of the ascending and descending pathways between brain and hand, there are striking developmental processes taking place in the brain gray and white matter during childhood up to adolescence, e.g., expansion of the white matter and pruning of the cortical gray matter (Giedd, Blumenthal, Jeffries, Castellanos, Liu, Zijdenbos, Paus, Evans & Rapoport 1999, Paus, Zijdenbos, Worsley, Collins, Blumenthal, Giedd, Rapoport

& Evans 1999, Martin, Friel, Salimi & Chakrabarty 2007, Lebel, Walker, Leemans, Phillips & Beaulieu 2008, Asato, Terwilliger, Woo & Luna 2010, Lebel & Beaulieu 2011). Ehrsson et al. (Ehrsson, Fagergren & Forssberg 2001) demonstrated that there is a greater activity in the fronto-parietal sensorimotor areas during the control of smaller forces than larger forces, with control of larger forces associated with increased activity in the M1 region. Fronto-parietal regions demonstrate significant developmental changes in the adolescent years (Sowell, Thompson, Holmes, Batth, Jernigan & Toga 1999, Lebel et al. 2008, Asato et al. 2010), and the pruning of the gray matter occurs later in the frontal and parietal areas (Sowell, Thompson, Holmes, Jernigan & Toga 1999) than in the M1. These associations between the development of cortical neural networks, including ascending and descending pathways on one hand, and the dexterity measured by our method are, of course, mostly empirical and speculative. Our results now raise the possibility that these processes continue into young adulthood. Moreover, they also seem to be reversed (or counteracted) by the mechanisms of aging in a way that is behaviorally measurable, in a way that has important clinical and therapeutic implications.

2.5.2 Effect of Sex

The effect of sex on motor skill is not well documented, necessarily predictable, or expected in dynamic finger function—contrary to the well-known effect of sex on muscle strength or BMI. Given those differences in strength across sexes, we

designed our test of dynamic sensorimotor function to require only very low levels of force (<300 gf). We have reported hints of a sex effect on dexterity in typically developing children (Vollmer et al. 2010), which may have been colored by a test protocol that tended to require large forces. But these new results now establish without a doubt that females exhibit lower ability to control instabilities with the fingertips than males at any age. The literature does not report consistent sex effects, and the issue remains very much debatable (Ruff & Parker 1993, Shinohara et al. 2003, Michimata et al. 2008, Vollmer et al. 2010). Our results add to this literature by providing a new example of performance differences between women and men.

Given that we have found the SD paradigm to be informative of local and systemic neuromuscular mechanisms (e.g., brain maturation, muscle contractile speeds, functional brain connectivity and networks, etc. (Valero-Cuevas et al. 2003, Talati et al. 2005, Venkadesan & Valero-Cuevas 2008, Vollmer et al. 2010, Holmstrom et al. 2011, Mosier et al. 2011, Dayanidhi, Hedberg, Valero-Cuevas & Forssberg 2013, Dayanidhi, Kutch & Valero-Cuevas 2013, Fassola et al. 2013, Lawrence et al. 2013), this clear sex effect is remarkable as it strongly suggests those sensorimotor differences in women are a function of specific mechanisms at the level of the muscles, spinal cord, and/or brain. This leads directly to testable hypotheses at each of these hierarchical levels. For example, does the excitability of motoneuron pools during the control of unstable forces change differently in men

versus women? What are the roles of hormonal cycles in the general excitability and controllability of the sensorimotor system? Are there differences in brain connectivity in sensorimotor areas across sexes as is now reported for cognitive areas? There is a growing consensus that male brains are structured to facilitate connectivity between perception and coordinated action, whereas female brains are designed to facilitate communication between analytical and intuitive processing modes (Ingahalikar, Smith, Parker, Satterthwaite, Elliott, Ruparel, Hakonarson, Gur, Gur & Verma 2014). Our methodology now allows us to systematically interrogate those differences in the context of the functionally critical areas of dexterity.

2.5.3 Effect of Clinical Condition

Our study also raises the similarly noteworthy question of why a condition that is presumably purely orthopedic (i.e., CMC OA) produces deficits in dynamic manipulation-and accelerated losses with age-comparable to those in a purely neurological condition (i.e., PD). Both the CMC OA and PD groups displayed significant differences ($p < 0.001$) in the compression dynamics (\dot{F}_f , \ddot{F}_f , and RMS_f) compared to the control participants (Figure 2.2), although no differences in compression force. That is, all three populations were able to compress to the same amount, but not in the same way. Similarly, detailed visualization of the finger force dynamics during compression via phase portraits (Figure 2.3) shows subjects with CMC OA and PD tend to demonstrate weaker correction strategies. The greater amount of dispersion

in the phase portraits of clinical patients suggests a compromised ability to execute corrections, or a different neural control strategy towards instability, not seen in control subjects (Dayanidhi, Hedberg, Valero-Cuevas & Forssberg 2013, Dayanidhi & Valero-Cuevas 2014). Whether these differences in neural control, or the mechanisms of executing neural control, are similar or different in CMC OA and PD remains an open question.

These results also challenge the notion that CMC OA is a strictly orthopedic condition given that we now see it produces sensorimotor deficits. The link between a disease of articular cartilage and deficits in sensorimotor integration capabilities is underappreciated and understudied in the literature. To elaborate, Figure 2.2 illustrates that the CMC OA and PD populations are essentially indistinguishable when plotting finger force velocity vs. finger force RMS. These results raise the question, what is it about chronic pain and damage to the joint that leads to changes in sensorimotor capabilities? Others have begun to speak about this and a picture is now emerging showing that chronic pain leads to reorganization of brain circuits. For example, subacute low back pain induces changes in connectivity and functional reorganization of the insula and sensorimotor cortex, even after only one year with moderate pain (Baliki, Petre, Torbey, Herrmann, Huang, Schnitzer, Fields & Apkarian 2012). Also, spontaneous pain due to knee OA is known to engage brain regions distinct from those activated by pressure-evoked pain, specifically prefrontal-limbic structures (Parks et al. 2011). The presence of acute pain will

naturally compromise hand function—but we now see that chronic pain also affects the performance of a dexterous task even if it requires very low forces and does not elicit pain. Our prior work suggests these deficits are credibly attributable to structural or functional changes in portions of the nervous system responsible for the neural control of dexterity.

At the other end of the clinical spectrum, PD starts out as a purely neurological degenerative disease characterized by upper and lower extremity rigidity, tremor, bradykinesia, and/or postural instabilities (Kopin 1993, Jankovic 2008). Our prior work has shown that the cortical networks associated with controlling instabilities in dexterity can involve the basal ganglia (Mosier et al. 2011), where degeneration of dopamine-producing cells plays a central role in PD (Jankovic 2008). Thus it is expected that we would detect deficits in sensorimotor function and, in turn, dexterous manipulation in this population. But our results allow us to go deeper than this. They allow us to, for the first time, i) systematically quantify behavioral deficits in PD and other neurological conditions, ii) disambiguate the contributions of different elements of the neuromuscular system to these deficits, and iii) easily and objectively quantify the effectiveness of different treatment regimens (e.g., absorption of medication or titration of deep brain stimulation level) during the daily-and even hourly-fluctuations in motor deficits in PD that traditional measures cannot. But it is also critical to note that PD leads to significantly greater

rates of decline of dexterity with age when compared to healthy aging or with patients diagnosed with CMC OA. This highlights the neurodegenerative nature of the disease, and underscores the need to quantify the effects of PD on sensorimotor processing and dexterous manipulation to better understand its neurodegeneration and treatment.

How do our results speak to ADLs? The SD paradigm falls clearly within the Body Functions and Structure Components of the International Classification of Function (ICF (*International classification of functioning, disability and health* 2001)). Understanding the link between SD performance and the Activity Limitations and Participation Restriction Components of the ICF requires further research. But as of now, we can say that the SD paradigm is likely very informative of systemic mechanisms that make dexterous function possible. That is, the SD paradigm reflects the potential to execute ADLs without the confounds of functional adaptations that mask the detrimental effects of disease. A clear example for the upper extremity is that of manipulating small and/or deformable objects such as beads or squeezing lemons, respectively. In both these cases, the manipulation task is unstable in same sense that the SD paradigm specifies: they require accurate dynamical regulation of the magnitude and direction of fingertip forces and motions (Dayanidhi, Hedberg, Valero-Cuevas & Forssberg 2013, Dayanidhi & Valero-Cuevas 2014). For the lower extremity, we have proposed that the SD paradigm may explain the risk of injury or falls (Lyle et al. 2013*b*, Lyle et al. 2014)

because the regulation of dynamical interactions with the ground is critical to locomotion and many sports activities, as mentioned above.

2.5.4 Systemic versus Limb-Specific Dexterity

Another fundamental aspect of this work is that we extended the concept of finger dexterity to limbs in general. We use the same definition of dexterity to quantify the sensorimotor ability of the leg to regulate dynamical interactions with the ground in a subset of our participants. In the context of lower extremity function, the LED test evaluates the ability of the sensorimotor system to control an unstable ground contact with the isolated leg; and avoids potential confounds often found in gait, posture and balance studies such as vestibular function, visuo-spatial perception, strength, whole-body balance, locomotor confidence, and inter-limb coordination. Clearly, our aim is not to study locomotion, but to focus on the fundamental sensorimotor capabilities of the leg. Further work is needed to establish its relationship to whole body gait, posture and balance capabilities. Nevertheless, our recent work on the lower extremity has demonstrated the validity and reproducibility of the LED test as a metric of dynamic leg function, and its correlation to whole-body agility. It has also clearly detected differences between young men and women (Lyle et al. 2013a, Lyle et al. 2013b, Lyle et al. 2014). As in the case of the fingers (Vollmer et al. 2010), we have shown that the LED test quantifies a previously unrecognized functional domain related to dexterity of the isolated leg

that cannot be seen as simply a covariate of available functional tests of strength, gait or balance. Here we extend that prior work on leg dexterity by measuring the same set of variables as for the finger in 188 healthy volunteer participants (Tables 2.1-2.3). To our knowledge, this is the first comparison of finger versus leg dexterity that allows us to distinguish between systemic and limb-specific sensorimotor capabilities. Interestingly, we find similar effects of age and sex in both finger and leg dexterity.

The age and sex effects on leg compression force (Figure 2.5, Table 2.3) naturally suggest that the same neural mechanisms and networks for the fingers (discussed above) are at work in the leg to some extent. Traditionally we have come to think of "dexterity" as specific to fingers (e.g., (Lemon 1997, Castiello 2005, Lemon 2008), and surely some features are. Phylogenetically speaking, however, legs evolved earlier and for the same purpose: to produce dynamical interactions with the ground. Thus the prior existence of neural circuits to regulate instabilities in ground contact during quadruped gait and brachiation likely served as the foundation from which specializations evolved for manipulation in the human hand. Therefore, our discussions above about the neurophysiological bases of age and sex effects apply here as well. But there are also important differences. We found no age and sex effects on compression dynamics (\dot{F}_1 , \ddot{F}_1 , and RMS_1), and most of these effects are far from significance even in this relatively large sample size (Table 2.2).

These similarities and differences between finger and leg dexterity, as quantified by the SD and LED tests, suggest the existence of specialized mechanisms for systemic versus limb-specific dexterity. First, it is clear that these results compel us to study in detail the neurophysiological bases of leg dexterity in health and disease, to at least to the level we have for the fingers. Moreover, the multiple time scales and latencies with which these dynamical tasks need to be controlled suggest a hierarchical organization of neural control, in agreement with current thinking (Kawato, Furukawa & Suzuki 1987, Loeb, Brown & Cheng 1999, Konen & Kastner 2008). But we must not be content with this generalization. Future work must leverage available techniques (e.g., EMG, fMRI (Holmstrom et al. 2011, Mosier et al. 2011), H-reflex, transcranial magnetic stimulation (TMS), coherence analysis (Yao, Salenius, Yue, Brown & Liu 2007), EMG weighted average (Dayanidhi, Kutch & Valero-Cuevas 2013), etc.) in specific and well-directed studies to disambiguate among peripheral, spinal and cortical contributions and mechanisms of dexterity. The SD paradigm allows such studies for the legs as it has for the fingers. Our findings about leg dexterity nevertheless have immediate utility, both scientifically and clinically.

In addition to providing insight into the nature of sensorimotor dysfunction in clinical populations, the fact that the LED test is able to discern sex differences (Figure 2.6, Table 2.2) may provide insight into why young women have a much greater likelihood of non-contact ACL tears than men (Arendt, Agel & Dick 1999).

Though the reasons are not clear, some theories include differences in anatomy, knee alignment, ligament laxity, hormone levels, muscle strength and conditioning, and neuromuscular control (Sigward et al. 2012, Lyle et al. 2013a). The clearly reduced dexterity we report in young women (both in fingers and legs) expands on previous results (Lyle et al. 2013a) with a smaller sample size where sex differences in dexterity were used to provide a neuromuscular explanation for the higher incidence of ACL tears and reduced agility in young female athletes. Moreover, given that we now show that these sex differences in leg dexterity are present throughout the lifespan also speaks to the fact that women over the age of 65 have a disproportionately greater occurrence of unintentional falls than men (Armstrong et al. 1994, Stevens & Sogolow 2005). Future work will include identifying those with reduced leg dexterity who may have a greater risk for ACL tears or falls and would benefit from preventative neuromuscular training programs.

Interestingly, we saw no clear effect of limb dominance on finger and leg dexterity in the subset of 81 participants who completed the SD paradigm with all four limbs. After all, voluntary fine-motor tasks such as writing, cutting, catching, and kicking exhibit strong effects of laterality. In fact, there is a multitude of evidence supporting both functional (e.g., strength and motor control) and anatomical differences at the cortical level between dominant and non-dominant limbs (Petersen, Petrick, Connor & Conklin 1989, Kovaleski, Heitman, Gurchiek, Erdmann & Trundle 1997, Adam, De Luca & Erim 1998, Grafton, Hazeltine & Ivry 2002, Ullen, Forssberg &

Ehrsson 2003, Özcan, Tulum, Pınar & Başkurt 2004, Michimata et al. 2008). It is reported that long-term preferential use of muscles results in a higher percentage of type I muscle fibers in the dominant hand and, in turn, changes in motor unit firing behavior (Adam et al. 1998). Furthermore, imaging studies have shown that the hemisphere contralateral to the dominant hand demonstrates more efficient motor control at lower activation levels and less crosstalk than the non-dominant hemisphere (Grafton et al. 2002, Ullen et al. 2003). One potential explanation is that we simply did not have enough subjects to demonstrate that latent effect, much as we did not find an age or sex effect in this same group of 81 subjects spanning multiple ages. This mirrors our prior work where we were not able to detect sex effects for the upper extremity in studies with smaller sample sizes (Dayanidhi, Hedberg, Valero-Cuevas & Forssberg 2013). But what is more striking, however, is that larger numbers may be needed to detect an effect of limb dominance, if it is even present.

Our lack of detection of limb dominance nevertheless raises important questions. As mentioned recently, it is likely that hemispheric specialization emerged to accommodate increasing motor complexity of tasks during primate evolution. That is, instead of the non-dominant limb being a lesser analogue of the dominant limb, Sainburg and colleagues (Mutha, Haaland & Sainburg 2013) have proposed an alternative view that motor lateralization reflects proficiency of each arm for

complementary functions in response to distinct movement control mechanisms associated with specific unimanual tasks. We speculate that the lack of effect of dominance suggests that the SD paradigm reveals and quantifies subcortical mechanisms for dynamical function that are not influenced by hemispheric differences-in accordance with theories of hierarchical neural control and phylogenetic development of the nervous system. There is evidence of subcortical contributions to motor control (i.e., dexterity) independent of limb dominance. In this hierarchical view of motor control, the cerebellum, basal ganglia, spinal cord, etc. are essential to executing and regulating motor function. In agreement with Sainburg and colleagues (Mutha et al. 2013), we speculate that hand (or leg) dominance is therefore likely a late arrival to the motor repertoire in humans that affects fine-motor tasks but not "low-level" stabilization mechanisms tested by the SD paradigm. This is supported by recent studies using fMRI to evaluate how hand dominance and task difficulty affect activation levels at the spinal cord (Ng, Wu, Lau, Hu, Lam & Luk 2008). They found significant differences in spinal cord activation levels when performing simple unilateral tapping tasks with the dominant and non-dominant hands-but they found no effect of hand dominance during a more complex unilateral tapping task. The SD paradigm may be engaging these systemic hierarchically common circuits to all limbs independently of cerebral lateralization.

How does this concept that dexterity requires both subcortical and cortical mechanisms agree with or revise current thinking? Very briefly, the literature on

cortical involvement in dexterous manipulation is large (e.g., the reviews (Schieber & Santello 2004, Lemon 2008, van Duinen & Gandevia 2011)). Our own fMRI studies agree with many others suggesting direct cortical involvement by showing the SD paradigm can systematically interrogate brain function for dexterous manipulation, which exhibits differential activity across cortical networks depending on the level of difficulty and behavioral goals of the task (Talati et al. 2005, Holmstrom et al. 2011, Mosier et al. 2011). We have also proposed the likely evolutionary advantage of the monosynaptic corticospinal tract to manipulation by enabling the time-sensitive transitions from the control of motion to the control of static force (Venkadesan & Valero-Cuevas 2008); and the competition between descending commands to grasp vs. manipulate, likely involving the phylogenetically older reticulospinal and the newer corticospinal tracts (Racz, Brown & Valero-Cuevas 2012). But our results here compel us to confront several inconvenient facts to the cortico-centric view of neural control of the hand. Those facts include time delays, our evolutionary history, and clinical symptomatology, which can be resolved by paying more attention (and due credit) to subcortical mechanisms. Investigators agree that many manipulation tasks (such as stabilization in the SD paradigm) occur at time scales for which spino-cortico-spinal delays would compromise closed-loop control. Neural control must, therefore, involve motoneuronal modulation by the spinal cord in human and non-human primates to some extent (Lemon 1993, Schieber 2011). In fact, neuroanatomists and electrophysiologists since the time of Sherrington have

sought to map the circuitry in the spinal cord (Pierrot-Deseilligny & Burke 2005) to understand the spinally-mediated excitation-inhibition mechanisms that contribute to voluntary function (e.g., (Raphael, Tsianos & Loeb 2010, Giszter & Hart 2013)) and to, for example, the clinical symptomatology of spastic hypertonia present in many neurological disorders including stroke, traumatic brain injury, cerebral palsy, multiple sclerosis, and spinal cord injury (e.g., (Zhang, Chung, Ren, Liu, Roth & Rymer 2013) and references therein). Therefore, much as Lemon has written "it may be too sweeping a generalization to suggest that cortico-motoneuronal connections are the sine qua non of independent digit movements" (Lemon 1993), our results indicate that it may be too sweeping a generalization to suggest that cortical mechanisms are the sine qua non of dexterity. Once again, this compels future work to disambiguate among peripheral, spinal and cortical contributions and mechanisms of dexterity.

Finally, this is the first time that to our knowledge a same paradigm is used to quantify both finger and leg dexterity. We report their correlation in Figure 2.6, indicating that the sensorimotor system may have a combination of systemic vs. limb-specific mechanisms, although the contribution of each remains unclear. The fact that this correlation is greater in female than in male participants ($\rho=0.529$ vs. $\rho=0.403$, respectively) suggests a much greater systemic component in women. We speculate that dexterity is actually the sum of two components: the basic systemic, plus the limb-specific. The stronger systemic component in women may

then suggest that men are able to add more of the limb-specific component and thus show less correlation overall. What could be the causes of this added plasticity for limb-specific dexterity in men? In addition to genetically imposed dimorphism (e.g., nature), sociobiological elements (e.g., nurture) such as differential exposure to physical activity, cultural biases, social expectations, etc., may play a role in the development and learning of motor function (Eccles & Harold 1991). Thus the differences in dexterity across sexes that we report, and in brain connectivity that others report, may be-at least in part-due to its phenotypical neurobiological consequence.

2.6 Acknowledgements

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Chapter 3

Outcome Measures for Hand Function Naturally Reveal Three Latent Domains in Older Adults: Strength, Coordinated Upper Extremity Function, and Sensorimotor Processing

3.1 Abstract

Understanding the mapping between individual outcome measures and the latent functional domains of interest is critical to a quantitative evaluation and rehabilitation of hand function. We examined whether and how the associations among six hand-specific outcome measures reveal latent functional domains in elderly individuals. We asked 66 healthy older adult participants (38F, 28M, 66.1 ± 11.6 years, range: 45-88 years) and 33 older adults (65.8 ± 9.7 years, 44-81 years, 51 hands) diagnosed with CMC OA, to complete six functional assessments: hand strength (Grip,

Key and Precision Pinch), BBT, NHPT, and the SD test. The first three principal components suffice to explain 86% of variance among the six outcome measures in healthy older adults, and 84% of variance in older adults with CMC OA. The composition of these dominant associations revealed three distinct latent functional domains: strength, coordinated upper extremity function, and sensorimotor processing. Furthermore, in participants with thumb CMC OA we found a blurring of the associations between the latent functional domains of strength and coordinated upper extremity function. This motivates future work to understand how the physiological effects of thumb CMC OA lead upper extremity coordination to become strongly associated with strength, while dynamic sensorimotor ability remains an independent functional domain. Thus, when assessing the level of hand function in our growing older adult populations, it is particularly important to acknowledge its multidimensional nature-and explicitly consider how each outcome measure maps to these three latent and fundamental domains of function. Moreover, this ability to distinguish among latent functional domains may facilitate the design of treatment modalities to target the rehabilitation of each of them.

3.2 Introduction

The hand is vital for human activities and independent living and influences the quality of task performance, especially those requiring dexterity (Light et al. 1999). As such, quantifying hand function is central to research and clinical care and

numerous outcome measures have been developed to evaluate treatment effectiveness and ultimately improve medical care (Cromwell 1976, Walker, Davidson & Erkman 1978, Mathiowetz, Kashman, Volland, Weber, Dowe & Rogers 1985, Hume, Gellman, McKellop & Brumfield 1990, Marx, Bombardier & Wright 1999, Light, Chappell & Kyberd 2002, Oxford Grice et al. 2003). The central question here is, What should we use to quantify hand function considering that that we have so many choices of assessment tools and even more outcome measures stemming from those tools? It stands to reason that the multi-dimensional nature of hand function would require multiple outcome measures for accurate assessment of ability. But the sheer number of available outcome measures creates a false sense of high-dimensionality. This motivates us to evaluate the associations, commonalities, and dissociations among outcome measures, and their ability to reveal latent functional domains. We propose that understanding the mapping between individual outcome measures and the latent functional domains of interest is critical to the quantitative evaluation and rehabilitation of hand function. To clarify, we define latent functional domains as the hidden dimensions underlying hand function. We believe this approach will address and help resolve the debate over the merits of available outcome measures.

In the motor function community, some advocate the preeminence of measures of hand strength or joint range of motion (Light et al. 1999). Others prefer outcome measures geared towards ADLs that feature coordinated upper extremity

function (Light et al. 1999) such as time limited measures (i.e., amount completed in a given time) like the BBT (Mathiowetz, Volland, Kashman & Weber 1985) and the Crawford Small Parts Dexterity test (Boyle & Santelli 1986). Yet still others emphasize work limits (i.e., time to completion) such as the NHPT (Oxford Grice et al. 2003) and the Functional Dexterity Test (Mathiowetz, Volland, Kashman & Weber 1985, van Lankveld, van't Pad Bosch, Bakker, Terwindt, Franssen & van Riel 1996). While all of these outcome measures have shown utility, it is recognized that they offer limited information (Light et al. 1999, Light et al. 2002, Duff, Aaron, Gogola & Valero-Cuevas 2015). As a result, new assessment tools were developed that include a battery of measures designed to assess a set of motor functional abilities like the Jebsen Hand Function Test (Jebsen, Taylor, Trieschmann, Trotter & Howard 1969) and TEMPA tests (Desrosiers, Hebert, Bravo & Dutil 1995). There are other measures focusing on sensory acuity like the Weber two-point discrimination (Dellon, Mackinnon & Crosby 1987) and the AsTex sensitivity tests (Miller, Phillips, Martin, Wheat, Goodwin & Galea 2009)—but sensorimotor control is difficult to test while disambiguating it from strength, coordinated upper extremity function, tactile and visual acuity, and speed. We stress that sensorimotor processing is integrative by definition, and must be considered independently of isolated motor or sensory function. One example of sensorimotor fingertip function

is the ability to dynamically control the magnitudes and directions of force vectors, as quantified by the SD test (Valero-Cuevas et al. 2003, Dayanidhi, Hedberg, Valero-Cuevas & Forssberg 2013, Lawrence et al. 2014).

But the questions remain: what latent domains describe hand function and how do individual outcome measure relate to latent functional domains of interest? In fact, the ICF by the World Health Organization (*International classification of functioning, disability and health* 2001) highlights the importance of quantifying latent functional domains related to body structure and function, activity, and participation, which clearly require several different assessment tools. Seen from this perspective it is difficult to define and justify a specific selection of-and hierarchy among-available assessment tools. Thus, several rehabilitation studies have begun to explore interactions among outcome measures (Hellstrom, Lindmark, Wahlberg & Fugl-Meyer 2003, Patterson, Gage, Brooks, Black & McIlroy 2010, Hart & Bagiella 2012, McDonough, Jette, Ni, Bogusz, Marfeo, Brandt, Chan, Meterko, Haley & Rasch 2013, Milot, Spencer, Chan, Allington, Klein, Chou, Bobrow, Cramer & Reinkensmeyer 2013, Egan, Davis, Dubouloz, Kessler & Kubina 2014). Similarly, here we examine whether and how the interactions and associations among six commonly used outcomes measures reveal latent functional domains in (i) healthy older adults and (ii) older adults with thumb CMC OA.

3.3 Methods

3.3.1 Participants and Procedures

Sixty-six healthy adult participants (38F, 28M, 66.1 ± 11.6 years, range: 45-88 years) completed the following assessments that utilize varying levels of strength requirements with their dominant hand (described in detail below): BBT, NHPT, SD test, and measures of finger and hand strength (grip strength, key pinch, and precision pinch). We then asked 33 adult participants (65.8 ± 9.7 years, 44-81 years, 51 hands,) diagnosed with and treated for CMC OA to complete the same assessments with their affected hand(s). These patients were evaluated at an average of 40 months after either surgical or conservative treatment by the same surgeon at Institut de la Main, Clinique Jouvenet in Paris, France between September 2005 and December 2011. All participants gave their informed consent to the experimental protocols, which were approved by the Institutional Review Boards at Rancho Los Amigos National Rehabilitation Center and the University of Southern California. The assessments were performed during a single session and participants were allowed to rest as often as needed, in between tests.

3.3.2 Data Analysis

Principal components analyses (PCA) were used post hoc to determine the associations among the dependent measures from all six assessments. PCA is a data

mining procedure that finds the best linear fit to the data using a series of perpendicular vectors or principal components (PCs) (Clewley, Guckenheimer & Valero-Cuevas 2008). Within each PC vector (i.e., column) the structure of the correlations and non-zero numerical values in each column quantify the relative positive or negative correlations among variables (Clewley et al. 2008). To put it simply, we used PCA as a method of dimensionality reduction that, in this case, examines the contributions of the dependent measures to hand function and the associations among these measures. Due to the differences in units and normal distributions among variables, and for comparison purposes, we calculated the standard score (z-score) of each variable and used their standardized normal distribution values for the PCA dataset (Jolliffe 2005). The PCs are presented in descending order quantifying their contributions to hand function such that the first principal component explained the largest amount of variance. We note that the first three PCs sufficed to capture approximately 85% of the total variance for both datasets; therefore, we limited our analysis to them. Significance was set at $p \leq 0.05$ and Matlab and SPSS were implemented for these analyses.

3.4 Results

The means, standard deviations, and ranges of each dependent measure are presented in Table 3.1. Clinical outcome measures in all healthy participants were within normal ranges when compared to previously published data (Mathiowetz,

Kashman, Volland, Weber, Dowe & Rogers 1985, Mathiowetz, Volland, Kashman & Weber 1985, Oxford Grice et al. 2003).

Table 3.1: Mean performance data from all upper extremity participants.

Outcome Measure	Performance	Mean±SD		Range	
		Healthy	CMC OA	Healthy	CMC OA
Grip (kg)	Higher is better	29.9±13.8	17.1±5.6	5.7-74.5	3.1-31.8
Key (kg)	Higher is better	7.9±2.6	5.1±1.7	2.7-14.9	2.0-11.0
Precision (kg)	Higher is better	6±2.4	5.3±1.7	2.3-14.1	2.5-12
BBT (score)	Higher is better	59.2±11.9	55.4±8.8	34-86	29-71
NHPT (s)	Lower is better	18.1±5.7	21.5±5.5	9.8-33.7	15.6-48
SD (g)	Higher is better	171.4±42.9	170±39.8	83.5-271.4	101.7-245.2

The PCA results from the healthy participants are presented in numerical form below (Table 3.2). Loading values quantify the strength and direction of the relationships between variables and range between -1 and 1, where 1 is total

positive correlation, 0 is no correlation, and -1 is total negative correlation.

Table 3.2: Association and dissociation of outcome measures in healthy older adults.

(Normalized loadings for ease of comparison, Underlining in each column indicates ≤ 0.40) positive and negative correlations, respectively, with the dominant variable, in bold.)

Outcome Measure	1st PC	2nd PC	3rd PC
Grip	<u>0.86</u>	<u>-0.61</u>	-0.04
Key	1.00	-0.24	-0.11
Precision	<u>0.88</u>	-0.25	<u>-0.54</u>
BBT	<u>0.48</u>	1.00	-0.11
NHPT	<u>-0.53</u>	<u>-0.99</u>	0.02
SD	<u>0.68</u>	-0.05	1.00
% Contribution	47.91%	25.03%	12.83%
Cumulative	47.91%	72.94%	85.77%

The 1st PC explains 48% of the variance and shows that the strength measures are the leading factors distinguishing participants. Key pinch strength representing the highest loading is positively associated with grip strength and precision pinch strength (0.86 and 0.88, respectively). The strength measures were also moderately positively correlated with BBT and SD performance (0.48 and 0.68, respectively)

and negatively associated with NHPT (-0.53). The 2nd PC, which explains an additional 25% of the variance, indicates that coordinated upper limb function (BBT) is negatively associated with finger dexterity (NHPT) and grip strength (1.00 versus -0.99 and -0.61). Furthermore, the 3rd PC explains another 13% of the variance, and indicates that sensorimotor coordination (SD) is the sole contributor and is negatively associated with precision pinch (-0.54). To further explain our results, we provide a visual representation of the respective loadings for each of the first three PCs, Figure 3.1. We then repeated our analysis in a group of participants diagnosed with and treated for CMC OA. Those results are presented numerically in Table 3.3 and visually in Figure 3.2.

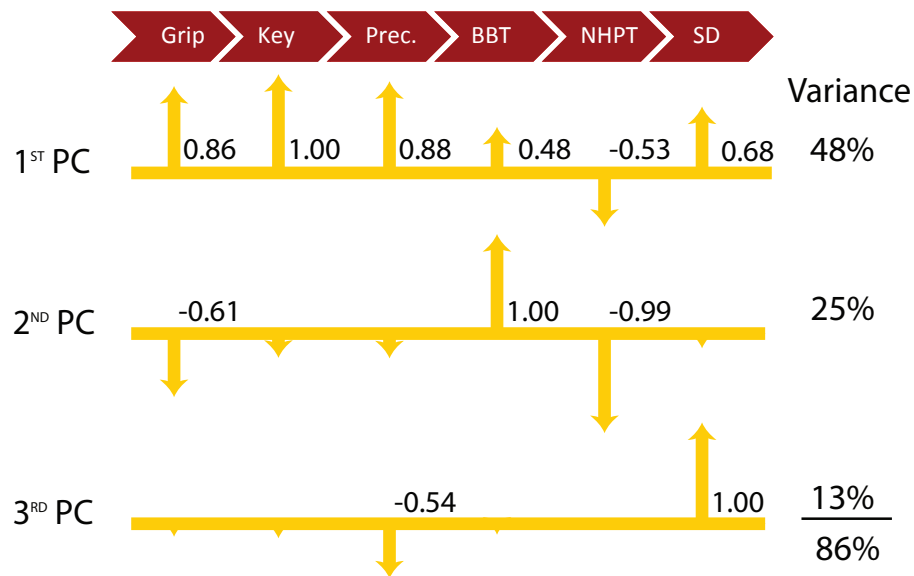


Figure 3.1: Visualization of latent functional domains in healthy older adults. The scaled loadings for the outcome measures of the first three PCs are illustrated above. All loadings are shown, but numerical values are only listed if they are $\leq \pm 0.40$. The signs of the loadings are indicated by the direction of the arrowheads. Note that a higher score is better for all test except for NHPT, where lower is better.

Table 3.3: Association and dissociation of outcome measures in older adults with thumb CMC OA.

(Normalized loadings for ease of comparison, Underlining in each column indicates ≤ 0.40) positive and negative correlations, respectively, with the dominant variable, in bold.)

Outcome Measure	1st PC	2nd PC	3rd PC
Grip	1.00	0.04	-0.04
Key	<u>0.96</u>	<u>-0.43</u>	0.32
Pres	<u>0.81</u>	<u>-0.53</u>	<u>0.74</u>
BBT	<u>0.79</u>	<u>0.62</u>	<u>-0.40</u>
NHPT	<u>-0.90</u>	<u>-0.52</u>	<u>0.42</u>
SD	-0.17	1.00	1.00
% Contribution	47.91%	25.03%	12.83%
Cumulative	47.91%	72.94%	85.77%

In participants with CMC OA, the 1st PC accounted for 51% of the total variance and revealed that outcome measures of hand strength (grip, key pinch, and precision pinch) again demonstrate the highest positive associations (1.00-0.81, respectively). We further report positive and negative associations with BBT (0.79) and NHPT (-0.90). The 2nd PC explained an additional 19% of the variance and indicated that sensorimotor processing (SD test) was the sole contributor and showed moderate associations with measures of finger strength (-0.43 and -0.53)

and coordinated upper extremity function (0.62 and -0.52). The SD test again demonstrated the highest loading in the 3rd PC, which explained 14% of the total variance. Additionally, we report a moderate positive association with precision pinch and NHPT (0.74 and 0.42) and a negative association with BBT (-0.40).

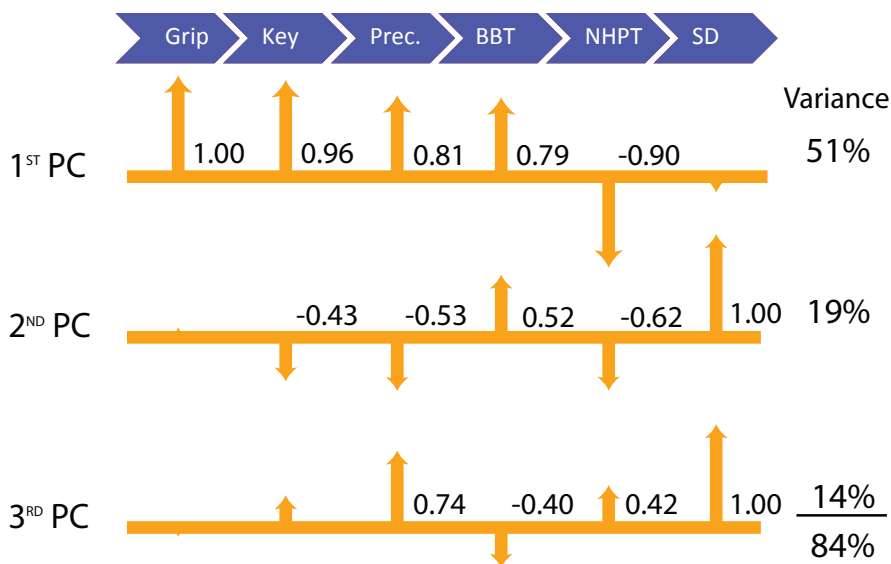


Figure 3.2: Visualization of latent functional domains in participants with CMC OA. The scaled loadings for the outcome measures of the first three PCs are illustrated above. All loadings are shown, but numerical values are only listed if they are $\leq \pm 0.40$. The signs of the loadings are indicated by the direction of the arrowheads..

3.5 Discussion

Understanding the latent domains of hand function has important implications for both the basic and clinical research communities. The multidimensional ICF model underscores the need to examine outcome measures across the three ICF domains, while at the same time, mapping them to meaningful functional domains.

This holds especially true when considering the highly complex nature of the hand and its impact on activity and quality of life. Therefore we applied a dimensionality reduction technique (e.g., PCA) to datasets from six hand-specific outcome measures to determine if and how they mapped into distinct functional domains. We find that the associations and disassociations among the six measures we included reveal three interpretable latent domains of hand function in older adults with and without CMC OA defined as strength, coordinated upper extremity function, and sensorimotor processing. It goes without saying that, although we do not go into detail in this publication, it is important to also consider the inherent psychometric properties (e.g., level of measurement, reliability, validity, etc.) of outcome measures when using them as assessment tools. We note that in this study all outcome measures have been previously shown to be reliable and valid (see Methods section for more detail).

In healthy older adult participants, 86% of the variance in hand function was explained by the first three PCs with each individually contributing to between 13 and 48% of the total variance. The 4th and higher PCs each contributed to relatively small percentages (4-9%) of total variance and were not considered in our analysis due to the potential for over interpretation. Not surprisingly, the 1st PC indicates that the three hand strength measures tend to be positively associated with each other (Table 3.2 and Figure 3.1) and that participants tend to vary most in their strength scores (i.e., because most variance is captured by the 1st PC).

Thus both hand and finger strength may be most susceptible to age- and health-related declines as they showed the greatest variability among participants. We also find that there are moderate associations between the measures of strength and those of coordinated upper extremity function and sensorimotor coordination. This supports the notion that, while not critical, at least a low-level of strength is required for (and correlated with) successful completion of daily activities and functional tasks (Skelton, Greig, Davies & Young 1994). There are mixed reports about the contributions of strength to hand function, particularly in older adults. Some have reported improvements in both maximal force production and hand function after exposure to exercise training regimens (Dellhag, Wollersjo & Bjelle 1992, Brorsson, Hilliges, Sollerman & Nilsson 2009). In contrast, others report no correlation between the level of force production and the ability to open everyday containers (Rice, Leonard & Carter 1998, Rahman, Thomas & Rice 2002). This agrees with a report that maximal strength is likely not a critical determinant of daily activities because they often require low force magnitudes (Smaby, Johanson, Baker, Kenney, Murray & Hentz 2004).

In our study, healthy older adults were then best distinguished by tests of coordinated upper extremity function (BBT and NHPT) (Figure 3.1, 2nd PC). The 2nd PC accounted for an additional 25% of the variance and revealed negative associations with measures of strength and little, if any, association with sensorimotor processing. Tests of whole arm function do just that-measure whole arm

function. As a result, it is natural to expect that they will not be as informative of hand function *per se* in individuals with, for example, some level of shoulder or elbow dysfunction. This is not a new problem, and has been addressed by many groups (Light et al. 1999, Light et al. 2002, Duff et al. 2015), which led to the development of specialized devices with the intention of isolating the hand from the arm (Memberg & Crago 1995). The usefulness of outcome measures featuring such devices is often questioned as they tend to be specialized for certain hand tasks, making their use as a widespread assessment of general hand function ultimately uninformative (Light et al. 1999). Therefore, when evaluating fine motor control, researchers and clinicians often turn to the NHPT, a reliable and validated measure of hand dexterity. Nevertheless, the information obtained from this measure tends to be limited to one's ability to pick up and place pegs into a board, rather than provide information about sensorimotor coordination or precision strength, and that specificity likely limits its potential for providing basic information on overall hand function (Duff et al. 2015). Moreover, the low and negative correlations among all other outcome measures in the 2nd PC support our prior work where we show that whole-arm function is independent of strength and sensorimotor ability.

The 3rd PC explained another 13% of the variance and also strongly suggested that the SD test captured a different functional domain than either of the other two, likely sensorimotor coordination as our prior work has shown (Valero-Cuevas et al. 2003, Vollmer et al. 2010, Dayanidhi & Valero-Cuevas 2014). The intricacy of

the sensorimotor system dictates that it cannot be quantified with a discrete value or score as with outcome measures geared towards strength or even coordinated upper extremity function. Therefore, one should consider the inclusion of more intricate methods to investigate sensorimotor ability that are decoupled from strength or whole arm function as much as possible in order to not dilute the information gained (Valero-Cuevas et al. 2003). As such, SD test offers a means to quantify the dynamic interaction between fingertip force magnitudes and directions during a dynamic sub-maximal pinch task, which we have shown is informative of sensorimotor ability (Valero-Cuevas et al. 2003, Talati et al. 2005, Venkadesan & Valero-Cuevas 2008, Vollmer et al. 2010, Holmstrom et al. 2011, Dayanidhi, Hedberg, Valero-Cuevas & Forssberg 2013, Dayanidhi & Valero-Cuevas 2014, Lawrence et al. 2014, Lightdale-Miric, Mueske, Dayanidhi, Loiselle, Berggren, Lawrence, Stevanovic, Valero-Cuevas & Wren 2015, Duff et al. 2015).

We find evidence in our results that support the fact that sensorimotor processing is distinct from strength or coordinated upper limb function. For example, notice that the SD test is independent of grip and key pinch strength (Figure 3.1, 3rd PC), and moderately negatively correlated with precision pinch strength (-0.54) in the same finger posture (i.e., tip-to-tip pinch). This complements our prior work that shows that declines in strength and dexterous manipulation are disassociated in older adults (Dayanidhi & Valero-Cuevas 2014). Recall that the SD test, by using

compliant slender springs, requires only very low forces in the order of 3N. Thus although the 'greatest mean compression force' is the measured variable, in reality the level of force is indicative of the maximal instability that can be controlled at low force levels. Secondly, this interpretation of a distinct functional domain of sensorimotor processing is consistent with fMRI studies showing that 1) force production and stabilization, two main features of dexterous manipulation, are represented by two distinct areas within the grasping network (Holmstrom et al. 2011) and 2) the areas of activation in the sensorimotor cortices are dependent on task dexterity requirements (Mosier et al. 2011). Finally, in the 3rd PC, the SD test showed no association with either the BBT or the NHPT (Figure 3.1). This combined with the lack of association in the 2nd PC that we discussed previously supports the notion that sensorimotor processing represents a domain of hand function not strongly correlated with coordinated upper limb function. These results mirror our prior work pertaining to the development of dexterity in children where sensorimotor processing was found to be a functional dimension distinctly different from strength and whole arm coordination (Vollmer et al. 2010).

Our study also allowed us to investigate the contributions of each domain of hand function in a group of older adults affected by thumb CMC OA. The first three PCs suffice to explain 84% of the total variance in hand function; therefore, we limit our interpretations to them. Interestingly, the associations among outcome measures found in healthy adults were altered in the presence of thumb CMC OA. The latent

functional domains of strength and coordinated upper extremity function seem to merge and show no association with sensorimotor processing in the 1st PC (Figure 3.2), which explained 51% of the total variance. This suggests that in the presence of the physiological effects of thumb CMC OA, upper extremity coordination is no longer its own independent domain and becomes strongly associated with strength, while dynamic sensorimotor ability remains an independent domain. Sensorimotor processing is the leading contributor in the 2nd PC (Figure 3.2) and showed moderate associations with outcome measures associated with finger strength (precision and key pinch) and coordinated upper extremity function (NHPT and BBT) that were not present in the healthy participants. This may suggest that the reductions of both strength and coordinated upper extremity function often associated with thumb CMC OA (Bagis, Sahin, Yapici, Cimen & Erdogan 2003, Dominick, Jordan, Renner & Kraus 2005, Kjeken, Dagfinrud, Slatkowsky-Christensen, Mowinkel, Uhlig, Kvien & Finset 2005) place greater emphasis on sensorimotor processing as a compensatory strategy for successful hand function. We further report a positive association of the SD test, which dominated the 3rd PC, with precision pinch strength (0.74) in participants with thumb CMC OA (Figure 3.2, 3rd PC), unlike in healthy participants where we report a moderately negative association (-0.54) (Figure 3.1, 3rd PC). This suggests that the pain and anatomical deformities associated with thumb CMC OA may also alter the association between the strength and sensorimotor processing latent domains.

It is important to note that the participants with thumb CMC OA were all female, while the healthy older adult group was both male and female to accurately represent the older adult population. We chose to only test women in the clinical group because thumb CMC OA is disproportionately more prevalent in women, starting at the fifth decade of life (Armstrong et al. 1994, Comtet, Gazarian & Fockens 2001, Haara, Heliovaara, Kroger, Arokoski, Manninen, Karkkainen, Knekt, Impivaara & Aromaa 2004); thus finding suitable male candidates would have been difficult, but also would have potentially introduced a sex effect in the SD test that we have reported in the past (Lawrence et al. 2014). For these reasons, we also ran our PCA separately for female and male healthy participants to compare against the all female thumb CMC OA group. While we do not show those results for succinctness, we found that the PCs found in the combined group of healthy participants remained unchanged when analyzing the data from only males or females. This gives us confidence that the differences we report between groups can, in fact, be attributed to the presence of thumb CMC OA.

How clinically informative of hand function are the three latent domains of hand function that we found? We argue that they are very informative because they are inherently compatible with ICF classifications of body structure and function, activity and participation, and inform those classifications with specific experimental data. That is, strength and sensorimotor processing fit within the structure and function category; and coordinated upper extremity function fits within activity

(reach to grasp) and participation (necessary for work, play and ADLs); however it is not as clear in case of the patients with OA where the domains are muddled. We note that the ICF itself recognizes that these classifications are not exclusive because strength is often needed for work and sensorimotor processing is needed to perform in-hand manipulation once objects are picked up, etc. Nevertheless, in our minds, our results do provide specificity to the ICF criteria in the context of hand function by providing a link to real-world outcome measures.

But most importantly, these three functional domains emerged naturally from the data. As such, our methodology provides a window into latent contributors to hand function and means to quantify them. This ability to naturally identify and quantify functional domains allows us to probe the underlying physiological mechanisms that enable, impair, or restore general manipulation ability in everyday life, particularly with respect to healthy aging and aging with a disability. By corroborating the existence of these three functional domains in older adults that we had seen in children, these results suggest that they are present throughout the lifespan-and are therefore an inherent property of human hands. The presence of these three latent domains in both development and aging motivates their study throughout the lifespan.

Understanding effects of aging on quality of life is now emerging as an important public health issue (Verbrugge, Lepkowski & Konkol 1991, Kemp & Mosqueda 2004, Covinsky 2006, Song, Chang & Dunlop 2006, Winstein, Requejo, Zelinski,

Mulroy & Crimmins 2012). It becomes even more so when we consider the added orthopedic and/or neurological effects when aging with-or into-a disability. In fact, we have a prior publication showing that both CMC OA and PD exacerbate the aging effect (Lawrence et al. 2014). As an extension, in this paper we focused on understanding the latent domains of functions in the context of healthy aging and aging with a disability. For example, our results suggest an underappreciated and understudied link between what is at its core a disease of articular cartilage, and sensorimotor integration capabilities for dexterous manipulation. This ability to quantify and describe functional domains should play a central role when quantifying age-related losses in hand function in general; and in particulate help us understand and optimize treatments for thumb CMC OA and other orthopedic and neurological conditions in our aging populations.

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Chapter 4

Strength, Multi-Joint Coordination, and Sensorimotor Processing are Independent Contributors to Overall Balance Ability

4.1 Abstract

For young adults, balance is essential for participation in physical activities but is often disrupted following lower extremity injury. Clinical outcome measures such as SLB, YBT, and the SLHB tests are commonly used to quantify balance ability following injury. Given the varying demands across tasks, it is likely that such outcome measures provide useful, although task-specific, information. But the extent to which they are independent and contribute to understanding the multiple contributors to balance is not clear. Therefore, the purpose of this study was to investigate the associations among these measures as they relate to the different contributors to balance. Thirty-seven recreationally active young adults completed

measures including VJ, YBT, SLB, SLHB, and the LED test. Principal components analysis revealed that these outcome measures could be thought of as quantifying the strength, multi-joint coordination, and sensorimotor processing contributors to balance. Our results challenge the practice of using a single outcome measure to quantify the naturally multidimensional mechanisms for everyday functions such as balance. This multidimensional approach to, and interpretation of, multiple contributors to balance may lead to more effective, specialized training and rehabilitation regimens.

4.2 Introduction

It is well-known that both the sensory and motor systems contribute to the ability to maintain balance. Sensory inputs are necessary to detect unstable conditions (i.e., perturbations to the system) and motor contributions are vital to initiate timely and appropriate responses to counteract these perturbations. Clinical outcome measures such as SLB, YBT, and the SLHB tests are commonly used to quantify balance in individuals when healthy (Ageberg, Zatterstrom & Moritz 1998, Lee, Kim, Ha & Oh 2014, Plisky et al. 2009, Wikstrom, Tillman, Kline & Borsa 2006) or following musculoskeletal injury (e.g., ankle sprains and ACL tears) (Harrison, Duenkel, Dunlop & Russell 1994, Hewett, Myer, Ford, Heidt, Colosimo, McLean, van den Bogert, Paterno & Succop 2005, Logerstedt, Grindem, Lynch, Eitzen, Engbretsen, Risberg, Axe & Snyder-Mackler 2012, Mandelbaum, Silvers, Watanabe,

Knarr, Thomas, Griffin, Kirkendall & Garrett 2005, Reid, Birmingham, Stratford, Alcock & Giffin 2007, Tropp & Odenrick 1988, Wikstrom, Tillman, Chmielewski & Borsa 2006) or to assess risk for lower extremity injury (Hewett et al. 2005, Fitzgerald, Lephart, Hwang & Wainner 2001, Myer et al. 2006, Zech, Hubscher, Vogt, Banzer, Hansel & Pfeifer 2010). Results obtained from these tests are used to represent the mechanisms of balance. However, the contributions of sensory inputs and appropriate motor responses necessary to perform well vary across them. Outcome measures that include smaller changes in lower limb or whole body position are typically considered measures of static stability of balance; whereas, measures that include larger changes in position are often referred to as dynamic stability of balance. One may argue that detection of smaller changes in position or motion would be more challenging for the sensory system to detect and less challenging to the motor system to counteract; conversely large changes in position or motion would be more easily detected by the sensory system and, in turn, place greater demands on the motor system to counteract in terms of strength and multi-joint coordination. As a result, interpretation of the outcomes with respect to underlying sensory or motor deficits becomes challenging when considering the range of static and dynamic measures used to quantify balance.

Unperturbed single limb balance during quiet standing balance tests generally result in relatively small joint excursions and are considered measures of static balance. This requires detection of smaller, subtler sensory stimuli and relatively

small motor responses to maintain balance. In contrast, successful performance on balance tests such as the SLHB and YBT involve larger changes in position and are considered measures of dynamic balance. The SLHB quantifies the ability to stabilize the COM after completing a forward hop on a single limb. The transition from a dynamic to a static state can be considered a perturbation to the COM, thus making it a measure of dynamic balance. Performance of both the SLB and SLHB is quantified using outcome measures related to COP movement because they represent corrective actions made to maintain balance (Tropp & Odenrick 1988). Additionally, performance of the YBT is scored by measuring the farthest distance reached with the free limb while maintaining balance on the stance limb. The maximal reach distances in each of three directions are considered measures of dynamic balance because changing the spatial orientation of the free limb acts as a perturbation to the COM with respect to the base of support (BOS), or stance limb. For more dynamic tests, while detection of larger joint excursions may be less challenging to the sensory system they also require greater motor responses with respect to lower extremity strength and multi-joint coordination (Lee et al. 2014, Ostenberg, Roos, Ekdah & Roos 1998). Accordingly, positive correlations between lower extremity strength and performance during these tests suggest that the ability to detect underlying sensorimotor deficits may be limited during these more dynamic tasks (Lee et al. 2014, Hubbard, Kramer, Denegar & Hertel 2007).

While balance tests are thought to provide insight into sensorimotor processing, it is difficult to test these mechanisms in isolation during traditional balance tests. Therefore, we introduce the LED test, which has been proven to quantify sensorimotor processing to control instabilities while controlling for the confounding factor of strength and whole-body equilibrium (Lawrence et al. 2014, Lyle et al. 2013*b*). The test is based on the principles of the upper extremity Strength-Dexterity (SD) test, which is a repeatable and informative paradigm that has successfully quantified differences in finger dexterity attributed to age, sex, and numerous clinical impairments (Lawrence et al. 2014, Dayanidhi, Hedberg, Valero-Cuevas & Forssberg 2013, Valero-Cuevas et al. 2003, Lightdale-Miric, Mueske, Dayanidhi, Loiselle, Berggren, Lawrence, Stevanovic, Valero-Cuevas & Wren 2015, Lightdale-Miric, Mueske, Lawrence, Loiselle, Berggren, Dayanidhi, Stevanovic, Valero-Cuevas & Wren 2015). The SD test quantifies sensorimotor processing for dynamic finger function because it is independent of strength (Valero-Cuevas et al. 2003, Venkadesan & Valero-Cuevas 2008) and engages distinct cortico-striatal-cerebellar networks in a context-sensitive way (Mosier et al. 2011, Vollmer et al. 2010). Building on this paradigm, the LED test quantifies the ability of the isolated lower limb to dynamically stabilize an unstable interface with the ground by controlling the force vectors and motions of the foot (Lawrence et al. 2014, Lyle et al. 2013*b*). Performance of the LED test is a measure of lower extremity sensorimotor processing that is also independent of strength (Valero-Cuevas et al. 2003), predictive of agility performance

in soccer athletes (Lyle et al. 2013*a*), and informative of age- and sex-related effects (Lawrence et al. 2014, Lyle et al. 2014). Understanding the relationships between LED test and clinical outcome measures can provide insight into the sensitivity of these measures for detecting sensorimotor deficits. Moreover, considering the LED test together with outcome measures will help elucidate how sensorimotor processing contributes to balance.

It stands to reason that balance likely requires a combination of strength, multi-joint coordination, and sensorimotor processing that are quantified to varying degrees using numerous outcome measures, several of which are described above. Given the varying demands across tests, it is likely that traditional balance tests provide useful, although test-specific, information regarding the contributors to balance. However, the extent to which these factors contribute to balance, and how these outcome measures relate to them is not clear. Therefore, the purpose of this study was to determine the relationships and hierarchy among these outcome measures for balance, strength and sensorimotor processing in healthy and active young adults.

4.3 Methods

4.3.1 Participants and Procedures

Thirty-seven young adults (18F, 19M) between the ages of 18 and 30 years (mean \pm standard deviation; age: 24.7 ± 2.7 years; body mass: 74.4 ± 14.2 kg; height: 1.8 ± 0.1 m) and engaged in recreational sports activities agreed to participate in this study. Participants were excluded if they had: i) any lower extremity injury or surgery within the last 12 months, ii) a current upper or lower extremity injury with persistent pain and/or inability to fully participate in sport, iii) a concurrent pathology or morphology that can cause pain or discomfort during physical activity, or iv) any physical, cognitive, or other condition that would impair their ability to perform the tasks proposed in this study. Prior to participation, testing procedures were explained to the participants and informed consent was obtained as approved by the Institutional Review Board of the University of Southern California Health Sciences Campus. Testing was performed in the Division of Biokinesiology and Physical Therapy's Human Performance Laboratory located in the Competitive Athlete Training Zone, Pasadena CA.

Participants attended a single session during which anthropometric measurements (height, weight, and leg length) were collected and foot dominance was self-selected based on participant response to which foot they preferred to kick a ball

for maximal distance. Each group completed the following battery of tests, described in detail below, in random order: LED, SLB, SLHB, and YBT. In addition, individuals performed the VJ test to assess lower extremity strength and power.

4.3.2 Instrumentation

Reflective kinematic markers were placed on the skin over the sacrum and bilaterally on the participant's shoes at the positions best projecting the anatomical landmarks of heel and toe. Three-dimensional motion analysis was performed using a marker-based, 11-camera digital motion capturing system (250 Hz; Qualisys, Gothenburg, Sweden). Ground reaction force (GRF) data were obtained using a 1.20 x 0.60m force plate (1500 Hz; AMTI, Newton, MA, USA) embedded into the floor surface. These data were collected synchronously using motion capture software (Qualisys Track Manager, v2.6, Gothenburg, Sweden) during the VJ and SLHB tests. The LED test system consisted of a helical compression spring (Century Springs Corp., Los Angeles, CA) mounted on a single-axis force sensor (Transducer Techniques, Temecula, CA) on a stable base with a platform affixed to the free end. The vertical component of the GRF was sampled with a data acquisition system (2000 Hz; Measurement Computing, Norton, MA) and recorded and displayed in real-time with custom software.

4.3.3 Data Analysis

This study considered five tests and 10 total outcome measures as dependent variables detailed above: YBT (3), SLHB (2), SLB (2), LED (2), and VJ (1). PCA was performed to identify the best linear fit to the data using a series of perpendicular vectors or PCs (Clewley et al. 2008). Due to the differences in units and normal distributions among variables, and for comparison purposes, we calculated the z-score of each variable and used their standardized normal distribution values as the PCA dataset (Jolliffe 2005). The PCs are presented in descending order quantifying their contributions to balance such that the first principal component explained the largest amount of variance. We note that the first five PCs captured at least 80% of the total variance; therefore, we limited our analysis to them. SPSS and Matlab were used for these analyses and the significance level was set at $p \leq 0.05$.

4.4 Results

The means and standard deviations of all dependent variables are presented in Table 4.1. Outcome measures on all of the tests, by all subjects, were within normal ranges when compared to previously published data (Plisky et al. 2009, Fitzgerald et al. 2001, Lawrence et al. 2014, Patterson & Peterson 2004, Springer, Marin, Cyhan, Roberts & Gill 2007).

Table 4.1: Mean performance data from all lower extremity participants.

Metric	Variable	Mean±SD
VJ	Power (W/kg;%BM)	48.1±9.6
YBT	YBT _A (%LL)	63.4±4.8
YBT	YBT _{PM} (%LL)	106.6±11.3
YBT	YBT _{PL} (%LL)	102.4±10.1
SLHB	COP _{ML} (mm/s)	0.03±0.01
SLHB	COP _{AP} (mm/s)	0.03±0.01
SLB	COP _{ML} (mm/s)	0.02±0.01
SLB	COP _{AP} (mm/s)	0.01±0.003
LED	F ₁ (N)	130.7±13.4
LED	RMS ₁ (N/s)	0.08±0.03

Our PCA data are presented in numerical form below (Table 4.2). Loading values quantify the strength and direction of the relationships between variables and range between -1 and 1, where 1 is total positive correlation, 0 is no correlation, and -1 is total negative correlation.

Table 4.2: Principle component loadings from lower extremity dataset.

(Normalized loadings for ease of comparison, Underlining in each column indicates ≤ 0.60) positive and negative correlations, respectively, with the dominant variable, in bold.)

Variable	1st PC	2nd PC	3rd PC	4th PC	5th PC
VJ	<u>0.67</u>	-0.03	<u>0.60</u>	<u>-0.54</u>	-0.37
YBT _A	<u>0.62</u>	0.07	-0.52	-0.15	1.00
YBT _{PM}	<u>0.80</u>	-0.50	0.40	0.41	-0.02
YBT _{PL}	1.00	-0.06	0.23	0.04	0.30
SLHB COP _{ML}	-0.19	1.00	<u>0.87</u>	0.03	0.04
SLHB COP _{AP}	-0.18	<u>0.86</u>	1.00	0.20	0.39
SLB COP _{AP}	<u>0.61</u>	<u>0.86</u>	<u>-0.70</u>	0.04	-0.31
SLB COP _{ML}	<u>0.68</u>	<u>0.80</u>	<u>-0.66</u>	0.17	-0.34
F ₁	0.52	-0.37	<u>0.60</u>	<u>0.94</u>	-0.19
RMS ₁	-0.50	0.18	-0.57	1.00	0.11
% Contribution	26.07%	23.53%	14.57%	10.49%	8.88%
Cumulative	26.07%	49.59%	64.17%	74.66%	83.54%

The 1st PC explained 26% of the total variance in balance with the highest loadings assigned to YBT_{PL} and YBT_{PM} (1.00 and 0.80, respectively). Furthermore, we report additional moderate, positive correlations between VJ, YBT_A, and SLB COP_{AP}, and COP_{ML} with loading values ranging from 0.68-0.61. The 2nd PC explained an additional 24% of the variance with all SLHB and SLB COP variables exhibiting the highest loadings (1.00-0.80, respectively). In the 3rd PC, the SLHB

COP measures featured the highest loadings, explaining 14% of the variance. Interestingly, while the relationships between SLHB and SLB COP variables were moderate to strong in both the 2nd and 3rd PCs, they were negatively correlated in the 3rd PC (-0.62 and -0.59), unlike the 2nd, which featured positive correlations. In addition to the disambiguation between static (SLB) and dynamic (SLHB) balance variables we report in the 3rd PC, we further note that F_1 showed a moderate positive association with SLHB variables while RMS_1 was positively correlated with SLB variability. We further report moderate positive correlations with VJ and F_1 . The 4th PC explained an additional 11% of the variance in balance and revealed that the LED variables were highly, positively correlated (1.00 and 0.94, respectively) with each other and no other metric. Finally, YBT_A solely dominated the 5th PC and explained 9% of the total variance. In order to further highlight our results, we provided a visual representation of the respective loadings for each of the first five PCs, first presented in Table 4.2, below in Figure 4.1.

4.5 Discussion

This is the first study, to our knowledge, to investigate the relationship among multiple balance tests and outcome measures traditionally used to assess balance in young individuals. The battery of measures examined in this study represent a range of static and dynamic tests that are commonly used to assess balance in

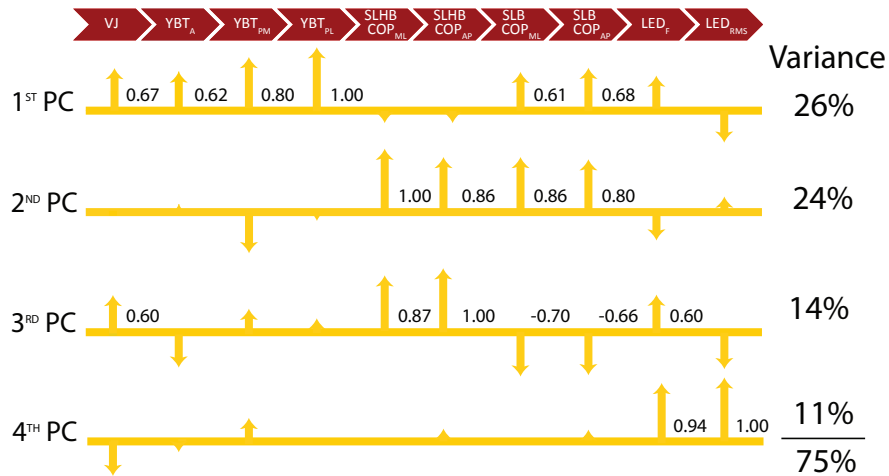


Figure 4.1: Visualization of PC loadings in lower extremity participants. The scaled metric loadings for the first five PCs are illustrated above. All loadings are shown, but numerical values are only listed if they are $\leq \pm 0.60$. The signs of the loadings are indicated by the direction of the arrowheads.

healthy individuals or following lower extremity injury or to identify those at greater risk for injury (Ageberg et al. 1998, Plisky et al. 2009, Harrison et al. 1994, Hewett et al. 2005, Logerstedt et al. 2012, Reid et al. 2007, Fitzgerald et al. 2001, Zech et al. 2010, Gribble et al. 2007, Horak et al. 1997, Hoffman & Payne 1995, Kidgell, Horvath, Jackson & Seymour 2007). The combination of measures of static and dynamic balance, strength, and sensorimotor processing in this study allow the unique opportunity to explore the relationships between the numerous components we speculate contribute to overall balance. Understanding the relationships and hierarchy among outcome measures in young healthy individuals using PCA provides some insight into the contributors to balance. In this manuscript, we present our PCA data in two distinct formats, numerically (Table 4.2) and graphically (Figure 4.1). For ease of comparison, we order the measures on a continuum from what can

be considered more dynamic (YBT) to more static (SLB) balance tests anchored at the extremes by the outcome measures most associated with strength (VJ) and sensorimotor processing (LED) (top to bottom, Tables 4.1 and 4.2; left to right, Figure 4.1). When considered together, 84% of the variance in balance is explained by the first 5 PCs with each individually contributing to 9-26% of the total variance. The 6th and further PCs each contribute to relatively small percentages of total variance and are not considered in our analysis due to the potential for over interpretation.

Our analysis indicates that balance is best distinguished by a combination of outcome measures from both static and dynamic test as the SLB and YBT are the most heavily loaded in the 1st PC. Together these measures explain 26% of the total variance in balance. YBT_{PL} features the highest loading and reveal strong and moderate positive relationships with YBT_{PM} and YBT_A , respectively. Multiple studies report correlations between lower limb strength (Lee et al. 2014, Hubbard et al. 2007), range of motion (Olmsted, Carcia, Hertel & Shultz 2002, Robinson & Gribble 2008), and YBT performance in all three directions. Therefore, it is not surprising that there is also a moderate positive correlation with VJ, a widely accepted estimate of leg power and strength (Patterson & Peterson 2004, Leard, Cirillo, Katsnelson, Kimiatek, Miller, Trebincevic & Garbalosa 2007, Tomioka, Owings & Grabiner 2001). The inclusion of these measures in the 1st PC suggests that the multi-joint coordination and strength required to perform more dynamic tests

are important contributors to balance. However, the presence of moderate positive correlations with SLB variability (COP_{ML} and COP_{AP}), the most static balance test, suggests that the detection and correction of smaller perturbations are also important to balance ability. Measurements of COP variability during SLB tests are validated methods of quantifying what is referred to as static balance or stability (Ageberg et al. 1998, Gribble et al. 2007, Springer et al. 2007). Relatively small displacements of the lower limb, particularly at the ankle, are used to maintain balance and are reflected in COP variability (Tropp & Odenrick 1988). The presence of the SLB variables in the 1st PC seems to indicate a moderate dependence on sensory inputs for detection of small perturbations while maintaining balance.

After considering the contribution of these measures to balance, an additional 24% of the variance is explained by a grouping of COP variables during both the SLHB and SLB in the 2nd PC. It is not surprising that these variables are strongly associated as both are measures of COP variability, which are representative of modulation of ML and AP COP by the motor system. While the mean values for SLHB variability are slightly, although, we emphasize not significantly, greater than the SLB (Table 4.1), we concede that is due to the more dynamic nature, and slightly increased strength demands, of the SLHB. When taken together, however, the correlations among the outcome measures from static and dynamic balance tasks support prior research that reported no differences performance on both static and dynamic postural control tasks (Gribble et al. 2007). Strong positive

correlations among these variables suggest that both small and large corrective actions during static and dynamic tests are important overall contributors to balance. Moreover, the negative correlation to YBT_{PM} supports our speculation that COP variables are indicative of separate contributions to balance than what is measured during more dynamic, multi-joint coordination- and strength-driven tasks.

In the 3rd PC, which further explains 13% of the total variance, COP velocities in the AP and ML directions during the SLHB are again the leading contributors. Interestingly, in this PC, SLHB measures are moderately negatively correlated with SLB measures, unlike the 2nd PC. The contrasting relationships between COP variables during SLS and SLHS observed between the PCs, as well as the slight differences in mean performance values presented in Table 4.1, support the notion that COP variability in these two tasks represent similar but distinct mechanisms of balance (Ageberg et al. 1998, Wikstrom, Tillman, Chmielewski & Borsa 2006, Fitzgerald et al. 2001, Myer et al. 2006, Horak et al. 1997, Kidgell et al. 2007, McGuine, Greene, Best & Levenson 2000). The SLHB is a standard objective measure often used to evaluate dynamic balance following training protocols and when examining patients following lower limb injury or surgery (Ageberg et al. 1998, Logerstedt et al. 2012, Reid et al. 2007, Myer et al. 2006). While static balance measures are of clinical relevance, in terms of function, emphasis is often placed on dynamic balance tests (e.g., SLHB and YBT) because they are more

representative of ADLs and have greater sensorimotor demands. To limit the potential influence of strength and distance hopped on performance of this test, we ask participants to hop a standardized distance equal to their LL. The characterization of the SLHB as a more dynamic measure of balance than the SLB is further supported by the moderate positive relationship with VJ. Moreover, the weak and discordant relationship with YBT variables could support the argument that the SLHB is less dynamic than the YBT and results in smaller perturbations to the COM within the BOS.

We find it particularly noteworthy that in the 3rd PC, LED compression force (F_1) is positively correlated with dynamic balance variables (SLHB) while LED force variability (RMS_1) is more closely associated with static balance variables (SLB). The dependent variable for the LED test is traditionally the average of the three hold phases with the highest mean compression force, F_1 . This is because the spring becomes increasingly unstable as it is compressed further. Thus the level of maximal sustained spring compression is informative of the maximal instability that can be controlled by the isolated leg. The springs are designed to reach these high levels of instabilities at very low forces (c. 100 N for the leg, or c. 10% of body weight). The F_1 is sensitive to sex differences (Lawrence et al. 2014, Lyle et al. 2014) and age effects (Lawrence et al. 2014), and correlate well with whole-body agility (Lyle et al. 2013a). More recently, F_1 shows strong correlations with single limb cross-country ski distance, which one can easily argue is a dynamic

measure, but shows no correlation with a static single limb balance test (Krenn, Werner, Lawrence & Valero-Cuevas 2014). Additionally, the force fluctuations (e.g., RMS) during the hold phases of the SD paradigm for the upper extremity were first introduced as a method of quantifying differences in performance (i.e., sensorimotor processing) attributed to several clinical conditions (Lawrence et al. 2014, Lightdale-Miric, Mueske, Dayanidhi, Loiselle, Berggren, Lawrence, Stevanovic, Valero-Cuevas & Wren 2015, Lightdale-Miric, Mueske, Lawrence, Loiselle, Berggren, Dayanidhi, Stevanovic, Valero-Cuevas & Wren 2015). Greater RMS indicates larger dynamical dispersion and suggests weaker (or looser) corrective actions by the neuromuscular controller enforcing the sustained compression. Now, in this study, we include force fluctuations during the LED test (RMS_1) as a complementary, but equally important, measure of sensorimotor processing of the lower limb in healthy individuals.

The 4th PC accounts for 11% of the total variance in balance. Strong and positive relationships between both LED variables (F_1 and RMS_1) are noted in this PC, suggesting that the sensorimotor control may uniquely contribute to balance. These results complement previous studies, including numerous of our own featuring the SD paradigm for the fingers, that find sensorimotor processing during dexterous tasks (e.g., dexterity) represents a different functional domain than strength or whole-arm coordination (Lawrence et al. 2014, Lyle et al. 2013*b*, Dayanidhi, Hedberg, Valero-Cuevas & Forssberg 2013, Valero-Cuevas et al. 2003, Venkadesan & Valero-Cuevas 2008, Mosier et al. 2011, Vollmer et al. 2010, Lyle et al. 2013*a*,

Dayanidhi, Kutch & Valero-Cuevas 2013, Dayanidhi & Valero-Cuevas 2014). While no correlations greater than 0.60 are noted with variables of other tests in this PC, LED variables are negatively correlated to VJ (-0.54), a measure of lower extremity strength and power, which further complements our prior work suggesting that lower extremity dexterity is independent of strength (Lyle et al. 2013*b*). In the 5th PC, YBT_A is the sole contributing variable to the 9% of the total variance explained. While the relative contribution to overall variance explained is comparatively small, the fact that YBT_A shows no correlation with the other YBT variables implies it may represent a different functional dimension than the posterior YBT directions. The anterior direction can be considered primarily uniplanar, whereas the PM and PL directions clearly require coordination of multiple joints across multiple planes. This is also supported by the data in the 1st PC that show strong correlations between the YBT PM and PL directions and only a moderate correlation with the anterior direction and again in the 3rd PC, where YBT_A shows weak negative correlations with the YBT posterior directions.

The data presented in this study speak to the fact that balance is dependent on multiple contributors. We find that the outcome measures of tests can be thought of as quantifying the strength, multi-joint coordination, dynamic and static stability, and sensorimotor processing contributors to balance-which we find cannot be assessed independently and simultaneously by any one single outcome measure. This makes it difficult to truly understand the sensorimotor mechanisms of balance,

let alone the effects of lower extremity injury on balance ability. This may begin to explain why there are conflicting reports of effects of injury on outcome measures of balance tests or effectiveness of training or rehabilitation protocols for improving these measures. For example, while several studies report differences between control and clinical groups in some or all measures associated with SLB tests (Harrison et al. 1994, Zech et al. 2010, Tropp & Odenrick 1988, Hubbard et al. 2007, Horak et al. 1997), others report no differences between or within groups. Previous authors suggest that the inconsistent reports may be attributed to the fact that the SLB test loses sensitivity over the time course of recovery and isn't challenging enough to be truly representative of sports-related activities, where balance deficits become more apparent (Olmsted et al. 2002, Hale, Hertel & Olmsted-Kramer 2007, Holme, Magnusson, Becher, Bieler, Aagaard & Kjaer 1999). There are also similar conflicting reports across more dynamic balance tests including the YBT. Multiple groups have reported significant differences between side-to-side YBT outcome measures (e.g., functional reach distances) in participants with chronic ankle instability (CAI) (Olmsted et al. 2002, Hale et al. 2007). However, in one study that reported side-to-side differences in participants with CAI, but no group differences between healthy participants and those with CAI (Hale et al. 2007). The inconsistencies in the literature in terms of success of both static and dynamic balance tests in the clinic support our hypothesis that these measures provide informative, yet limited, information about the mechanisms of balance ability. It is important to point out

that our study was conducted in recreationally active young adults with no recent lower extremity injuries. Our results compel future studies in clinical populations to develop and assess the ability of outcome measures to gauge the efficacy of rehabilitation regimens for lower extremity injuries, including, but not limited to CAI and ACL tears.

We successfully identify distinct relationships among outcome measures that suggest they together reveal latent functional contributors to balance. After considering the origin, nature, and use of each outcome measure, we propose that the latent contributors to balance they reveal are those of: strength, multi-joint coordination, and sensorimotor processing. They represent distinct functional domains, which are revealed by the relationships among the loadings in our PCA results. The multiple strong to moderate correlations (loadings) in the 1st PC suggest that a combination strength, multi-joint coordination, and static stability (i.e., detection of small perturbations from the sensory system) are the leading contributors to balance. However, in the subsequent PCs, other contributors gain prominence. The 2nd PC placed strong emphasis on a combination of static and dynamic balance variability. The fact that they are not strongly correlated with the other outcome measures strengthens our assertion that both static and dynamic balance are similar functional features that are distinct from strength or multi-joint coordination. These results indicate the combined corrective actions by the motor system during both the static and dynamic balance tests are important contributors to balance.

While the SLB and SLHB tests have similar origins and functional features, there are differences that warrant consideration. The more dynamic nature of the SLHB naturally leads one to assume that there would be different strength and coordination requirements, which is supported by the negative correlations with SLB variables and positive correlation with VJ revealed in the 3rd PC. The opposite loading signs of the SLHB in the 2nd and 3rd PCs speak to the fact that it may be informative of both static and dynamic balance, but the moderate correlation with VJ emphasizes that dynamic stability should be considered in the context of submaximal force performance to reduce the influence of strength, which, as we mentioned previously, can dilute the information gleaned from such dynamic outcome measures. Additionally, the correlations we report between the LED test variables and COP variability during both the SLB and SLHB indicate that the LED test may be a useful tool to quantify sensorimotor processing during both static and dynamic balance measures. Finally, our analysis further indicated that sensorimotor processing, as quantified by the LED test, was another distinct contributor to balance (4th PC) that also tended to be independent of strength. This confirms our prior work for both the upper and lower extremity (Lawrence et al. 2014, Lyle et al. 2013b, Dayanidhi, Hedberg, Valero-Cuevas & Forssberg 2013, Venkadesan & Valero-Cuevas 2008, Lyle et al. 2013a, Lyle et al. 2014, Dayanidhi, Kutch & Valero-Cuevas 2013, Dayanidhi & Valero-Cuevas 2014), and mirrors work about

the development of dexterity in children where the SD test is a functional dimension distinct from strength and whole-arm coordination (Vollmer et al. 2010). These results in lower extremity function also mirror our findings in the upper extremity (Lawrence, Dayanidhi, Fassola, Requejo, Leclercq, Winstein & Valero-Cuevas 2015) despite the obvious evolutionary, anatomical, and functional differences and suggest fundamental, body-wide mechanisms for function. We do acknowledge, however, that sensory or motor constructs (e.g., proprioception, vision, motor control, etc.) are not specifically quantified in this study. We also note that these data represent balance ability in healthy individuals. It is not clear how these results would change if individuals with sensory or motor deficits are included.

Our results support the well-accepted notion that balance is a complex, albeit everyday, task-but provide a quantitative context within which to understand its contributors. Thus, we lend evidence to the idea that depending on a single outcome measure to quantify balance, its deficits, and its rehabilitation is arguably deficient. We recommend using a combination of complementary assessments to quantify its multiple contributors: strength, multi-joint coordination, stability (both static and dynamic), and sensorimotor processing. This will not only improve assessment accuracy on an individual level, but also facilitate the development of customized rehabilitation or training regimens to target improvements of individual contributors deemed deficient or in most need of attention. Furthermore, the ability of

the novel LED paradigm to successfully quantify sensorimotor processing, in addition to the correlations with both static and dynamic balance measures reported in this study, make it a useful tool to quantify and promote that specific contributor. Thus it complements the other well-accepted measures of strength, and multi-joint coordination currently in use in both the research and clinical settings. Note that because the LED test requires very low forces and tests the isolated leg while the hip and torso are held steady, it is particularly well suited to clinical, post-surgical and post-injury populations who cannot perform other outcome measures mostly geared towards healthy athletic young adults.

4.6 Acknowledgments

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Chapter 5

Sensorimotor Processing for Lower Extremity

Dexterity: Influences of Sex and Athletic Ability

5.1 Abstract

Sustained compression of deformable and unstable objects with the isolated leg exhibits time-varying forces. This force variability may provide a window into the neural control of dynamical regulation of ground reaction forces. We re-analyzed Lower Extremity Dexterity (LED) test data from 40 participants: 20 skilled athletes (10F, 10M, 26.4 ± 3.5 yrs) and 20 non-skilled athletes (10F, 10M, 24.8 ± 2.4 yrs). We used delayed embedding to reconstruct the phase portraits of the time series force data and characterized them by their density (interquartile range) and geometrical features (trajectory length and convex hull properties). A two factor repeated measures ANOVA revealed significant main effects of sex and athletic ability in the trajectory length ($p=0.014$ and $p<0.001$), interquartile range ($p=0.008$

and $p < 0.001$), volume ($p = 0.034$ and $p = 0.002$), and sum of edge length ($p = 0.033$ and $p < 0.001$), respectively. *Post hoc* analyses indicate that female non-skilled athletes have significantly greater estimated marginal mean values of trajectory length ($p = 0.003$), interquartile range ($p = 0.018$), volume ($p = 0.017$), and sum of edge length ($p = 0.025$) than the other groups, indicating greater stochasticity in the phase portraits and larger convex hulls. These results show that skilled athletes have increased sensorimotor ability for dynamic regulation of instabilities during ground contact compared to non-skilled athletes; and that non-skilled female athletes have the poorest ability of the four groups. Moreover, our nonlinear approach to quantifying sensorimotor ability suggests that reduced sensorimotor ability may be a risk factor for knee injury.

5.2 Introduction

It is well accepted that depending on the specific sport investigated, female athletes participating in agility-based sports have a four to six times greater incidence of non-contact knee injury than their male counterparts (Hewett, Lindenfeld, Riccobene & Noyes 1999, Yoo, Lim, Ha, Lee, Oh, Lee & Kim 2010, Huston & Wojtys 1996). It is speculated that sex differences in anatomical structure and function including joint alignment (Q-angle), joint laxity, strength, hormone levels, and more recently neuromuscular control are major contributors for the disproportionate number of injuries in females (Hewett 2000, Hewett et al. 1999, Yoo

et al. 2010). When considering an isolated joint (e.g., knee) during lower extremity function, neuromuscular control is of considerable importance in terms of preventing injuries, particularly ACL tears. Males tend to exhibit muscle-dominant neuromuscular control strategies to control joint stability while females display ligament-dominant strategies (Hewett 2000). This muscle-dominant strategy is described as a protective mechanism to reduce strain on the joint ligamenture during dynamic motions. Additionally, sex differences in muscle recruitment patterns and synergies are also well-reported and speculated to be contributors to injury risk (Hewett et al. 1999, Lephart et al. 2002).

Athletic training programs are designed to improve levels of strength, agility, and neuromuscular control and have the added benefit of reducing the risk of lower extremity injury. It has been shown previously that neuromuscular training programs improve measures of performance and movement biomechanics associated with lower extremity injury (Hewett 2000, Hewett et al. 1999). However, to our knowledge, the effect of training programs on sensorimotor processing has not been investigated. Moreover, given that female athletes often display decreased baseline levels of performance and are at greater risk of injury compared to their male counterparts they may especially benefit from comprehensive neuromuscular training programs. Our prior research shows sex differences in sensorimotor processing for low force dynamic tasks across the lifespan (Lawrence et al. 2014) and it is of interest to understand if sensorimotor processing for dynamic leg function is influenced

by athletic ability. Therefore, the purpose of this study is to use nonlinear dynamical analyses, namely the delayed embedding theorem, to reconstruct the attractors from time series data collected during LED test performance between skilled and non-skilled athletes of both sexes. We hypothesize that i) skilled athletes will have enhanced sensorimotor ability compared to non-skilled athletes and ii) sex differences in sensorimotor ability will be more evident in non-skilled athletes than in skilled athletes.

5.3 Methods

5.3.1 Definitions and motivation

The nonlinear analysis detailed in this paper is based on the theory of dynamical systems, where the time evolution of a system is defined in the phase space. Generally speaking, nonlinear systems may exhibit deterministic chaos. In a nonlinear system that is purely deterministic, all its future states are fixed once the present state is fixed. But it can be chaotic if small differences in initial conditions yield widely diverging outcomes, rendering long-term prediction impossible. To study such systems, we can usually assume that the stochastic component is small and does not change the nonlinear properties of the system. We can then define a vector space, namely the *state space* or *phase space* of the system. Every point in the state space specifies a state of the system and vice versa. This property allows us to

study the dynamics of the system through the study of the points it visits in state space. At this point it is to be noted that, except for dynamical models with defined mathematical equations of motion, for experimental systems there is usually no unique choice for its phase space. In the case of nondeterministic systems, we can still consider the concept of state space, but usually by only taking into account a set of states and transition rules between them (Kantz & Schreiber 2004). For deterministic systems we can usually find their finite m -dimensional vector space, where the state is defined by a vector $x \in R^m$. If the system is discrete its dynamics is described by a m -dimensional map $x_{n+1} = F(x_n)$. If the system is continuous, its dynamics are defined by a set of m first-order differential equation, $\frac{d}{dt}x(t) = f(x(t))$.

A sequence of points that represent a solution to the above equation given some initial conditions is called a *trajectory* of the dynamical system. A geometric representation of the trajectories of the system in the phase space is called *phase portrait*. For a system with bounded solutions and dissipative tendencies (meaning that on average the volume of the phase space containing the initial conditions tends to contract with the evolution of the system state), a set of initial conditions will evolve towards (i.e., be attracted to) a certain subset of the phase space. This subset is defined an *attractor* for the system, and it is invariant under the system dynamical evolution. Examples of attractor are fixed points and limit cycles (Kantz & Schreiber 2004). In the case of deterministically chaotic systems attractors may

exhibit very complicated geometrical structures, for this reason they are usually called *strange attractors* (Grassberger & Procaccia 2004).

This theoretical foundation motivates *attractor reconstruction* as a scientific technique. It is the construction of phase portraits that exhibit subspaces that are visited preferentially, which, has been successfully applied to characterize the variability and stability of dynamic biological systems (Harbourne & Stergiou 2009). For example, attractor reconstruction can characterize the level of anesthesia (Fedotenkova et al. 2013) and classify epileptic seizures (Sharma & Pachori 2015) when applied to electroencephalographic signals and to assess heart function when applied to electrocardiograms (Perc 2005). Here we focus on attractor reconstruction as a geometric characterization of the effects of athletic ability and sex on the ability to stabilize an unstable object with the isolated leg.

5.3.2 Participant Demographics

This retrospective analysis used nonlinear techniques to quantitatively assess the differences in LED test performance between 20 skilled athletes (10F, 10M, 26.4 ± 3.5 yrs) and 20 non-skilled athletes (10F, 10M, 24.8 ± 2.4 yrs). All participants gave their informed consent prior to participation and the Institutional Review Boards at the University of Southern California (Los Angeles, CA, USA) and the University of Innsbruck (Innsbruck, Austria) approved the study protocol.

5.3.3 Data Collection and Analysis

All participants were asked to perform the LED test with their self-reported dominant leg. Leg dominance was determined by asking participants which leg they use to to kick a ball for distance. Data acquisition hardware (National Instruments, Austin, TX) sampled the signal conditioner of the sensor at 2000 Hz with and we used custom MATLAB (v2015b, Mathworks, Natick, MA) software to process and analyze the data. We identified the LED hold phases, defined as the periods of maximal sustained compression (at least 10 for each participant), and calculated the mean compression force of the hold phases. In this analysis, we considered the three hold phases with the highest mean compression force values held stable for at least 3 seconds. The hold phases were then filtered with a Butterworth bandpass filter between 3 Hz and 30 Hz. We also quantified the magnitude of the force fluctuations with measures of RMS (RMS_1) and standard deviation (σ).

5.3.4 Attractor Reconstruction

Real-world dynamical systems are generally too complex to directly observe these attractors. Usually not all the variables involved are observable, moreover both sampling and quantization digitalization effects represent a breach of the differentiability whose validity is also substantially weakened in the presence of noise. For these reasons, methods are needed to reconstruct the mapping function between the one-dimensional observed variable (the time series of force) and its attractor (if

it exists). The goal is to obtain a phase portrait which preserves the topological and dynamical properties, of the original system (Takens 1985), while revealing its attractor.

One of the tools for attractors reconstruction is the delayed embedding theorem (Takens 1985), stating that plotting the vector sequence,

$$Y(i) = (y_i, y_{i+\tau}, y_{i+2\tau}, \dots, y_{i+(m-1)\tau}), \quad (5.1)$$

provides a reconstructed attractor with the same properties of the original system; where tau (τ) is the embedding delay, m is the embedding dimension, and y_i is the value of the time series at time i . The underlying idea is that the variables in a deterministic dynamical system are generically connected, influencing one another. Every subsequent point of a given measurement y_i is the result of a combination of the influences from all other variables of the system. For this reason, it can be treated as a substitute second system variable (or heuristic state variable), which carries information about the influence of all other variables during the time interval τ . By the same reasoning, all the other substitute delayed coordinates can be introduced obtaining the m -dimensional phase portrait (in the m -dimensional heuristic state space), provided an appropriately large enough m . It is crucial to state that the information carried by the heuristic variables is identical to that

carried by the original (but hidden) system variables with the exception that properties associated with the system's dynamics have no particular physical meaning (Perc 2005).

We emphasize that the embedding parameters τ and m must be properly chosen. The embedding delay τ must be large enough so that the information gained from measuring the value of $y_{i+\tau}$ is significantly different from the information already known from the value of y_i . This will allow the proper "unfolding" of the attractor in the phase space. Conversely, τ should not be larger than the typical time interval in which the system loses memory of its prior state. Figure 5.1 shows an example of the influence of the choice of τ in the reconstruction of a Lorenz Attractor. Several approaches have been proposed to choose the optimal embedding delay, but for this analysis we focus on and employ the first minimum of the mutual information function (Perc 2005). Given a time series with a minimal embedding dimension, m_o (i.e., in m_o -dimensional space), the reconstructed attractor is a one-to-one image of the attractor in the (hidden) original phase space. If the attractor is embedded in a lower m -dimensional space ($m \leq m_o$), its topological structure is no longer preserved due to the consequences of a flattening projection. Much like the 2D shadow of a 3D object, points that are far from each other in the 3D object can be projected to lie close to each other in the 2D shadow. Such points are called *false neighbors*. The false nearest neighbors method (Kennel, Brown & Abarbanel 1992) exploits these properties to find the proper embedding dimension. For a given m ,

for every point p_i in the m -dimensional space, a near neighbor p_j is taken ($p_j: \|p_i - p_j\| \leq \varepsilon$) and the normalized distance in the $m+1$ -dimensional space is computed by,

$$R_i = \frac{|y_{i+m\tau} - y_{j+m\tau}|}{\|p_i - p_j\|}. \quad (5.2)$$

If $R_i > R_{th}$, the point has a false nearest neighbor. When m is chosen close to m_o , the ratio of false neighbors is zero or sufficiently small. Typically $0 \leq R_{th} \leq 10$ and $0 \leq \varepsilon \leq 0.1\sigma$, where σ is the standard deviation.

5.3.5 Spatial Features of the Phase Portraits and Convex Hulls

Once we reconstructed the attractors by creating the phase portrait with the appropriate embedding dimension m_o , we used several geometric features to characterize the spatial properties of the attractor (Fedotenkova et al. 2013). Each feature provides a quantitative index of the geometric and distribution properties of the reconstructed attractors that speaks to characterizing information of density, perimeter, area and volume or their combination. The first feature we used is the *Length of the Phase Trajectory* (TL) defined as,

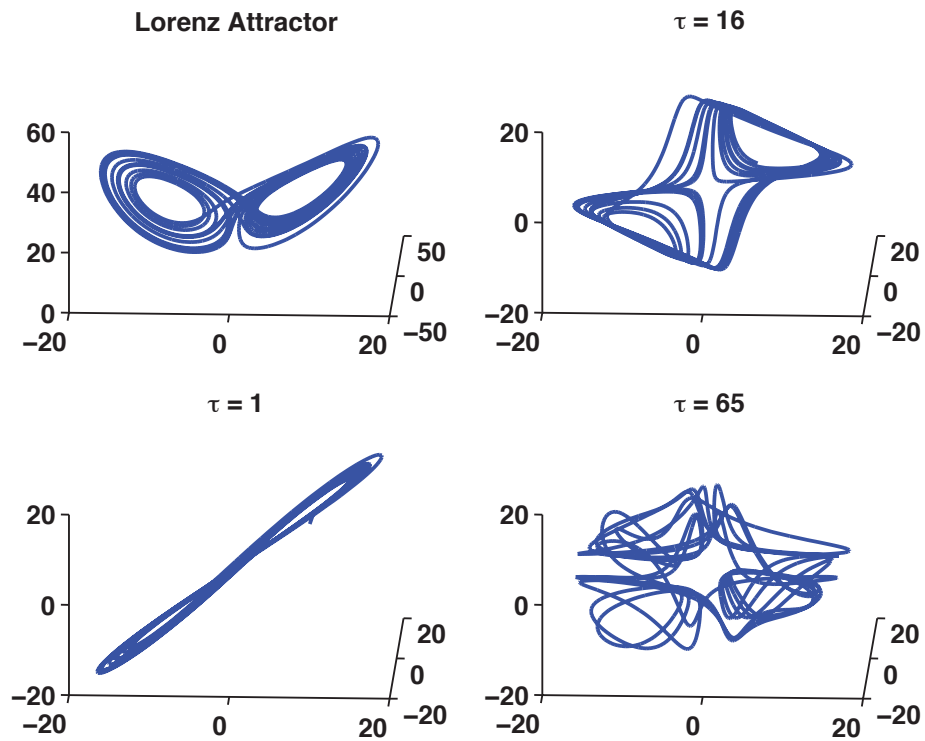


Figure 5.1: Effects of the embedding delay on the reconstructed attractor. The exact attractor (TOP LEFT) and its appropriate reconstruction (TOP RIGHT) are shown in the top row. When the chosen τ is too small (BOTTOM LEFT) the reconstructed attractor appears compressed without well-evolved folding regions. When the chosen τ is too large (BOTTOM RIGHT) the resulting attractor shows trajectories folding and wrapping around very frequently, giving the appearance of a stochastic component.

$$TL = \sum_N^{i=1} \|Y(i+1) - Y(i)\|, \quad (5.3)$$

where Y is the reconstructed phase portrait and N is the number of points that the time series contains (see equation (1)) (Fedotenkova et al. 2013). With this feature the distance between every consecutive $(m-1)$ -dimension is considered. TL is an indirect measure of the level of stochasticity of the state space. In fact, as a signal becomes more chaotic, two initially close points in the state space move further from each other and consequently have a longer TL. Figure 5.2 shows examples of how TL increases with the level of chaos in the signal. With increasing levels of signal complexity the state space trajectory becomes longer and exhibits more complex forms.

Second, the *Interquartile Range of the Euclidean Distance from the Centroid* (IQR) is considered. In general, the interquartile range measures the statistical dispersion of the distribution of a set of points. In particular, it defines the difference between the 25th and 75th percentile of the distribution of points. Thus it describes the middle 50% of observations. We applied the interquartile range to the distribution of the Euclidean distance of the points belonging to the phase space trajectories to the trajectory centroid. If the interquartile range of the distances is large, it means that the middle 50% of observations are spaced wide apart. When

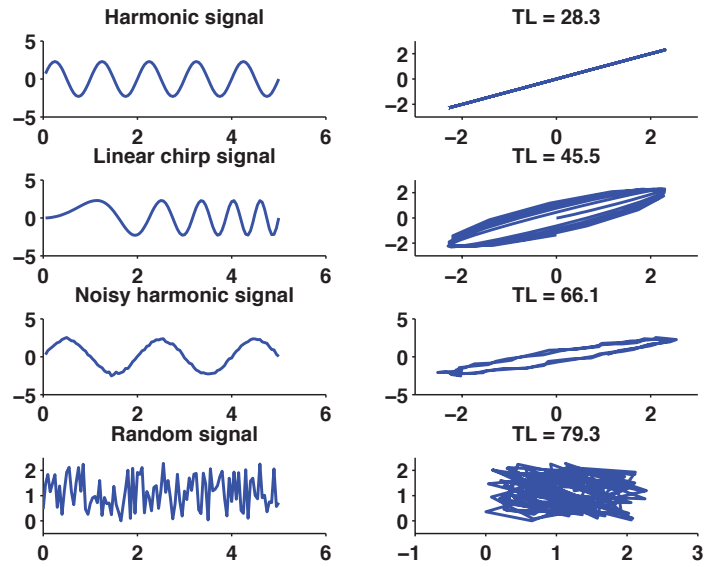


Figure 5.2: Examples of time series signals (LEFT) and their reconstructed attractors with corresponding TL values (RIGHT). Greater noise in the signal results in reconstructed phase portraits with more stochastic traits and a larger associated TL.

computing IQR for the distance of phase portrait points from the centroid, it provides a measurement of how scattered the points are. Finally, to assess the overall geometry of the reconstructed attractor, we computed its convex hull and we used the *Sum of the Length of the Edges* of the convex hull (SE) and its *Volume* (V) as its representative features (Fedotenkova et al. 2013). The former is an index of the perimeter/area of the attractor, while the latter quantifies the spatial spread of the points forming the phase portrait. We note that one limitation of comparing the features of the convex hulls is that they must be in the same dimension.

5.3.6 Data and Statistical Analyses

Matlab and TISEAN (v2.1.0, TISEAN, Frankfurt, Germany) are used to reconstruct the attractors. A two-factor repeated measures ANOVA (sex, athletic ability, and sex*athletic ability) and *post hoc* analyses are then used to compare the features among groups and are performed with SPSS (v23, IBM, Armonk, NY). Significance is set at $p \leq 0.05$.

5.4 Results

5.4.1 Attractor Reconstruction and Associated Convex Hulls

First, the optimal time delays, τ , for all hold phases were determined by using the first local minimum of the mutual information function and plotted in a histogram. The maximum value from the histogram was considered the optimum time delay for attractor reconstruction. Next, to select the appropriate the embedding dimension, m , we computed the number of false nearest neighbors for $m = 1:5$ with the threshold $R_{th} = 10$ for all hold phases. The dimension at which the number of false nearest neighbors reaches zero was chosen as optimal and those values are plotted in a histogram. As with the time delay, the maximum value from the histogram was selected as the embedding dimension. The values for τ and m for the attractor reconstruction for this analysis are 21 data points and 3 embedded dimensions, respectively. Representative phase portraits from female and male

skilled and non-skilled athletes and the associated convex hulls are illustrated in Figures 5.3 and 5.4, respectively.

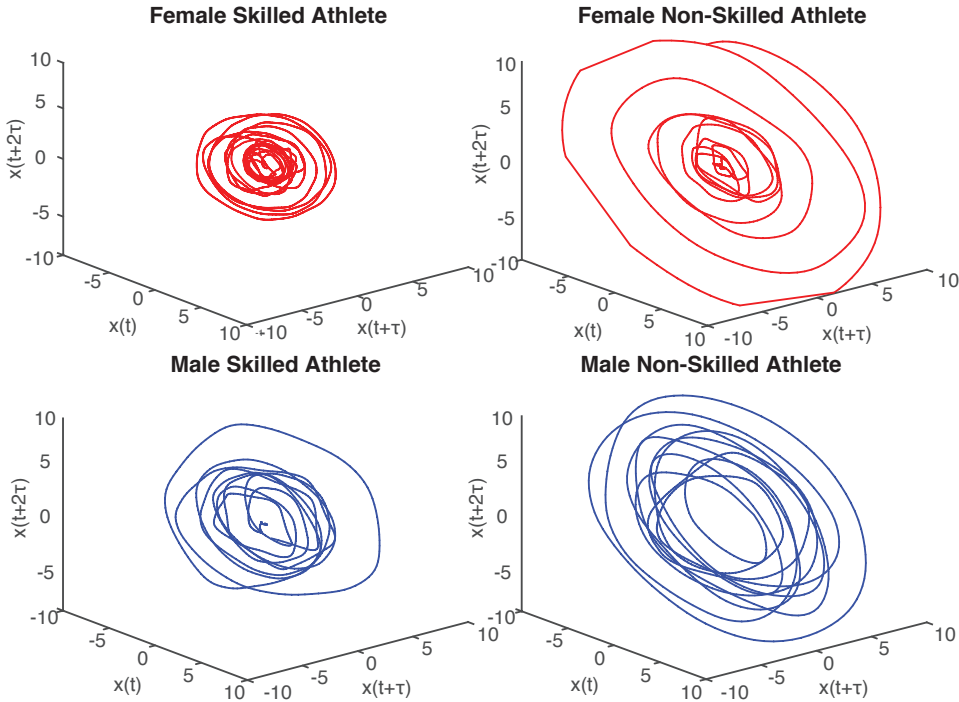


Figure 5.3: Representative phase portraits from female skilled (TOP LEFT) and non-skilled (TOP RIGHT) athletes and male skilled (BOTTOM LEFT) and non-skilled (BOTTOM RIGHT) athletes are presented above. TL, DP, and IQR are computed from the phase portraits.

5.4.2 Comparison of Spatial Features

The mean LED compression forces, magnitude of the force fluctuations, and spatial features detailed in the Methods were computed from the reconstructed phase portraits of female and male skilled and non-skilled athletes and the means and standard deviations are shown in Table 5.1 below. First, in terms of mean LED compression force, ANOVA revealed significant sex differences ($p=0.007$) with

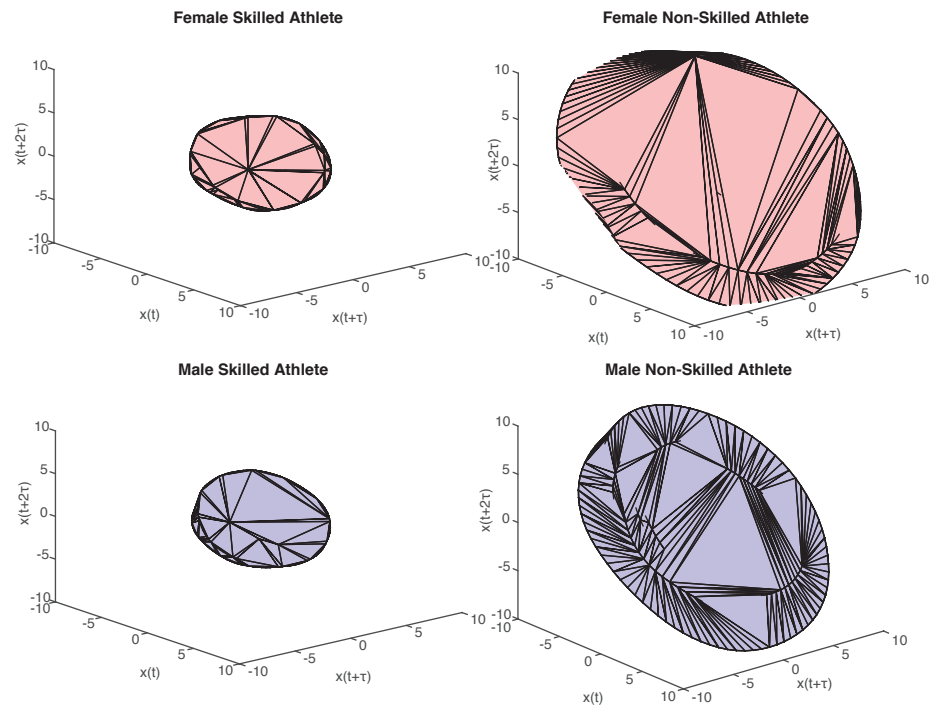


Figure 5.4: Convex hulls from the phase portraits shown in Figure 5.3 are illustrated above. V and SE are computer from the convex hulls.

males exhibiting higher mean compression forces than females, which is consistent with prior work (Lawrence et al. 2014), but finds no within sex difference in athletic ability ($p=0.968$). Calculations of the magnitude of the force fluctuations revealed effects of athletic ability (RMS: $p=0.041$, : $p=0.037$), but not sex (RMS: $p=0.223$, : $p=0.162$). Next, a two factor repeated measures ANOVA revealed significant main effects of sex and athletic ability in the spatial features TL ($p=0.014$ and $p<0.001$), IQR ($p=0.008$ and $p<0.001$), V ($p=0.034$ and $p=0.002$), and SE ($p=0.033$ and $p<0.001$), respectively (Table 5.2). Moreover, there were significant interactions between the main effects for the features TL ($p=0.007$), V ($p=0.01$), and SE ($p=0.046$). Further *Post hoc* analyses indicated that female non-skilled athletes have significantly greater estimated marginal mean values of TL, IQR, V, and SE than male non-skilled athletes (TL: $p=0.003$; IQR: $p=0.018$; V: $p=0.017$; SE: $p=0.025$), indicating greater stochasticity and dispersion of points in the phase portraits and larger convex hulls. However, these sex differences were not present in skilled athletes (TL: $p=0.975$; IQR: $p=0.664$; V: $p=0.755$; SE: $p=0.842$).

Table 5.1: Means and standard deviations of all features

Feature	Skilled Female	Non- Skilled Female	Skilled Male	Non- Skilled Male
Mean LED Force (N)	122.7±13.1	123.4±22.1	136.6±19.4	133.4±31.1
RMS	1.01±0.002	1.02±0.004	1.01±0.002	1.02±0.003
Standard Deviation	0.129±0.003	0.187±0.001	0.121±0.001	0.199±0.001
Trajectory Length	249.9±147.8	520.2±310.2	259.7±161.8	332.9±203.2
Interquartile Range	2.4±1.4	4.9±3.4	2.0±1.7	3.2±2.0
Volume	592.6±1278.6	4709.4±8800.3	686.8±1611.1	1320.6±1970.6
Sum of Edge Lengths	539.2±400.5	1526.6±972.8	533.8±425.5	1074.2±764.7

Table 5.2: Two-factor repeated measures ANOVA

Feature	Sex	Athletic Ability	Sex * Athletic Ability
Mean LED Force	p=0.007*	p=0.968	p=0.277
RMS	p=0.223	p=0.041*	p=0.164
Standard Deviation	p=0.162	p=0.037*	p=0.205
Trajectory Length	p=0.014*	p<0.001*	p=0.007*
Interquartile Range	p=0.008*	p<0.001*	p=0.088
Volume	p=0.034*	p=0.002*	p=0.01*
Sum of Edge Lengths	p=0.033*	p<0.001*	p=0.046*

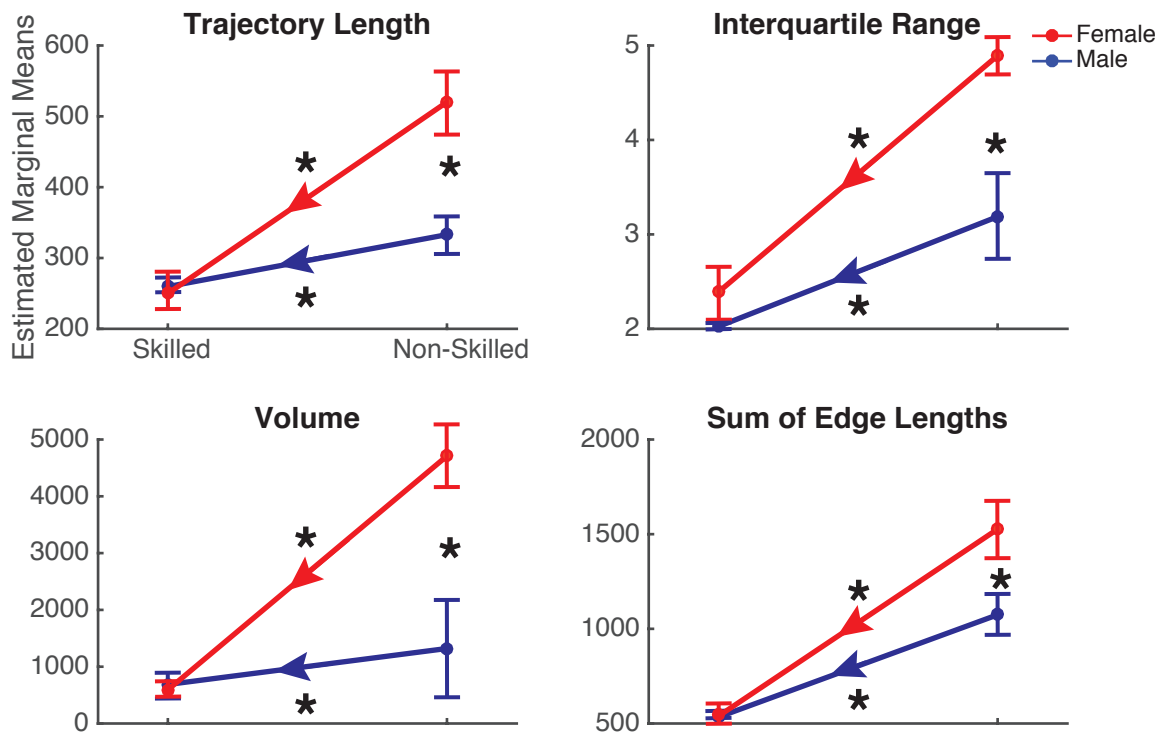


Figure 5.5: The significant main effects of sex and athletic ability and their interactions for TL (TOP LEFT), IQR (TOP RIGHT), V (BOTTOM LEFT), and SE (BOTTOM RIGHT) are illustrated above. * indicates significance level of 0.05.

5.5 Discussion

Several studies employ kinematic and biomechanical analyses to understand the effects of sex and athletic training on lower extremity ability and their implications for injury risk (Hewett et al. 1999, Huston & Wojtys 1996, Yoo et al. 2010). Here we present a novel nonlinear dynamical approach (i.e., attractor reconstruction) that successfully quantifies the effects of both sex and athletic ability on sensorimotor processing for lower extremity dexterity in young adults. We examine four spatial features of the phase portraits of the reconstructed attractors and show increasing variability in the distributions of the points in non-skilled athletes compared to skilled athletes and in females compared to males. This suggests that, from a nonlinear dynamical systems view point, an increasing level of variability is a symptom of weaker sensorimotor ability. We further show the strong sex differences in non-skilled athletes are not present in skilled athletes, with female non-skilled athletes demonstrating the weakest sensorimotor ability of the four groups.

Non-skilled female athletes have the greatest risk for non-contact knee injuries than trained counterparts and the contributors include higher landing forces and imbalances in lower extremity muscle strength and firing patterns (Hewett 2000). Recently several groups have advocated the development and implementation of neuromuscular screening designed to help detect those at risk for ACL tears and ankle sprains and training regimens designed to mitigate those risks (Hewett et al.

2005, Mandelbaum et al. 2005, Richie Jr. 2001, Hewett 2000). Moreover, a prospective study on the effect of neuromuscular training in the incidence of ACL tears by Hewett et al. reports that untrained female athletes have a 3.6 times higher incidence of knee injury than trained female athletes and 4.8 times higher than trained male athletes (Hewett et al. 1999). These initial successes in improving neuromuscular control at the joint level with training regimens (Hewett et al. 1999, Mandelbaum et al. 2005) have paved the way for more advanced assessments of sensorimotor processing.

Our prior work on sensorimotor processing for dexterous ability showed strong sex differences in both upper and lower extremity dexterity across the lifespan as per the mean compression force during the SD paradigm (Lawrence et al. 2014). A separate study indicated that female athletes exhibit reduced LED compression force and higher limb stiffness during landing compared to male athletes, which may contribute to the higher incidence of ACL tears in females (Lyle et al. 2014). Sensorimotor processing to dynamically regulate ground reaction forces with the isolated leg may also have a contributing role in athletic ability. For example, the LED test is predictive of agility, the ability to quickly and efficiently change direction, in young soccer players (Lyle et al. 2013*b*). The LED test may also be a predictor of gliding skill in cross-country skiing as it correlates well with single limb gliding distance (Krenn et al. 2014).

The mean compression force during the hold phases of the SD paradigm was the variable used to successfully quantify sensorimotor ability in numerous publications (Dayanidhi, Hedberg, Valero-Cuevas & Forssberg 2013, Dayanidhi, Kutch & Valero-Cuevas 2013, Dayanidhi & Valero-Cuevas 2014, Lyle et al. 2013*a*, Lyle et al. 2013*b*, Lyle et al. 2014, Lawrence et al. 2014, Lawrence et al. 2015, Vollmer et al. 2010, Lightdale-Miric, Mueske, Dayanidhi, Loiselle, Berggren, Lawrence, Stevanovic, Valero-Cuevas & Wren 2015, Lightdale-Miric, Mueske, Lawrence, Loiselle, Berggren, Dayanidhi, Stevanovic, Valero-Cuevas & Wren 2015, Valero-Cuevas et al. 2003). We find that the mean compression force is sensitive to the covariates of age and sex, but is unable to discern differences between groups (i.e., healthy vs. clinical populations and skilled vs. non-skilled athletes). More recently, measures of SD paradigm force fluctuations magnitudes (i.e. RMS and standard deviation ()) have been applied to investigate the differences in neural control strategies between healthy and clinical populations (Lawrence et al. 2013, Lightdale-Miric, Mueske, Dayanidhi, Loiselle, Berggren, Lawrence, Stevanovic, Valero-Cuevas & Wren 2015, Lightdale-Miric, Mueske, Lawrence, Loiselle, Berggren, Dayanidhi, Stevanovic, Valero-Cuevas & Wren 2015). In the current study, we find that mean compression force is sensitive to sex differences ($p=0.007$), but not athletic ability ($p=0.968$). Moreover, calculations of the magnitude of the force fluctuations revealed effects of athletic ability (RMS: $p=0.041$, σ : $p=0.037$), but not sex (RMS: $p=0.223$, σ : $p=0.162$) (Tables 5.1 and 5.2). However, the nonlinear nature of both

human function and the SD paradigm suggests that a nonlinear analytic approach is a more appropriate method of analysis and may be sensitive to multiple covariates.

Nonlinear time series analyses offer tools that bridge the gap between experimentally observed irregular behavior and deterministic chaos theory and many complex real-world phenomena have been characterized by them (Fang & Chan 2009). This analytic approach has been successfully applied in numerous scientific areas including physics, chemistry, and biomedical engineering. More recently, nonlinear dynamic methods have been successfully used in biomedical applications to characterize biosignals from electrocardiography (ECG), electromyography (EMG), electrooculography (EOG), and electroencephalography (EEG) (Rodríguez-Bermúdez & García-Laencina 2015). One feature of nonlinear analyses is that they often assume an infinite time scale, which is not the case during LED test performance where hold phases have a finite length of time on the order of seconds. Therefore, in this study, we chose to consider the spatial features of the reconstructed phase portraits rather than other nonlinear analytic techniques (i.e., maximal Lyapunov exponents, Poincaré maps, Hurst exponents) as infinite time scales are not a requirement for use (Perc 2006). The phase portraits from time series force data during the hold phases of the LED test were reconstructed via the delayed embedding (Takens') theorem, a validated method of attractor reconstruction (Takens 1985). The basic idea behind attractor reconstruction is that the past and future of time series data contains information about unobserved state variables that can be used

to define the current state of the system (Takens 1985). These reconstructed phase portraits are a heuristic way of characterizing dynamical systems (i.e., LED test performance) and their underlying sensorimotor mechanisms. In this study, we find that comparisons of four spatial features of the reconstructed phase portraits are sensitive to both sex and athletic ability (Tables 5.1 and 5.2). These results support the hypothesis that a nonlinear analytic approach is more informative of sensorimotor ability its covariates.

Our nonlinear dynamical analysis revealed that several features of the phase portraits and their convex hulls have significant main effects of both sex and athletic ability (Table 5.2, Figs. 5.3-5.5). Two features of the phase portraits (TL and IQR) showed effects of sex and athletic ability (TL: $p=0.014$ and $p<0.001$; IQR: $p=0.008$ and $p<0.001$). The TL feature, in particular, highlights a more chaotic behavior and IQR speaks to the more distributed and scattered nature of the phase portraits. We note that typically a larger trajectory in the phase portrait is an indicator for a stronger attractor, since points belonging to further portions of the phase space are pulled into the attractor basin. The attractors associated with non-skilled athletes and female participants were larger, but the points composing the phase portrait trajectories were more scattered (TL) and showed more variability in the distribution (IQR), which is an indicator of a weakening of the associated attractor. The features V and SE were also significantly affected by sex and athletic ability (Table 5.2), and this was further supported by the data presented in Figures

5.3 and 5.5, where we reported larger phase portraits and convex hulls in non-skilled athletes and female participants (V: $p=0.034$ and $p=0.002$; SE: $p=0.002$ and $p<0.001$). We found significant significant interactions between sex and athletic ability for the features TL ($p=0.007$), V ($p=0.01$), and SE ($p=0.046$) (Table 5.2, Fig. 5.5), indicating that the effect of athletic ability depends on the sex of the participant. Finally, a strong sex difference was present in non-skilled athletes in the features TL ($p=0.003$), IQR ($p=0.018$), V ($p=0.017$), and SE ($p=0.025$), but not in skilled athletes (TL: $p=0.975$; IQR: $p=0.664$; V: $p=0.755$; SE: $p=0.842$), which is illustrated in Figure 5.5.

We find that skilled athletes have increased sensorimotor ability for dynamic regulation of ground reaction forces with the leg. Interestingly, the sex difference we report in prior work (Lawrence et al. 2014) is present only between non-skilled males and females. Given that female athletes have the greatest risk for ACL tears and other lower extremity injuries, this work seems to indicate that females may particularly benefit from training regimens designed to enhance sensorimotor ability. This nonlinear analysis of LED data shows clear differences in the functional domain of dexterity between sexes, and between elite and recreational athletes. But are these differences in sensorimotor ability, and therefore risk of injury, due to genetics, athletic training, or both? We will explore this important question by incorporating leg dexterity into training regimens to enhance sensorimotor ability

and test its potential as a countermeasure reduce injury risk in athletes, particularly females.

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Chapter 6

Conclusions and Future Work

This work extends previous research by showing similar effects of age on both finger and leg dexterity as well as for the first time, a sex effect on both across the lifespan. We also find that finger dexterity is reduced in the presence of certain clinical conditions (i.e., CMC OA and PD). Additionally we introduce advanced nonlinear analysis methods to highlight between group differences in neural control strategies previously undetected by traditional linear analyses.

This current work adds to our fundamental understanding of sensorimotor processing across the lifespan although more work is needed to complete the picture. Our hope for the future is that this work leads to innovative and novel methods of detection of reduced sensorimotor ability for not only risk assessment and injury prevention, particularly in the lower extremity, but also for the early detection of orthopedic and neurologic clinical conditions where dexterity is affected (i.e., PD, CMC OA). This would open research avenues dedicated to rehabilitative (return to

work/play after injury) and preventative (training-based) interventions specifically focused on sensorimotor processing.

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