The Pennsylvania State University

The Graduate School

College of Health and Human Development

IMPAIRMENTS IN THE STABILITY OF HAND FUCTION IN PATIENTS WITH NEUROLOGICAL DISORDERS

A Dissertation in Kinesiology

by

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Submitted in Partial Fulfillment of the Requirements

for the Degree of Doctor of Philosophy

August 2016

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ABSTRACT

The concept of synergy provides a theoretical framework for movement stability resulting from the neural organization of elements that contribute to salient performance variables. Analysis of synergies has been performed within the uncontrolled manifold hypothesis, in which variance is decomposed into two components depending on whether it affects task performance or not. Then, the two components are reduced to a single index reflecting the relative amount of two variance components; this index is typically used as a synergy index. The method has proven to be able to quantify synergies in a variety of elemental spaces for a variety of tasks. In this dissertation, a series of studies exploring synergies stabilizing the hand action in various subpopulations are presented. Subpopulations include patients with Parkinson's disease, multiple sclerosis, cortical stroke, and healthy controls. The application of the concept of synergy to patient groups has allowed quantifying aspects of impairments related to movement stability and agility and also provided insights into neural mechanisms of synergic control. The evidence presented in the dissertation has led to the following main conclusions. First, impaired control of movement stability is commonly seen in persons with impairments in subcortical brain structures. The impairments are seen as low synergy indices during steady states of performance and delayed/reduced drop in the synergy indices before quick action (low anticipatory synergy adjustments). Second, these two components of the impairments in the control of stability may have distinct neurophysiological mechanisms and they could be selectively involved in different disorders. The results consistently suggest subcortical loops as being crucial for high stability of task performance. Third, the changes in synergy indices could be seen at the early stages of the PD and even in subclinical stages of disorder involving the basal ganglia, when traditional clinical examination fails to show any impairment. Lastly, changes in motor synergies are sensitive to treatment in PD patients. These features potentially make synergy indices a powerful

tool to objectively quantify the impairments of motor symptoms and also a useful biomarker for early detection of motor changes.

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Acknowledgements

First, I would like to express my sincere gratitude to my advisor, Dr. Mark Latash. It has been a great privilege to have his guidance and support in studying motor control. Mark has been always admirable, found time whenever I seek for his help, and offered his invaluable advice. I deeply appreciate him for being such a wonderful advisor. I would also like to thank the members of my committee: Dr. Kristina Neely, Dr. Robert Sainburg, and Dr. Xuemei Huang. I have been extremely fortunate to get their help and resources to conduct my studies at Hershey. Moreover, their insightful comments and feedback based on their expertise in clinical research has been essential for my dissertation.

I trust Mark's decision very much and it is partly due to people at the lab. They have been not only good colleagues that I work together but also great friends. There are so many great memories with them to remember. I am indebted to Jaebum Park, Stanislaw Solnik, Yen-Hsun Wu, Yang Xu, Nemanja Pazin, Tao Zhou, Florent Paclet, Satyajit Ambike, Luke Wilhelm, Pinar Arpinar Avsar, Shoko Kaichida, Sasha Reschechtko, Ali Falaki, Daniela Mattos, Behnoosh Parsa, Mu Qiao, Daniele Piscitelli, Omid Rasouli, Mariusz Furmanek, and Fariba Barani. I am also grateful to wonderful collaborators at Hershey: Dr. Mechelle Lewis, Raghda Clayiff, Santos Mellisa, Grace Shyu, Michael Goldenberg, Mary Albers, Guangwei Du, Eun Young Lee, Candice Maenza, and Dr. Elisabeth Lucassen. Without their help, none of my research would have been possible.

Lastly, and most importantly, I would like to thank support and love from my family. My parents and my younger sister have always had faith in me, it encouraged me to move forward and seek my dreams, and I am deeply thankful for that.

Chapter 1 Introduction

The ability to control the stability of actions is a critical feature of motor control, particularly because most everyday movements are performed under poorly predictable external conditions. The stability of actions is controlled by both feedforward and feedback mechanisms and its impairments are a common consequence of many neurological problems. For example, walking while holding a cup filled with water is a trivial everyday task for most people. However, not spilling the water can turn into a challenging task for patients with Parkinson's disease or multiple sclerosis because of impaired control of stability. The comprehensive integration of all involved elements (e.g., joints, muscles, digits, etc.) is required to maintain the stability of the cup with varying body states during walking and also with possible perturbations in the environment. The consequences of the loss of stability include not only water spills but more serious risks, such as falls, which might cause secondary problems including fracture.

Impairments in the control of the stability result from two main factors that are likely to have different underlying pathophysiologies. First, altered patterns in the coordination of the involved elements that may not be as effective as patterns seen in healthy individuals are often demonstrated to accomplish motor tasks. In some cases, patients adopt a default strategy for motor actions and tend to be less flexible in response to external conditions. Second, the anticipatory adjustments of action that occur in a feedforward manner to perform the desired motor performance are often impaired in neurological patients. The increased co-contraction of muscles (e.g., overgrip during prehension) that may occur in order to compensate for the impaired control of stability is frequently observed in patient groups, even though the motor performance may become fatiguing and energetically wasteful.

Recently, a concept of task-specific stability was introduced (Latash et al., 2007); within this approach, synergies are defined as neural organization that ensure stability of salient performance variables. The main idea of synergy is that sets of elements can be organized to stabilize performance variables that are related to the task. If a system stabilizes a performance variable, the intertrial variations in directions that lead to changes in that variable are expected to be low as compared to variations in directions that keep the variable constant. The synergy concept has been applied to various tasks involving multidigit object manipulation, multidigit force production, and multijoint whole body actions. Although the concept has a solid theoretical background and its quantification methods have been shown to be practical, its applications to impairments in the control of stability have been limited.

The majority of studies included in this dissertation applied the concept of synergy to better understand impairments in the control of stability in various patient groups with neurological disorders including Parkinson's disease, stroke and multiple sclerosis. The application of the methodology was particularly beneficial as both of the above-mentioned factors that potentially contribute to impairments in the control of stability could be assessed. Therefore, the results of the assessments of patients with various neurological disorders may provide insights into differentiating impairments in the particular disorder(s), and these insights could help the clinicians to optimize treatment and rehabilitation of deficits in motor function. The presented studies focus on the motor function of the hand in particular because of the importance of the hand for many of the activities of daily living, because impairments in the hand function happens commonly across neurological disorders, and because the forces produced by individual digits can be recorded accurately.

Chapter 2 Literature Review

2.1. Motor control and coordination

2.1.1. Neural control of movement

It is a major goal of the research on motor control to understand the particular functions of individual areas and circuits of the brain. With recent advances in brain imaging techniques, maps of the functional connectivity of the human brain has been augmented with information on the distributed systems that involve multiple cortical areas as well as subcortical structures, such as the basal ganglia and cerebellum. However, with the expanding knowledge on the brain areas that are involved in various functional activities, it is not always what kind of information is actually transferred between those areas. In particular, with respect to motor control, it remains unclear because of controversies in the understanding of how motor actions are controlled; what parameters of movements are transmitted from the central nervous system (CNS) to the peripheral structures.

Currently, two major theoretical approaches describe the neural control of human movement. The first approach comes from control theory and assumes that the neuronal networks in the CNS pre-compute neural signals that generate the desired mechanical variables, such as forces and displacements. Within a recently developed form of this approach, the process of computing neuronal signal is termed ‘inverse internal models’ (reviewed in Wolpert & Ghahramani, 2000). It is called inverse because the systems implement this process inversely, starting from desired consequences, to find adequate neural signals.

In the process of computing the input signals to generate movement, the neural controller has to solve a chain of problems related to redundancy. First, it needs to define the final joint angles and their trajectories that satisfy the task, which are usually not unique when the task

involves kinematically redundant set of joints. The second step is to define patterns of joint torques to move the body segments along the planned trajectories. The third step is to compute patterns of muscle forces that ensure the required pattern of joint torques. The next step is to find the level of excitation of motoneuronal pool that produces a required pattern of muscle force. Considering that alpha-motoneurons produce action potential based on the combined effect of signals from the brain and peripheral endings and moreover these are all threshold elements, it is very unlikely that the central nervous system could compute an input to an alpha-motoneuronal pool that generates the desired output.

Since the signals have to be computed through this process before the movement initiation and also there is time delay of neural conduction to reach muscles, systems are further assumed to be able to predict the peripheral consequences of the descending neural signals. This computation process of prediction is termed ‘forward internal models’ or ‘direct models’ and it involves similar steps to the inverse model in the opposite order.

The alternative is an approach based on physical laws. The physical principle of movement generation in this approach is that parameters of physical laws that link peripheral variables are manipulated by the CNS to produce movements (Latash, 2010a; 2014). A particular example of this approach is the equilibrium-point (EP) hypothesis (Feldman 1986), which equates parameters used by CNS to control movements with subthreshold depolarization of the alpha-motoneuronal pools of the involved muscles. Manipulating the these parameters results in changes in the threshold (λ) of the tonic stretch reflex (TSR), which links active force changes to muscle length changes.

On the muscle force-length graph of a single muscle, λ is the point on the length axis when the muscle starts to show signs of electrical activation during very slow stretch. With a given λ, when there is a certain constant external load, the muscle-load system will be in

equilibrium at a certain muscle length. The combination of the muscle force and length at equilibrium is called EP. A change in the external load leads to a change in muscle length, which in turn triggers the TSR that alters the level of muscle activation to result in a new EP. The EP hypothesis views λ as a neural control variable for movement production and, when the λ changes, the whole force and length relationship of the muscle shifts along the length axis (Figure 2-1). Within the EP hypothesis, the status of a muscle (EP_0) can change involuntarily as a consequence of a change in the external load (to EP_1), voluntarily with a shift in λ (to EP_2), or as a result of both effects (to EP_3).

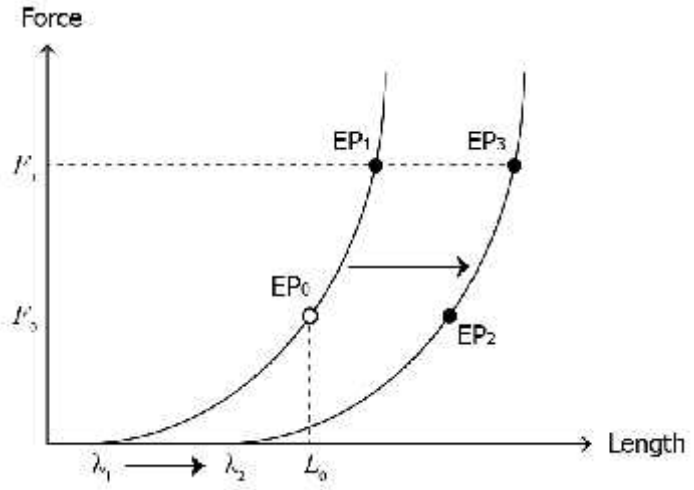

Figure 2-1. A muscle is in an equilibrium point (EP_0) at a certain length L_0 with a certain level of external force F_0. Within the EP hypothesis, movements are consequences of a change in the external load and/or a voluntary shift in λ.

The generalization of the EP hypothesis to a multi-muscle system in order to describe all natural movements of one or more joints resulted in the referent configuration (RC) hypothesis. The RC is defined as a set of referent values for salient performance variables related to body configuration. When actual body configuration and RC are the same, all of the muscles are at their thresholds for activation through the TSR loops. The difference between the RC and the

actual configuration (AC) that is sensed by proprioception leads to the activation of motoneurons and their innervated muscles so that the AC moves toward the RC. If the RC is attainable, the AC will coincide with the RC and stay at an equilibrium state with zero muscle activation. However, the AC may not be able to reach the exact RC because of anatomical and/or external constraints. For example, in order to grip an object with the thumb and index finger, the RC that defines the distance between the two digits is set inside the object, while the AC of the hand is constrained by the size of the object (Feldman, 2011).

Recently, the idea of hierarchical control has been proposed within the RC hypothesis (Latash, 2010b). According to this idea, the top RC is defined for task-related salient variables at a higher level of the hierarchy. The top RC will then project onto several RCs at the next lower level, for example, the joint or the digit level. This chain of RC transformations continues to the muscle level where the RC corresponds to the λ. Each of these transformations is few-to-many, which generate infinite combinations of RCs at the lower level corresponding to RC at the higher level.

2.1.2. Motor coordination and synergies

The problem of motor redundancy has been a central issue in the field of motor control (Bernstein, 1967). Redundancy implies that, at any level of description of human movements, there are more elements than are minimally necessary to perform the task. Bernstein addressed this issue by focusing on kinematic redundancy. For example, when a person tries to reach a certain point in space with the right index finger, the task is to match the coordinate of the fingertip to the coordinate of the target point. Even if we assume that the task is performed with the right upper extremity only and without manipulating the hand configuration, one can perform

the task with seven degrees of freedom in total by using the shoulder, elbow, and wrist joints, which provide an infinite number of joint configurations that can successfully accomplish the task. This becomes a problem when we try to understand how one of the joint configurations actually happens among the infinite number of options. This problem seems inevitable for any movement considering how rich the human motor system is. Even for the movement of a joint with one degree of freedom, we still confront the same problem at the muscle and motor unit levels (Latash et al., 1996).

Many solutions have been proposed to deal with the problem of selection of particular motor patterns, especially based on optimization principles with various cost functions, such as the minimization of movement time, torque, energy, or fatigue (Nelson, 1983; Wolpert et al., 1995; Prilutsky & Zatsiorsky, 2002). In more recent optimization approaches, several criteria have been combined to better explain the observed movements (Galna & Sparrow, 2006; Yamasaki et al., 2011). However, there is no single optimization principle that fits human movements in general and it is unclear how the CNS decides what to minimize for different tasks. It would be more appropriate to infer that the CNS tends to execute movements in a way that the above costs (objective functions) are kept reasonably low.

An alternative view of the apparently redundant design of the neuromuscular system is the principle of abundance (Gelfand & Latash, 1998; Latash, 2000). According to this principle, the CNS facilitates families of solutions that are equally able to solve the task and allows the solution to emerge given the current status of the system (Latash, 2012a). The abundance of the system allows the motor behavior to exhibit a stable level of performance with flexible choice of specific solution. For example, a person can hold a mug filled with coffee with various configurations of the holding upper extremity. This enables one to keep the mug vertical and, at the same time, to complete secondary tasks, such as opening a door by pressing down on the

handle with the elbow. This principle applies when the same task is performed repetitively resulting in variable patterns, which all lead to solving the problem accurately.

The principle of abundance led to the development of the concept of synergy. It is noteworthy that the word "*synergy*" ("word together" in Greek) has been used previously in the field of motor control with different definitions. First, the term is used often in the clinical field to describe the stereotypical patterns of muscle activation that are seen in some patients with neurological impairments, such as post-stroke hemiparesis (Brunnstrom, 1970; Bobath, 1978). The stereotypical movements in the extremities are characterized as flexion synergy or extension synergy, depending on the movement patterns that are predominant across the joints. These stereotypical movement patterns interfere with voluntary movements. Hence "synergy" is used with a strongly negative connotation. In the second definition, the term is often called "*muscle synergies*" or "*modes*", and it is used to represent certain sets of elemental variables that show parallel changes in their magnitudes. Several studies that have used the word with this meaning have suggested methods to organize muscles into groups with proportional changes in their activation levels (Buchanan et al., 1986; d'Avella et al., 2003; Krishnamoorthy et al., 2003; Ting & Macpherson, 2005; Tresch et al., 2006).

Finally, according to the definition used in this dissertation, synergy is the neural organization that ensures the high stability (low variability) of an important performance variable through co-varying adjustments of elemental variables (Latash, 2012b). This definition is based on the principle of abundance because it suggests that apparently redundant sets of elemental variables are organized to co-vary in a task-specific way to ensure stability and flexibility of important features of performance (Latash et al., 2007). Among the diverse meanings of stability, the one that is appropriate here is dynamic stability (reviewed in Latash, 2015; Latash & Huang, 2015), i.e., the ability of a system to maintain a desired state or trajectory despite variations in the

initial state and small transient perturbations. Dynamic stability is a crucial behavioral property to possess considering that the internal states that initiate the action vary all the time and the environmental states in which the action takes place are often poorly predictable. To address this stability property, actual perturbations can be applied to the system, and its reaction can then be quantified. Another method is to observe the natural variability of actions across repetitive trials.

For the latter approach, the concept of uncontrolled manifold (UCM) has been applied to quantify synergies (Scholz & Schöner, 1999). The UCM represents a subspace within the space of elemental variables in which a desired value of a performance variable is constant. At the level of inter-trial variances within the space of elemental variables, the existence of synergy for a task-related performance variable implies that the variance is relatively small in directions orthogonal to the UCM (V_{ORT}) and relatively large in directions within the UCM (V_{UCM}) (Latash et al., 2002c). In other words, if a performance variable is stabilized by the covaried adjustments of elemental variables, V_{UCM} is expected to be larger than V_{ORT}. For example, the three panels of Figure 2-2 illustrate three possible outcomes when the task is to produce the total force of 10 N with two fingers and the performance is measured over repetitive trials. The covariation of finger forces shown in the left panel is an example of synergy stabilizing total force; it is characterized by the cloud of data points elongated along the UCM (solid line, $F_1 + F_2 = 10$). In the middle and right panels, the clouds of data points are either circular or elongated along the direction orthogonal to the UCM (dashed line), in which cases, there is no synergy between the two fingers that stabilize their total force output. The structure of variance that reflects the relative amounts of V_{UCM} and V_{ORT} has been utilized as an index of synergy to test hypotheses regarding which performance variables are stabilized for specific tasks (Scholz et al., 2000; Latash et al., 2001; Scholz et al., 2001; Gorniak et al., 2009).

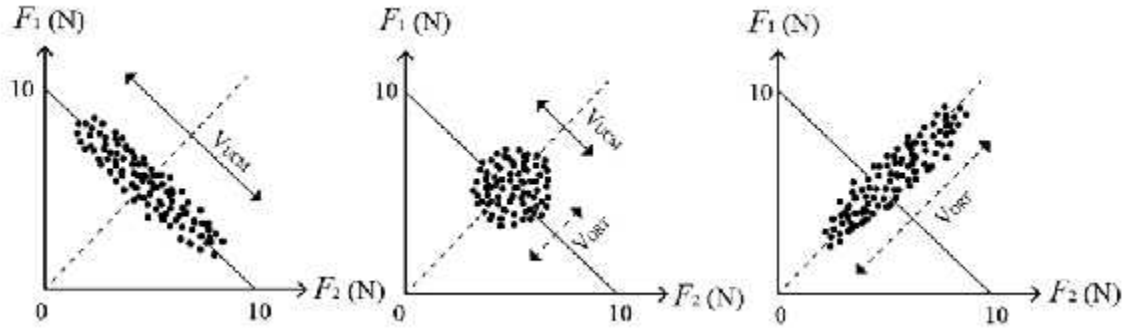

Figure 2-2. Clouds of data points measured in several trials in the experiment are illustrated. The solid line ($F_1 + F_2 = 10$) represents the UCM of this task. Variance of data points along the solid line (V_{UCM}) does not affect total force (performance variable) while variance along the dashed line, which is orthogonal to the solid line, (V_{ORT}) does.

One of the important features of synergies is that the CNS can adjust them without changing the overall performance of the system (Latash, 2008). The ability to purposefully destabilize a performance variable becomes very useful when a quick change in action is planned because, the system otherwise has to act against its own stability (Hasan, 2005). The feed-forward attenuation of synergies in preparation of an action is called anticipatory synergy adjustments (ASAs). Typically, V_{ORT} gradually increases and/or V_{UCM} gradually decreases 200-300 ms prior to the action, which results in a drop in the synergy index until the time of action initiation (Olafsdottir et al., 2005; Shim et al., 2006) or prior to a predictable perturbation (Kim et al., 2006; Krishnan et al., 2011).

ASAs have been compared with another well-studied anticipatory motor control process, anticipatory postural adjustments (APAs, Massion, 1992). It has been noted that both ASAs and APAs were delayed and reduced in magnitude in the healthy elderly (Woollacott et al., 1988; Olafsdottir et al., 2007a) and both are even further impaired in patients with PD (Bazalgette et al., 1987; Park et al., 2012). On the other hand, the most prominent difference between the APAs and ASAs is that they have distinct characteristic timings. Several recent studies of standing posture

addressed both of those phenomena and showed that APAs were consistently preceded by ASAs (Klous et al., 2011; Krishnan et al., 2011). These observations suggest a possibility that the two different mechanisms of anticipatory control may result from a single neural process with two distinct phases. It has been proposed that a distributed neural network including basal ganglia, cerebellum, thalamus, and cortex are involved in the generation and execution of APA (APAs, Massion, 1992; Jacobs et al., 2009; Ng et al., 2011). However, neural mechanisms of synergic control are currently all but unknown.

2.1.3. Neurophysiological structures and synergies

There are several neural structures that may contribute to the formation of synergies. First of all, at the spinal cord level, the Renshaw cell system could play the role of synergies via the system of recurrent inhibition (Latash, 2008). The Renshaw cells receive excitatory input from alpha motoneurons and project back to the motoneurons of the same pool. In case that one of the motoneurons stops firing for some reason, its Renshaw cells become less active and this leads to disinhibition to the other motoneurons and a net increase in the amount of excitation. Such mechanism could play a role in stabilization of the output of the motoneuronal pool (Hultborn et al., 2004).

Structures in the brain could also contribute to the formation of synergies, likely because of their high plasticity in the rearrangement of neural projections. In particular, subcortical structures have been implicated in the organization of motor synergies (Thach et al., 1993; Houk et al., 1996). Recently, the notion of distributed processing modules (DPMs) has been introduced to describe neurophysiological circuits involving the basal ganglia and cerebellum (Houk, 2005). It has been hypothesized that DPMs include cerebral cortical areas that are individually regulated

by loops involving the basal ganglia and the cerebellum. Since DPMs are assumed to link groups of neurophysiological variables, it could potentially be a mechanism to facilitate synergy formation. These speculations suggest strongly that the neural substrate of synergies can be distributed among many structures within the CNS.

2.2. The Human Hand

2.2.1. Anatomy of the hand and wrist

The hand is an anatomically complex structure. It contains a large number of bones, ligaments, and intrinsic muscles that are confined to the hand and the tendons of the extrinsic muscles, together with nerves and vessels (Jenkins & Hollinshead, 2002). The hand consists of 27 bones in total: 8 carpal bones compose the wrist, 5 metacarpals are the skeleton of the palm, and 14 phalangeal bones form the digits (Figure 2-3). The eight carpal bones are arranged in two rows: scaphoid, lunate, and triquetrum in the proximal row, and trapezium, trapezoid, capitate, and hamate in the distal row. The carpals articulate each other with adjacent bones. The carpal bones in the proximal row also articulate with the radius and the articular disc on the ulna, which allow for various movements of the wrist. The remaining distal carpal bones articulate with the metacarpals to form the carpometacarpal (CMC) joints. The movements of the CMC of the other digits are fairly restricted compared to those of the thumb. The proximal end of each metacarpal and phalanx is its base, the distal end is its head, and the shaft intervenes between the base and the head. The heads of the metacarpals again articulate with the bases of the proximal phalanges to form the condylar-type metacarpophalangeal (MCP) joints. There are two phalanges for the thumb and three for the other digits. The interphalangeal (IP) joints, which articulate between the phalanges, are hinge joints that allow only flexion and extension. The two IP joints at each finger

are called the proximal IP (PIP) joint and the distal IP (DIP) joint. The movements that occur at each joint and the involved muscles are listed in Table 2-1.

The muscles for hand movements can be divided into two groups: the intrinsic muscles, which have their whole structure located within the hand, and the extrinsic muscles, which have their muscle bellies in the forearm with their tendinous insertion located within the hand (Figure 2-4).

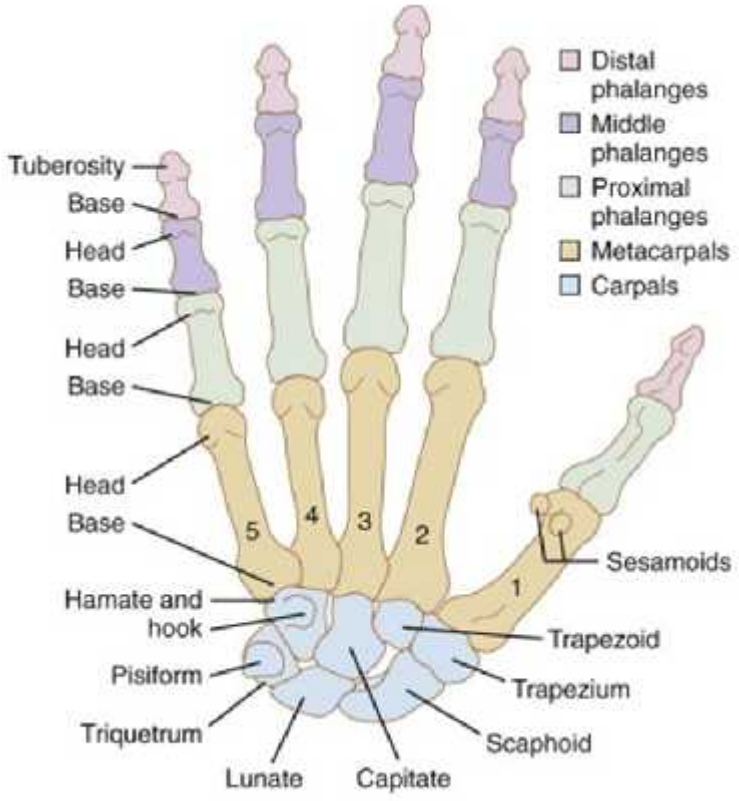

Figure 2-3. Bones of right hand and wrist. Palmar view. Note that the thumb is rotated approximately 90 degrees relative to the rest of the digits. Reprinted from Rehabilitation of the hand and upper extremity, 6th edition, Skirven TM, Page 4, Copyright 2011, with permission from Elsevier.

Table 2-1. Muscles producing movements at the wrist and hand (Abrahams et al., 2008)

Joint		Action	Muscles
Wrist		Flexion	Flexor carpi radialis, flexor carpi ulnaris, palmaris longus.
		Extension	Extensor carpi radialis longus and brevis, extensor carpi ulnaris.
		Abduction	Flexor carpi radialis, extensor carpi radialis longus and brevis, abductor pollicis longus, extensor pollicis brevis.
		Adduction	Flexor carpi ulnaris, extensor carpi ulnaris.
Thumb	CMC	Flexion	Flexor pollicis brevis, opponens pollicis, flexor pollicis longus.
		Extension	Abductor pollicis longus, extensor pollicis longus, extensor pollicis brevis.
		Abduction	Abductor pollicis brevis, abductor pollicis longus.
		Adduction	Adductor pollicis.
		Opposition	Opponens pollicis, flexor pollicis brevis.
	MCP	Flexion	Flexor pollicis longus, flexor pollicis brevis and first palmar interosseous.
		Extension	Extensor pollicis longus, extensor pollicis brevis.
	IP	Flexion	Flexor pollicis longus.
		Extension	Extensor pollicis longus.
Fingers	MCP	Flexion	Flexor digitorum profundus, flexor digitorum superficialis, lumbricals, interossei, flexor digiti minimi brevis (little finger).
		Extension	Extensor digitorum, extensor indicis (index finger) and extensor digiti minimi (little finger).
		Abduction	Palmar interossei; when flexed, the long flexors assist.
		Adduction	Dorsal interossei, the long extensors and abductor digiti minimi (little finger).
	IP	Flexion	PIP: flexor digitorum superficialis and flexor digitorum profundus. DIP: flexor digitorum profundus.
		Extension	With the MCP joints flexed: extensor digitorum, extensor indicis, and extensor digiti minimi. With the MCP joints extended: interossei and lumbricals.

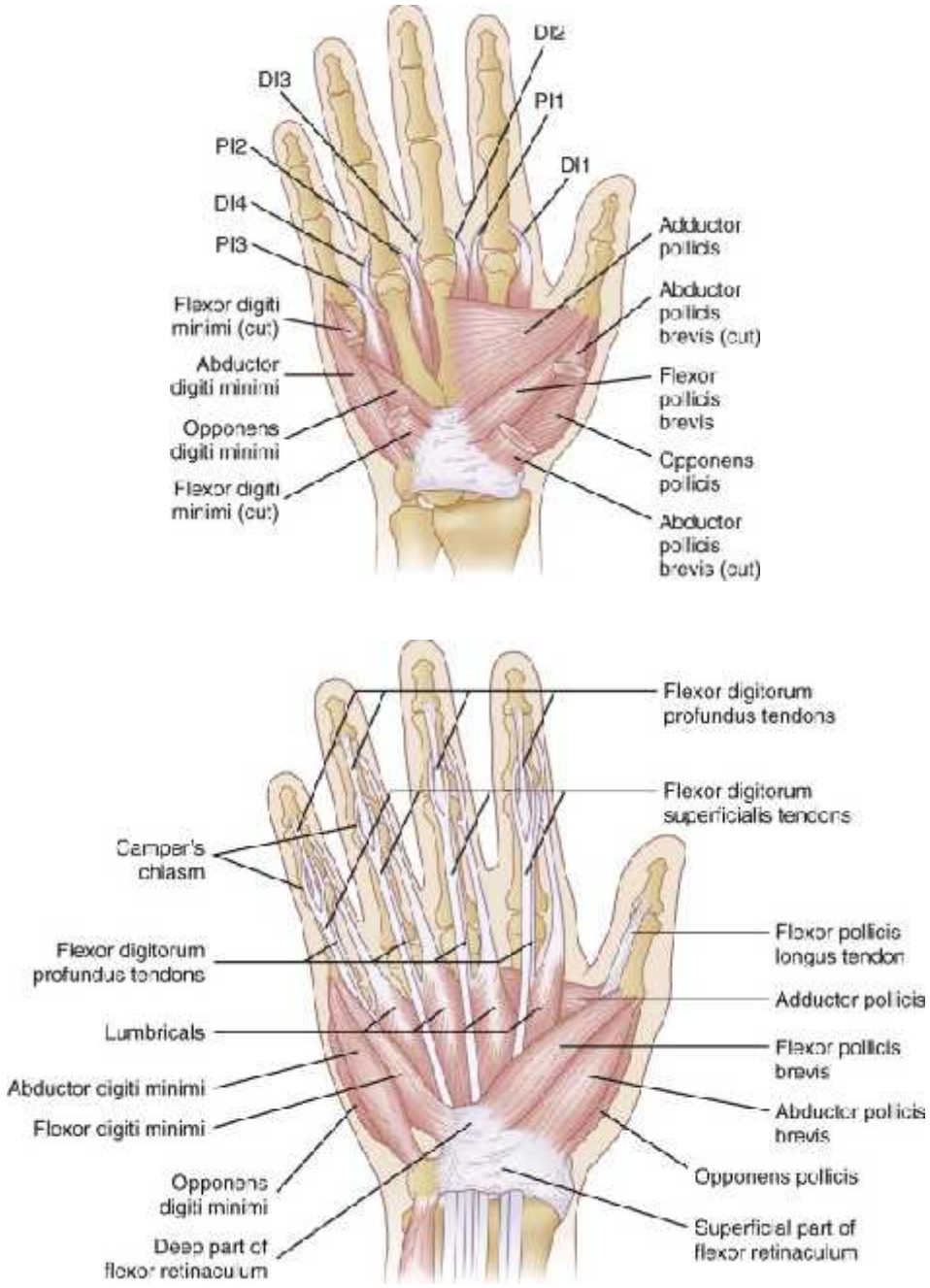

Figure 2-4. Deep (upper) and superficial (lower) muscles of the right hand. Palmar view. DI, dorsal interosseous; PI, palmar interosseous. Reprinted from Rehabilitation of the hand and upper extremity, 6th edition, Skirven TM, Pages 10-11, Copyright 2011, with permission from Elsevier.

The intrinsic muscles are digit-specific in their actions because their tendons insert on the specific phalanx, whereas the extrinsic muscles have multitendoned structure that act on several digits. For finger flexion, two extrinsic flexor muscles are involved in the action: the flexor digitorum profundus (FDP) and the flexor digitorum superficialis (FDS). The FDP acts primarily as a flexor at the DIP joints of all of the fingers through its tendinous attachments on the distal phalanges. With continued action, the FDP will also flex the PIP and MCP joints and even assist with wrist flexion. In a similar way, the FDS acts on all four PIP joints through its attachment to the middle phalanges and, with continued action, the FDS will also aid in flexing the MCP and wrist joints.

2.2.2. Finger interaction and mode hypothesis

There is limited individuation in both movement and force production by fingers. For example, if you try to flex one finger toward the palm, you will notice that you cannot do it without accompanying movements of the other fingers. The same applies when you try to press down with one finger exclusively while all of the fingers contact on the surface. There will be involuntary force production in the other fingers. This lack of finger independence in finger force production, which is known as enslaving (Li et al., 1998; Zatsiorsky et al., 2000), has been examined in studies which have shown that the magnitude varies according to the following factors. Enslaving effects are typically higher when the ring finger is the task (pressing) finger and smaller when the index finger is the task finger. In addition, the strength of the enslaving effect is typically smaller on the fingers of the dominant hand compared to those on the non-dominant hand and it varies across individuals, especially as a result of factors, such as age or practice (Shinohara et al., 2004; Wu et al., 2013a).

The neural control of hand muscles is a primary factor contributing to enslaving. Hand muscles, with the most dense monosynaptic projections from the primary motor cortex (M1) to their motoneurons, have the ability to control fine movements and force production at individual fingers (Lemon, 1993). These M1 neurons that provide input to any given hand muscle are distributed over a large cortical territory, and they overlap extensively with the territories of the neurons providing input to other muscles. Moreover, the outputs from one M1 neuron diverge to multiple muscles. This complex organization of convergence and divergence may contribute to the incomplete finger individuation (Schieber, 2001; Schieber & Santello, 2004) and possibly to the covariation of individual finger forces.

The notion of finger modes (Danion et al., 2003b) was introduced as a hypothetical variable reflecting desired involvement of an individual finger. The idea is that CNS can change individual finger modes one at a time. A change in a finger mode results in motion and/or force generation by all the fingers of the hand. The relationship between finger modes and finger forces is linked with enslaving according to the following formula:

$$F = E \cdot M$$

where F is a finger force vector, M is a finger mode vector, and E is an enslaving matrix that can be estimated experimentally with single finger pressing tasks. The finger mode is frequently used as an elemental variable in the UCM analysis because the enslaving effect may induce structure in the variance of individual finger forces that is unrelated to the task. Using modes as elemental variables allows eliminating this potential confounding effect.

2.2.3. Multi-digit synergies

The hand is a particularly attractive model for the study of coordination of multi-element systems because it demonstrates exceptionally well-stabilized output variables, such as net force and moment, and also highly sophisticated manipulation of hand-held objects. One can design different tasks by changing the number of involved hands and/or digits in order to compare the system's performance depending on the level of analyses. Moreover, it is relatively easy to record the force and moment production of individual elements (digits). Due to these advantages, a number of studies have expanded our understanding of multidigit synergies. In particular, pressing force production tasks have been an excellent model to demonstrate multidigit synergy stabilizing total force in a simple and efficient way (Latash et al., 2001; Scholz et al., 2002; Shim et al., 2005b).

Another frequently used model is prehensile tasks that require the modulation of forces and/or moments of force on a hand-held object. Prehensile actions are considered as organized at two hierarchical levels (Arbib, 1985). At the upper level, the desired mechanical action is shared between the thumb and the set of four fingers (the virtual finger), while, at the lower level, the action of the virtual finger is distributed among the four fingers. Experimental studies have shown that prehensile synergies for resultant normal force, resultant tangential force, and resultant moment of force are formed to stabilize the overall mechanical actions of the hand on the object at one or both levels of the hierarchy (Gorniak et al., 2009; Latash & Zatsiorsky, 2009). Prehensile tasks certainly address more practical functions of the hand compared to the pressing tasks and allow their results to be more applicable to synergies in everyday movements. Analysis of synergies during prehensile tasks is typically performed at the level of digit forces and moments, because one-hand prehensile tasks involve 30 elemental variables (six force/moment

vectors of each digit) and estimation of the comprehensive enslaving effects among these variables remains a challenging problem.

The indices of multidigit synergy have been shown to be sensitive to factors, such as practice, aging, and neurological disorders (Shinohara et al., 2004; Latash & Anson, 2006; Olafsdottir et al., 2007a; Olafsdottir et al., 2008b; Wu et al., 2013a; Latash & Huang, 2015). More specifically, several studies, which have applied the concept of synergies to multidigit pressing and prehensile tasks in healthy elderly subjects, have shown reductions in the synergy and ASA indices. However, other studies in the elderly have showed that the synergies have adaptive properties. They can be improved with strength training of the hand or with practice to adjust finger force production according to the various instability levels. Studies on neurological disorders will be addressed in the following section.

2.3. Motor function in neurological disorders

2.3.1. Stroke

Motor outcome following stroke varies depending on the size and location of the lesions (Chen et al., 2000; Shelton & Reding, 2001; Wenzelburger et al., 2005; Mani et al., 2013). Typically, the deficits in motor function result from weakness, spasticity, abnormal patterns of movement (referred to as "abnormal synergies") and poor intersegmental coordination (Levin, 1996; Beer et al., 2000; Warlow, 2008). After a unilateral stroke, such deficits are most prominent on the contralesional side, while ipsilateral deficits are also present and affect functional independence (Wetter et al., 2005; Schaefer et al., 2009).

Motor deficits of the hand are especially common in stroke survivors. These deficits cause particular difficulties in the performance of the activities of daily living (Raghavan, 2007). Decreased grip strength has been used to describe hand impairments after stroke (Sunderland et al., 1989; Kamper et al., 2006). Other deficits in the performance of skillful manipulative tasks have been often referred to as a loss of dexterity (Canning et al., 2004; e.g., Nowak et al., 2007). A loss of dexterity is generally used to describe poor, unskillful, and clumsy performance of a task. Therefore, the methods used to quantify a loss of dexterity may not always reflect the same features of motor action. Possibly due to this reason, the correlations between the strength and dexterity in various studies have not been consistent.

Some studies have suggested that weakness and loss of dexterity in motor performances are interrelated in stroke patients, because dexterity is often quantified by grading the performance of a stereotypical task that requires a prerequisite amount of strength (Canning et al., 2000). Indeed, in a study that used a task that required minimal muscle strength, the maximal strength and dexterity measures were not related while both were deteriorated (Ada et al., 1996). Another study performed on patients with subcortical strokes showed that the loss of dexterity, quantified by McCarron scores (McCarron, 1997), might still exist even after strength restoration (Thickbroom et al., 2002). These results suggest that the recovery of grip strength is indicative of restored corticospinal excitability, but it does not guarantee the recovery of dexterity, possibly because the ability to produce individual digit movements remains quite impaired (Lang & Schieber, 2003; Li et al., 2003). Methods that quantify dexterity without confounding effects of strength as well as a more exact and objective definition of dexterity are needed.

Dexterity has been defined more thoroughly as the ability to find a motor solution for any external situation, that is, to adequately solve any emerging motor problems correctly, quickly, rationally, and resourcefully (Bernstein, 2014). With this expanded definition, the concept of

dexterity can be applied to the performance of any task that is not restricted to hand function. Although the last feature, resourcefulness, was mentioned as the heart of dexterity in the above reference, the first three features (accuracy, speed, and efficiency) are usually considered when quantifying dexterity (e.g., Nowak et al., 2007). Resourcefulness helps to perform movements despite external influences and also to initiatively change the process of movement with anticipation (Bernstein, 2014). Both of the properties of resourcefulness are exactly reflected in the concept of synergy and ASAs.

When applying the first property of resourcefulness, a loss of dexterity implies loss of the skillful coordination of effectors (joints, muscles, digits, etc.) to meet changing environmental demands, which can be quantified as indices of synergy. To date, not many studies have applied a concept of synergy that is in line with this definition. A study of the kinematics of reaching movements after unilateral strokes has applied the UCM method to examine joint coordination (Reisman & Scholz, 2003). The study showed that the patients had greater difficulty moving their arms to the required spatial location, which was reflected in the longer movement time, poor accuracy, and altered patterns of the involvement of the participating joints. However, the patients showed strong multijoint synergies that stabilize the endpoint trajectories in both the affected and less-affected limbs and they were compatible to those of the healthy controls. These results were somewhat unexpected although its generalization is limited because of the characteristics of the patients (8 right hemisphere damaged patients). Another study has applied the UCM method to determine the effect of practice in bimanual coordination in stroke survivors (Kang et al., 2014). The study has showed an increased synergy index with decreased V_{ORT} after training, which is in line with the earlier study in healthy subjects (Wu et al., 2014).

Anticipatory adjustments of synergy have not yet been explored in stroke studies. However, other impairments in anticipatory controls in stroke patients have been well

documented. In a study that applied self-initiated predictable perturbations, anticipatory postural adjustments were reduced in individuals with hemiparesis, especially on the paretic side (Slijper et al., 2002). Anticipatory adjustments of grip forces for grasping and lifting or pulling an object are impaired in patients with acute (Nowak et al., 2003) and chronic strokes (Kamper et al., 2006) and in a patient group with subcortical strokes (Raghavan et al., 2006).

2.3.2. Parkinson's disease

Parkinson's disease (PD) is a progressive neurodegenerative disease that has primary pathophysiology of the loss of dopaminergic cells in substantia nigra pars compacta (Watts et al., 2012). In PD patients, deprived of normal dopaminergic inputs, discharge patterns of basal ganglia become abnormal and lead to disturbances in multiple basal ganglia-thalamic-cortical circuits (DeLong & Wichmann, 2007). More specifically, a decrease in dopamine release in the striatum would result in an increase in the activity of the internal segment of the globus pallidus and substantia nigra pars reticulata. Increased basal ganglia output could translate into less movement through inhibition of thalamocortical projection neurons. The clinical features of the disease are characterized mainly by motor symptoms such as bradykinesia, rigidity, resting tremor, and postural instability.

Among the motor symptoms, postural instability is generally manifested in the late stages of PD, after the onset of other the motor features (Jankovic, 2008), and it often results in an inability to stand or even sit as the disease progresses. To assess the impairment of postural stability in a clinical setting, a patient is quickly pulled backward or forward by the shoulders in order to observe the degree of response to the perturbation. An experimental study applied backward and forward surface translations to identify the specific deficits in PD patients with

postural instability (Horak et al., 1992). The postural instability in that study was associated with excessive antagonist activity and inflexibility, which were reflected in electromyographic (EMG) patterns and which were not able to effectively adapt to changing environmental conditions.

For motor coordination of the hand in PD, impaired manual dexterity is often a core symptom. This reflects the impaired control of the stability of hand, considering that dexterous manipulations depends on coordination of fingertips in order to stabilize objects in dynamic task conditions (Lawrence et al., 2014). Many studies have assessed dexterity in PD using timed manual tests such as coin rotation test (Bohlhalter et al., 2011; Foki et al., 2015) and pegboard test (Haaxma et al., 2010; Proud & Morris, 2010; Earhart et al., 2011) and considered impaired dexterity as a presenting symptom in PD. However, there are limitations in that poor performances of those tests could reflect bradykinesia, a cardinal feature of PD, reflected in hand movements. In studies on grasping and object manipulation in PD patients, with individual finger force measurements, it has been shown that bradykinesia was accompanied by excessive grip force production (Fellows et al., 1998; Nowak et al., 2005; Neely et al., 2013), unstable force output (Vaillancourt et al., 2002) and impaired anticipatory control mechanisms (Santello et al., 2004; Muratori et al., 2008). Similar changes were also documented for bimanual grasping tasks in PD (Gorniak et al., 2013).

In PD patients, the loss of dexterity is indeed reflected in synergy indices. A recent study used the framework of the UCM in multi-digit pressing tasks to show that PD is associated with significant impairments in multi-digit synergies (Park et al., 2012). In that study, patients with PD showed significantly reduced indices of synergies that stabilize the total force. Moreover, the adjustments of the synergy index in preparation to the quick force pulse (ASAs) were delayed and lower in magnitude. The patients who were tested in that study were at an early stage of PD (Hoehn-Yahr stage I-II). Interestingly, even the stage I patients, whose symptoms were limited to

only one side of the body, demonstrated similar changes in both hands. A follow-up study explored the effects of dopamine-replacement medications on the synergy indices by using the same protocol (Park et al., 2014). In their off-medication condition, the patients demonstrated synergy and ASA indices that were further reduced compared with the results in the on-medication condition. These results suggested the possible involvement of dopamine-sensitive neural pathways in the states of multidigit synergies. However, the above-mentioned studies in PD have failed to show any significant correlation between synergy indices and UPDRS (Unified PD Rating Scale) score, possibly because of the very narrow range of scores in the early-stage PD patients.

2.3.3. Multiple sclerosis

Multiple sclerosis (MS) is an inflammatory disorder of the brain and spinal cord in which focal lymphocytic infiltration leads to damage of myelin and axons (Compston & Coles, 2008). Initially, in most cases, the inflammation is transient and results in a wide range of neurological deficits in a relapsing-remitting pattern. Although compensatory processes can arise from the redundancy (abundance) of the individual systems or tracts, the pathological changes gradually become extensive throughout the whole brain and ultimately lead to chronic deficits. The clinical manifestations of MS are wide ranging because plaques of demyelination of varied size and shape can involve cerebellar cortex and subcortical white and grey matter, cerebellar white matter, brain stem and spinal cord (Love, 2006). The frequently presenting motor symptoms include balance and mobility impairments, weakness, fatigue, ataxia, and spasticity (Feinstein et al., 2015).

While mobility dysfunction appears in more severe states of MS, balance problems occur even in the very early stages (Martin et al., 2006; Krishnan et al., 2012b) and are an important

contributor to walking difficulties and falls (Gunn et al., 2013). Impaired balance in patients with MS has been characterized by the reduced ability to move toward limits of stability (Cattaneo & Jonsdottir, 2009) and delayed anticipatory postural adjustments with self-induced or externally triggered perturbations (Krishnan et al., 2012a; Aruin et al., 2015). Due to the variable nature of the CNS damage in MS, the cause of the impaired control of stability is probably multifactorial.

Disabilities in manual dexterity are commonly presented in patients with MS (Johansson et al., 2007). Interestingly, certain aspects of impaired finger coordination in patients with MS are similar to those in patients with PD. In a variety of tasks requiring the manipulation of a hand-held object, patients with MS show unusually high grip force magnitudes (Iyengar et al., 2009), increased grip force variability (Marwaha et al., 2006), and an altered relationship between grip and tangential forces (Krishnan et al., 2008; Krishnan & Jaric, 2008). Such changes are also exhibited in bimanual tasks (Gorniak et al., 2014).

Chapter 3 Goals of the dissertation

The main focus of the dissertation is to explore changes in synergies stabilizing the hand action in the above-mentioned neurological disorders and to try to link these changes to specific neural structures. The neural substrates that are responsible for the formation and changes of synergies are basically unknown. Therefore, the synergies in patients with motor disorders are a largely unexplored area of study and potentially powerful framework for addressing their impairments in motor coordination. Based on a handful of previous studies (Reisman & Scholz, 2003; Park et al., 2012; Park et al., 2013b), it has been hypothesized that subcortical structures are crucial for the control of movement stability. Identifying the differential effects of cortical and subcortical disorders on motor performance and synergies might lead to a better understanding of the involvement of those structures in control of stability in the general population.

More importantly, the methodology that was used to quantify synergies in the above-cited studies might provide a more objective tool for quantifying the impairments in the control of stability in patients with various neurological diseases. Because functional changes of the hand appear in the early stages of a variety of neurological diseases, this method might be sensitive enough to detect hand dysfunction in individuals without pronounced motor deficits and possibly develop into a standard clinical assessment of hand function in clinical practice. If certain changes are shown to be specific to certain disorder(s), the method could be a tool that allows for the early detection of the subtle altered status. Therefore, these lines of studies are worth exploring due to the important potential for the early detection of diseases, such as PD (Olanow & Obeso, 2012), and the need for behavioral biomarkers for optimal treatment (Miller & O'Callaghan, 2015).

In chapter 4, main experimental setup used in all of included studies, pressing setup, was described. The experimental procedures for pressing tasks and data analysis were also introduced. In the following chapters, a sequence of six research studies that have been published or are in the process of publication in peer-reviewed scientific journals are presented.

Chapter 5 includes four studies related to PD. First study investigated the changes in synergies in patients with PD. The multidigit synergies were quantified in an ecologically relevant task, that is, manipulation of a hand-held object. To provide a link between the pressing task used in earlier studies and the prehensile task, the pressing tasks were also included in the protocol. Second study explored whether indices of synergies in PD are sensitive to DBS. Synergy indices both during steady-state tasks and ASAs were quantified in PD patients with positive DBS effect on their motor symptoms. Third study explored the finger force changes during accurate force production without visual feedback in patients with PD. The main purpose of the study was to see whether PD patients could use an adaptive strategy to compensate for their loss of stability reflected in the reduced synergy and ASA indices. Last study in this chapter includes a group of professional welders – persons at high risk for PD – and has explored whether these persons show changes in synergy indices. These subjects were all apparently healthy without obvious neurological deficits. However, the manganese (Mn) exposure makes welders susceptible to Mn toxicity, which manifests as a type of Parkinsonism.

Chapter 6 presents a study exploring whether multidigit synergies are affected in patients with MS. Considering that many MS lesions reside in subcortical structures, it was hypothesized that the synergy and ASA indices would be significantly reduced in MS patients.

Chapter 7 presents a study exploring the changes in multidigit synergies during pressing tasks in unilateral mild cortical stroke patients. Based on a previous study (Reisman & Scholz, 2003), the hypothesis was that the stroke group would show differences from control subjects and

between the ipsilesional and contralesional hands in overall performance indices, but not in synergy and ASA indices.

Chapter 4 Methods

The methods of all studies included in this dissertation involve “pressing setup” described in this chapter. Main tasks used to quantify synergies composed of MVC task, single-finger ramp task, and accurate force pulse production task. MVC and ramp tasks not only provide additional information for subjects’ motor performances and also are required to set the task level of force pulse task for each subject and to analyze the results in mode space.

4.1. Pressing setup

Four piezoelectric force sensors (model 208A03; PCB Piezotronics, Depew, NY) were used to measure vertical forces produced by the fingers. The sensors were attached to a customized flat wooden panel. Each sensor was covered with sandpaper (300-grit) to increase the friction between the fingertips and the top surface of the sensors. The positions of the sensors in the medial-lateral and anterior-posterior directions were adjusted according to the individual hand and finger anatomy to achieve a comfortable hand posture. A wooden piece was placed underneath the subject’s palm to help maintain a constant hand and finger configuration during the tests (Figure 4-1). The four force signals were digitized at 300 Hz with a 16-bit resolution using a customized LabView program.

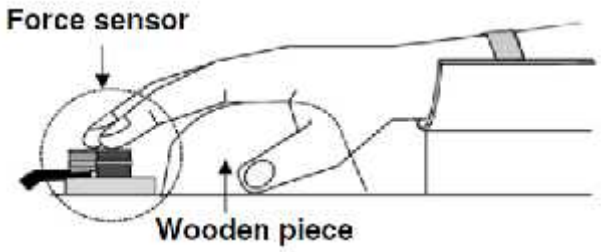

Figure 4-1. The pressing setup.

4.2. Experimental procedures

For the tests performed using the pressing setup (MVC, ramp, and force pulse tasks), subjects sat in a chair facing a 19-in. computer monitor positioned at eye level. The monitor showed real-time finger force feedback. The right forearm was strapped into a wrist-forearm brace to avoid forearm and wrist movement during trials. Prior to each trial, all sensor signals were set to zero when subjects placed their fingertips on the sensor centers and relaxed their hand. As a result, the sensors measured only active downward forces.

4.2.1. MVC task

In the MVC task, subjects were instructed to press on the sensors with the four fingers together as hard as possible in a self-paced manner and achieve maximal total force level within 8 s. The subjects were instructed to relax immediately after reaching a maximal force. The feedback showed the sum of the four finger forces (F_{TOT}). The maximal total force (MVC_{TOT}) and the forces of individual fingers (MVC_i; i = I, index; M, middle; R, ring; and L, little) were measured. The subjects performed two consecutive attempts and the trial with the higher MVC_{TOT} was selected to set further tasks with the pressing setup.

4.2.2. Single-finger ramp tasks

Subjects were required to press with one of the fingers (the task finger) and match with its force the template shown on the screen (Figure 4-2A). The 20-s template consisted of a horizontal segment at zero force for the first 4 s, followed by a slanted line from 0% to 40% of the force of the task finger measured in the MVC test over the next 12 s, and a horizontal segment at 40% of MVC_i for the last 4 s. Subjects were asked to pay no attention to possible force

production by other fingers (non-task fingers) and to keep all the fingers on the sensors at all times.

4.2.3. Accurate force pulse production task

In this task, subjects were asked to produce quick force pulses into a target by pressing with all four fingers. During each trial, the feedback on F_{TOT} was provided on the computer screen (Figure 4-2B). Two horizontal lines showed an initial force level (set at 5% of MVC_{TOT}) and a target level (set at 25% of MVC_{TOT}; with ±5% error margins). The instruction was to press on the sensors with all four fingers and match F_{TOT} with the initial force level as accurately as possible. A vertical line was shown corresponding to 5 s after the trial initiation. Once the cursor crossed the vertical line, the subjects were required to produce a very quick force pulse to the target at a self-selected time within the next 5 s. Each subject performed at least 25 trials and additional trials (over the minimum 25) were given if the subject made a major mistake (for example, pressing before the cursor reached the vertical line, pressing several times within 1 trial, or changing the baseline force slowly in preparation to pressing).

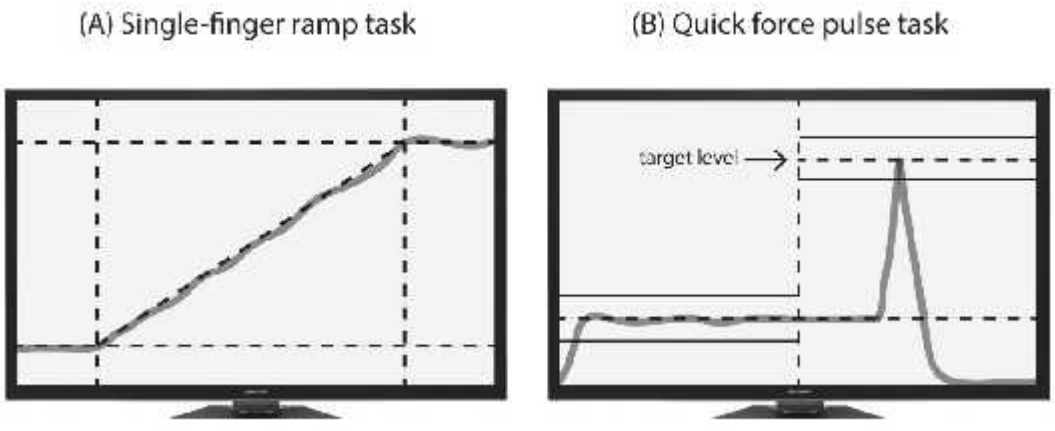

Figure 4-2. The feedback screen during single-finger ramp tasks (A) and quick force pulse production tasks (B).

4.3. Data analysis

4.3.1. Single-finger ramp tasks

The enslaving matrix (**E**) reflects the involuntary force productions by non-task fingers when an instructed finger produces force (Zatsiorsky et al., 2000). The **E** matrix was computed using the data from the single-finger ramp trials for each subject. For each single-finger trial, linear regressions of the force produced by individual fingers against F_{TOT} over a 10-s time interval were computed. The first and last 1-s intervals were excluded to avoid edge effects. The regression coefficients in $F_{i,j} = f_i^0 + k_{i,j} \times F_{TOT,j}$ were used to construct:

$$\mathbf{E} = \begin{bmatrix} k_{I,I} & k_{I,M} & k_{I,R} & k_{I,L} \\ k_{M,I} & k_{M,M} & k_{M,R} & k_{M,L} \\ k_{R,I} & k_{R,M} & k_{R,R} & k_{R,L} \\ k_{L,I} & k_{L,M} & k_{L,R} & k_{L,L} \end{bmatrix}$$

Where i,j = [I, M, R, L]; j represents a task finger; $F_{i,j}$ and $F_{TOT,j}$ indicate the individual i-finger force and F_{TOT}, respectively, when j-finger was the task-finger. An overall index of enslaving, EN_j, was computed for each finger as the average $k_{i,j}$ across the non-task fingers when j-finger was the task-finger: $EN_j = \sum k_{i,j}/3$ ($i \neq j$).

4.3.2. Accurate force pulse production tasks

The trials with the following errors were excluded from further analysis: the peak force was outside the ±5% error margins of the target force, the time to peak force was over 1 s, the baseline force was not stabilized prior to pressing, and/or the force pulse showed multiple peaks. Overall, the total number of excluded trials varied between 4 and 10 among subjects. The number of included trials was 20±1 for all subjects since we collected extra trials (over the minimum 25) in case the subject made mistakes that could be recognized during the testing procedure. The following variables were computed only for the accepted trials.

The time (t_0) of initiation of F_{TOT} change was defined as the time when the first derivative of force (dF/dt) reached 5% of its peak value in that particular trial. All the accepted trials for each hand and each subject were aligned with respect to t_0.

An index of multi-finger force stabilizing synergy was computed within the framework of the uncontrolled manifold (UCM) hypothesis (Scholz & Schöner, 1999; Latash et al., 2001). Finger forces were transformed into finger modes (**m**) with the help of the **E** matrix. The variance in the mode space across all the accepted trials was quantified separately in two sub-spaces for each time sample. The first sub-space (UCM) corresponded to no changes in F_{TOT}. The second sub-space was the orthogonal complement (ORT) to the UCM; variance within ORT changed F_{TOT}. The two variance components (V_{UCM} and V_{ORT}) were further combined into a single metric, a synergy index, ΔV, which was computed for each time sample:

$$\Delta V = (V_{UCM} - V_{ORT})/V_{TOT},$$

where each variance index is normalized by the number of degrees-of-freedom in the corresponding spaces; V_{TOT} stands for total variance.

We interpret $\Delta V > 0$ as sign of a F_{TOT} – stabilizing synergy; a higher ΔV implies a stronger synergy. For further statistical analysis, ΔV was log-transformed (ΔV_Z) using the Fischer transformation applied for the computational boundaries, from -4 to 1.333.

The average value of ΔV_Z was computed for the steady-state interval (between -600 and -400 ms prior to t_0). Anticipatory synergy adjustment (ASA) was quantified using two indices, the difference in the ΔV_Z between steady state and t_0 (ΔV_{SS-t0}) and the time of initiation of the ΔV_Z drop (t_{ASA}). The time of initiation of changes in ΔV_Z was defined as the time when ΔV_Z dropped below its average steady-state value (ΔV_Z) by more than 2 SD. Negative values of t_{ASA} mean that ΔV_Z started to drop before the initiation of F_{TOT} changes.

Chapter 5 Parkinson's disease

5.1. Prehension Synergies and hand function in early-stage Parkinson's disease

Although hand motor dysfunction is a well-documented early consequence of PD (e.g., micrographia, McLennan et al., 1972; Viviani et al., 2009), problems with finger coordination are not mentioned among the cardinal signs of PD. A series of recent studies in patients with early-stage PD documented changes in finger interaction and coordination indices during isometric force production tasks (Park et al., 2012; Park et al., 2013a; Park et al., 2014). In particular, those studies reported lower maximal force, higher indices of unintentional force production by fingers that are not required to produce force (Li et al., 1998; Zatsiorsky et al., 2000), and changes in indices of multi-finger synergies. According to the principle of abundance (Latash, 2012a), synergies were defined as co-variation among commands to elements (individual fingers) that stabilize (reduces inter-trial variance of) total force. Patients with PD showed significantly reduced indices of synergies during steady-state force production and an impaired ability to adjust synergies in preparation to a quick force pulse (Olafsdottir et al., 2005). These results suggest impairments in both creating task-specific stability of salient variables (Schöner, 1995b) and adjusting it in anticipation of a quick action. It has been hypothesized that the latter impairment may lead to problems with the initiation of various movements resulting, in particular, in episodes of freezing of gait common in PD (Park et al., 2014).

A study of patients on and off their PD medications has shown that both synergy indices and ASAs are sensitive to dopamine replacement therapy (Park et al., 2014). Although the early results suggest that synergy indices may be promising new measurements of PD-related motor

dysfunction, only modest correlations of these indices with the Unified PD Rating Scale-motor subscales (UPDRS-III) were found. One reason may be the narrow range of UPDRS scores typical of early-stage PD (Park et al., 2012). Indeed, in a study of patients with multi-system brain degeneration leading to a combination of parkinsonian and cerebellar clinical signs, significant correlations were found between UPDRS scores and synergy indices (Park et al., 2013b).

The current study had two main goals. First, we quantified multi-digit synergies in a more ecologically relevant task, that is, manipulation of a hand-held object. The prehensile manipulation was selected to mimic common everyday actions such as moving a glass of water to one's mouth and taking a sip. We also have added a functional hand task – the "glass-and-water" task – designed to detect impairments in an action relying on digit coordination in early-stage PD.

We expected patients with PD to perform slower than healthy controls (cf. bradykinesia) across all the tasks and show higher indices of enslaving (Hypothesis 1). Based on the aforementioned studies with pressing tasks, we expected patients to show lower indices of multi-digit synergies (Hypothesis 2). Note that this hypothesis is non-trivial: Several earlier studies have shown that faster actions are associated with lower synergy indices (Goodman et al., 2005; Friedman et al., 2009). We explored the second hypothesis at two levels of the hypothetical control hierarchy: At the upper level, the task is assumed to be shared between the thumb and a virtual finger (VF), an imagined digit with the mechanical action equal to the combined action of the four fingers (Arbib, 1985), whereas at the lower level VF action is shared among the four fingers. We also expected PD patients to show reduced ASAs (Hypothesis 3), although the object manipulation task involved relatively slow force and moment of force changes as compared to the force pulse production tasks (see Results).

To provide a link between the pressing task used in earlier studies (Park et al., 2012; Park et al., 2013a; Park et al., 2014) and the prehensile task, we also asked our participants to perform the accurate force and force pulse production during pressing tasks. We expected a correlation

between the synergy indices recorded in the pressing and prehensile tasks (Hypothesis 4). We also explored correlations between the synergy indices, UPDRS scores, and performance indices in the glass-and-water test.

Methods

Subjects

Eight patients with PD (aged 63.93 ± 9.54 years; 7 males) and eight age-matched control subjects (CS; aged 63.97 ± 6.84 years; 7 males) were tested. The participants were selected from a larger pool of subjects of an ongoing clinical and neuroimaging correlation study in which all PD subjects were recruited from a movement disorder clinic and diagnosed by movement disorder specialists. CS were recruited from spouses and friends of the patients, as well as through flyers posted in the local community. All participants were right-handed according to their preferential hand use during writing and eating, and all the tests were performed with the right hand. None of the CS had any known neurological disorders or arthritis in their upper extremities.

Descriptive data for all subjects are presented in Table 5-1. For PD subjects, Unified PD Rating Scale part III – motor scores (UPDRS- III) ranged between 6 and 34. Disease duration from time of diagnosis was between 0.7 and 10.3 years, with a median duration of 2.3 years. The levodopa equivalent daily dose (LEDD) was estimated for PD subjects according to a published formula (Tomlinson et al., 2010) and none of the patients showed signs of postural instability or drug-induced dyskinesia. All PD patients had tremor scores of 1 or 0 (both for rest tremor and kinetic tremor) for their right hand. PD subjects were tested while on their prescribed antiparkinsonian medication. UPDRS was administrated on the day of testing by clinical specialists at Hershey Medical Center. The study protocol followed the Helsinki principles and

was reviewed and approved by the Pennsylvania State University-Hershey Medical Center Institutional Review Board. Written informed consent was obtained from all subjects.

Table 5-1. Description of study participants

Subject	Sex, M/F	Age, yr	Handed-ness, R/L	Symptom Onset	Years Since Diagnosis	UPDRS motor score	Med, On/Off	Total LEDD, mg
PD group								
1	M	68	R	Bilateral	3.1	8	On	175
2	M	47	R	R	10.3	6	On	1097.5
3	M	77	R	R	1.1	17	On	350
4	F	63	R	R	0.8	13	On	400
5	M	63	R	R	8.7	21	On	635
6	M	70	R	R	0.7	11	On	50
7	M	67	R	R	6.9	34	On	900
8	M	54	R	L	1.5	19	On	460
CS group								
1	M	60	R					
2	M	76	R					
3	M	59	R					
4	M	69	R					
5	M	54	R					
6	M	62	R					
7	M	61	R					
8	F	66	R					

Abbreviations: M/F, male/female; R/L, right/left; UPDRS, Unified Parkinson's Disease Rating Scale; Med, medication; LEDD, levodopa equivalent daily dose.

Apparatus

- Pressing setup

  This setup is described in chapter 4.

- Prehension setup

  Five six-component force-moment transducers were mounted on a handle. A Nano-25 transducer (ATI industrial automation, Apex, NC, USA) was used for the thumb and four Nano-

17 transducers (ATI industrial automation, Apex, NC, USA) were used for the four fingers. The thumb transducer was mounted opposite to the transducers for the four digits (Figure 5-1). The transducers were attached in such a way that the X-axes of all five transducers were parallel to the central vertical axis of the handle. The center points of the sensors for the index and middle fingers were 4.5 cm and 1.5 cm above the midpoint of the handle, respectively. The center points of the sensors for the ring and little finger were 1.5 cm and 4.5 cm below the midpoint of the handle, respectively. The thumb sensor was located at the midpoint of the handle. The horizontal distance between the sensor surfaces was 6 cm. The centers of all the sensors were within one plane referred to as the grasp plane. The total mass of the handle with five sensors and 0.3 kg-weight attached was 0.619 kg. Sandpaper (100-grit) was attached to the contact surface of each sensor to increase the friction between the digits and the transducers. A 6-component (3 position and 3 angle components) magnetic tracking device (Polhemus FASTRAK, Rockwell Collins, Colchester, VT) was affixed to the top of the handle using a wooden base (2.5 × 15 × 0.2 cm). The tracking device samples the handle translation and rotational kinematics at 60 Hz. A circular level with 2° tolerance was attached at the center of wooden base and used as a feedback device for the subject to keep the handle orientation close to vertical at all times.

Experimental procedures

The experiment comprised five tasks: 1) Maximal voluntary contraction (MVC) tasks, 2) single-finger ramp tasks, 3) quick force pulse production tasks, 4) prehension tasks, and 5) a glass-with-water test. The subjects performed all five tasks in the above order with their dominant (right) hand. The pressing setup was used for the first three tasks, and the prehension setup was used for the prehension task only. The entire experiment lasted for approximately 1 h. Before

each task, subjects were given instructions and a demonstration by an experimenter, after which they practiced for 1-3 min.

- Pressing tasks

  The procedures were as explained in chapter 3.

- Prehension tasks

Subjects sat with an erect posture facing the prehension setup. They were asked to use their right hand to hold the handle with each digit tip placed on the center of the corresponding sensor. When holding the handle, the subject's right upper arm was abducted at approximately 45° in the frontal plane and internally rotated approximately 30°, the elbow was flexed at approximately 90°, and the wrist was in a neutral supination-pronation position. Subjects rested their left hand on their lap. A stand holding two horizontal wooden rods was used to indicate two targets, one lower and one higher (Figure 5-1).

The prehension task was used to simulate component movements of taking a sip from a glass. Each trial consisted of 5 consecutive parts. Subjects were asked to: 1) lift the handle by about 1 cm in order to match the top of the handle to the lower target level; 2) lift the handle up to the higher target level (phase 1: vertical movement); 3) move the handle horizontally towards their mouth and stop about 15 cm away from the face (phase 2: horizontal movement), 4) tilt the handle about 45° as if taking a sip (phase 3: tilting movement), and 5) return the handle back to the starting position. Each of the 5 parts lasted for about 4 s and the experimenter verbally indicated when each part was to start. Subjects were asked to move fast during phases 1, 2, and 3. After each movement part, subjects were asked to keep the handle stationary without deviations from the vertical (keeping the air bubble in the center of the level), except for phase 3 when the handle rotated. Phases 1, 2, and 3 were used for the data analysis. Movement distances for both

phase 1 and phase 2 were about 25 cm. Each subject performed 25 trials. Before each trial, the signals from the sensors were set to zero while the subjects were not touching the sensors.

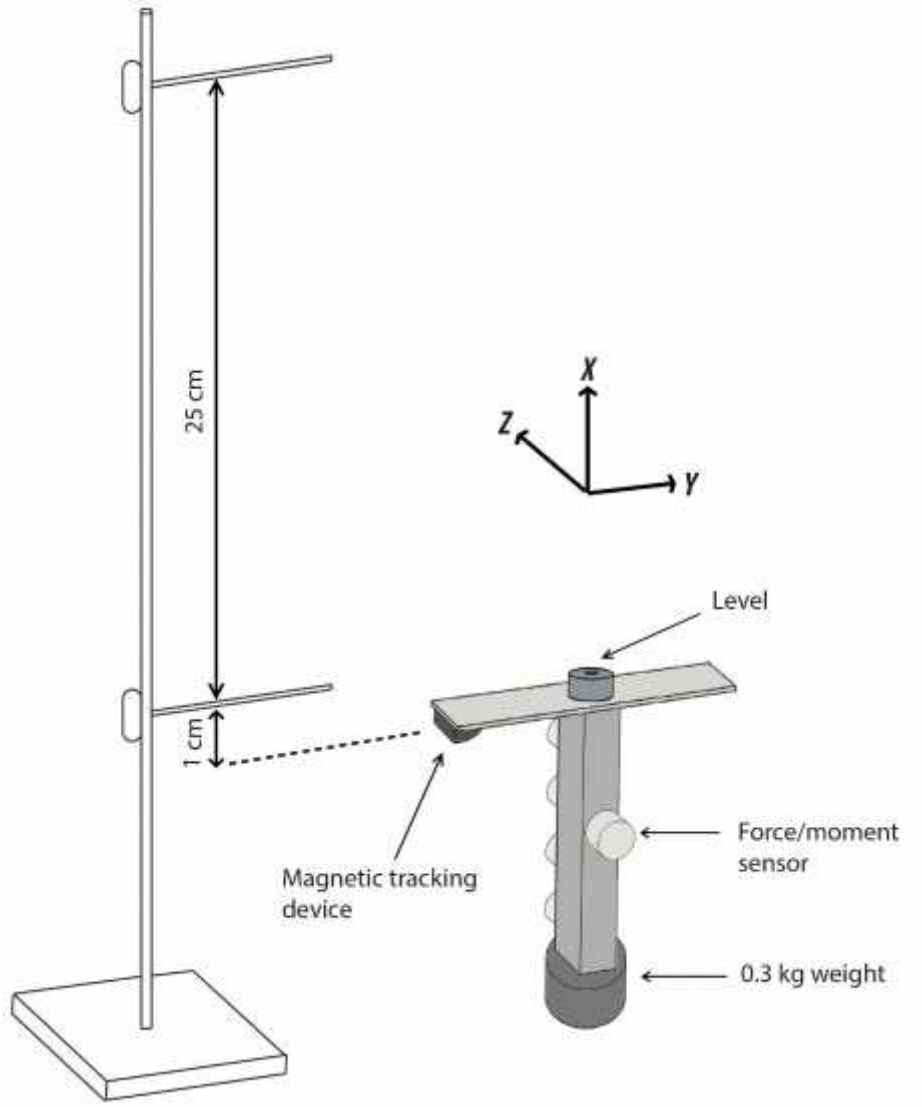

Figure 5-1. The prehension setup.

- Glass-with-Water test

Subjects performed the glass-with-water test while standing in front of a table with a plastic tray (44.5 × 29.2 cm). Four target positions were marked on the four corners of the tray. A plastic glass (6.6 cm diameter on the bottom, 8.8 cm diameter on the top, and 15.2 cm in height, 70 g) full of water (the level of water 3 mm below the rim, 610 ml) was placed on one of the targets (the far right corner). Subjects were asked to move the glass from a target to the next target counterclockwise and complete three circles ending at the same target position where they started. They were instructed to perform the task as quickly as they could, just touching each of the targets with the bottom of the glass with no dwell time, and to spill as little water as possible. Movement time was measured with a stopwatch, whereas the amount of water spilled was measured using a scale.

Data analysis

The force data were digitally low-pass filtered with a zero-lag, fourth-order Butterworth filter at 10 Hz. The data processing was done using a customized Matlab code.

- Pressing tasks

See chapter 4.

- Prehension tasks

The movement times (*MT*) for each phase, tangential velocity in phases 1 and 2, and angular velocity about the Y-axis in phase 3 were computed for each phase. The initiation (t_{START}) and termination (t_{END}) of movement in each phase were defined as the points where the velocity (tangential velocity for phases 1 and 2; angular velocity for phase 3) first reached 5% of its

maximal value and dropped below 5% of its maximal value in that trial, respectively. The data were quantified over three time periods in each phase, initial steady state (SS1), final steady state (SS2), and the movement duration, where SS1 refers to a 1-s interval starting 0.5 s before the movement initiation and SS2 refers to a 1-s interval starting 0.5 s after the movement termination. The trials were aligned by the t_{START} and time was normalized to 100 points over the movement duration. The intervals before and after the movement were not time normalized.

The data analysis was performed at two hierarchical levels (Arbib, 1985). At the upper level, the VF-TH level, the resultant force and moment components are shared between the thumb (TH) and virtual finger (VF, an imagined digit with the mechanical action equal to the combined actions of the four fingers). At the lower level, the IF level, VF action is shared among the four fingers. An index (ΔV) of synergy was calculated for several performance variables, which are the left-side variables in the following equations:

At the VF-TH level:

$$F^N = F_T^N + F_V^N$$

$$F^T = F_T^T + F_V^T$$

$$M_T = M_T + M_V$$

At the IF level:

$$F_V^N = F_I^N + F_M^N + F_R^N + F_L^N$$

$$F_V^T = F_I^T + F_M^T + F_R^T + F_L^T$$

$$M_V = M_I + M_M + M_R + M_L$$

where subscripts at the force variables (F) and moment of force variables (M) refer to the digits (I – index; M – middle; R – ring; L – little) and TOT relates to the resultant moment of force produced by all five digits. Superscripts in the above equations refer to the normal force (N) or

tangential force (T). At each level, ΔV was quantified for each of the force and moment variables. All trials were aligned for each phase starting 2 s before t_{START} and ending 2 s after t_{END} for each subject. The variances of each performance variable across trials were quantified separately in the UCM and ORT sub-spaces for each time sample. The synergy index, ΔV, was computed in the same way as in the force pulse production task. Note that $\Delta V > 0$ indicates a synergy stabilizing a certain performance variable at the selected level (Shim et al., 2005a; Gorniak et al., 2009). This index was log-transformed (ΔV_Z) using a Fischer transformation applied to the boundaries of each level. Mean values of ΔV_Z for SS1 and SS2 were computed and the mean value of ΔV_Z of these two steady states was used for statistical analysis. We also quantified the magnitude of the ΔV_Z drop ($\Delta\Delta V_Z$), which was defined as the difference in ΔV_Z between the mean value for SS1 and t_{START}, to investigate the modulation of ΔV_Z in preparation to quick action.

Safety margin (*SM*) is the proportion of normal force exerted beyond what is required to prevent object slipping (Burstedt et al., 1999); local *SM* was computed for the thumb as:

$$SM_T = \frac{(F_T^N - |F_T^T|/\mu)}{F_T^T}$$

where the superscripts *N* and *T* refers to normal and tangential forces of the thumb and μ is the coefficient of static friction between the finger and sandpaper interface that was about 1.4 (previously measured, Zatsiorsky et al., 2002).

- Glass-with-water task analysis

The total time (T_{WATER}) of moving the glass with water three times around four targets was measured by a stopwatch. The amount of water remaining in the glass at the end of the test was measured using a scale. For further comparisons, TWATER was normalized by the amount of water remaining in the glass: $MT_{WATER} = T_{WATER}/W_{NS}$,

where W_{NS} stands for the amount of non-spilled water.

Statistics

Standard descriptive statistics were used, and the data are presented as means and standard errors. The *MVC* and outcome variables of the quick force pulse production task ($\Delta V_{SS,}$ $\Delta V_{SS-t0,}$ and t_{ASA}) were compared between groups using a t-test. Mixed-design ANOVAs with repeated measures were used to explore how outcome variables (*EN*, *MT*, F_G, ΔSM_{TH}, V_{UCM}, V_{ORT} and ΔV_Z) were affected by factors *Group* (PD and CS), *Finger* (*I*, *M*, *R*, and *L*), and *Phase* (phases 1, 2, and 3; phases 1 and 2 for F_G and ΔSM_{TH} comparisons). The data were checked for violations of sphericity and Greenhouse-Geisser criterion was used to adjust the degrees-of-freedom when necessary. Pair-wise comparisons were performed with Bonferroni corrections to explore significant effects of ANOVAs.

The relationship between ΔF_T^N and ΔF_T^T in PD and CS was explored by linear regression, with ΔF_T^T as the dependent variable. The difference between the groups was tested using a dummy variable (0/1) identifying the PD subjects (Gujarati, 1970). In the first multiple regression analysis, the dummy variable and ΔF_T^N are independent variables. If the regression coefficient of the dummy variable is significant, the intercepts are significantly different between groups. To test slopes, the same analysis was done with the addition of the interaction term to the model. In these analyses, the slopes of the two lines are different if the regression coefficient of the interaction term is significant.

Pearson correlation coefficients were used to determine significant relationships between variables. For some analyses, we excluded phase 3 results for computational reasons. All statistical tests were performed with SPSS 19.0 (SPSS Inc, Chicago, IL, USA).

Results

Pressing tasks

- Maximal voluntary contraction and enslaving

Maximal force values (*MVC*) produced by the patients with PD were smaller than those produced by the healthy controls, on average by 24% ($p < 0.05$). These data are presented in Table 5-2. Both groups showed substantial force production by the non-task fingers during single-finger ramp force production tasks. The enslaving index (*EN*) in the PD group was larger than in the CS group (Table 5-2). These findings were supported by a two-way repeated measures ANOVA on *EN* with factors *Group* (PD and CS) and *Finger* (I, M, R, and L), which showed significant main effects for *Group* [$F_{[1,14]} = 6.15$, $p < 0.05$] and *Finger* [$F_{[3,42]} = 21.17$, $p < 0.001$] without other effects. Post-hoc comparisons confirmed that $EN_I < EN_M$, $EN_L < EN_R$ ($p < 0.05$).

Table 5-2. Performance characteristics for pressing tasks

	MVC	Enslaving				Quick force pulse				
	(N)	EN_I	EN_M	EN_R	EN_L	V_{UCM}	V_{ORT}	ΔV_{SS}	ΔV_{SS-t0}	t_{ASA}
PD	68.9	0.041	0.070	0.103	0.052	0.12	0.03	1.68	0.30	-0.10
	7.7	0.009	0.016	0.015	0.014	0.04	0.02	0.11	0.10	0.05
CS	90.8	0.014	0.036	0.065	0.038	0.17	0.01	2.33	0.76	-0.20
	6.4	0.005	0.012	0.010	0.006	0.03	0.00	0.10	0.09	0.02

Means and standard errors (upper and lower lines) of maximal voluntary force (MVC), enslaving indices (*EN*), variance indices (V_{UCM} , V_{ORT} , and ΔV_Z) at steady-state, magnitude (ΔV_{SS-t0}) and time (t_{ASA}) of anticipatory synergy adjustments (ASA) are presented. *I*, index; *M*, middle; *R*, ring; *L*, little fingers. PD – Parkinson's disease group; CS – control group.

- Multi-digit synergies and ASA in quick force pulse production

During the steady-state phase of the pressing task, both PD and CS groups showed higher magnitudes of variance in the finger mode space compatible with unchanged total force (V_{UCM}) as compared with variance that affected total force (V_{ORT}). V_{UCM} was lower and V_{ORT} was higher in the PD group. These effects were confirmed with a two-way repeated measures ANOVA with factors *Group* and *Variance*, which showed significant effects of *Variance* [$F_{[1,14]} = 52.16$; $p < 0.001$] and *Group* × *Variance* [$F_{[1,14]} = 4.83$; $p < 0.05$].

The difference between V_{UCM} and V_{ORT} differed between the two groups resulting in a significant group difference in the synergy index, ΔV. The magnitude of the log-transformed ΔV, ΔV_Z, at steady state in the PD group was smaller than in the CS group, on average by 28% ($p < 0.05$; see Table 5-2).

Prior to the force pulse initiation, ΔV_Z showed a decline starting about 100-200 ms prior to t_0. The magnitude of the drop in ΔV_Z was smaller in the PD group, on average by 60% ($p < 0.05$). The CS group showed an earlier initiation of the drop in ΔV_Z in preparation to the force pulse as compared to the PD group; this difference was, on average about 50%, but due to the large inter-subject variability the group effect was not significant.

Prehension task

- Performance indices

Patients with PD performed the handle manipulation task slower than the CS group. Movement times (*MT*) in the PD group were longer than in the CS group, on average by 57% for phase 1 (0.72 ± 0.06 s in PD and 0.46 ± 0.03 in CS), 83% for phase 2 (1.06 ± 0.11 s in PD and 0.58 ± 0.05 in CS), and 83% for phase 3 (0.75 ± 0.08 s in PD and 0.41 ± 0.04 in CS). These findings were supported by a two-way repeated measures ANOVA on *MT* with factors *Group* and

Phase, which showed significant main effects of *Group* [$F_{[1,14]} = 25.22$, $p < 0.001$] and *Phase* [$F_{[2,28]} = 14.27$, $p < 0.01$] without interactions. Post-hoc comparisons confirmed that *MT* in phase 2 was longer than *MT* in phases 1 and 3 ($p < 0.001$). The *MT* difference also was reflected in different magnitudes of the peak velocity in the two groups (Figure 5-2, left panels).

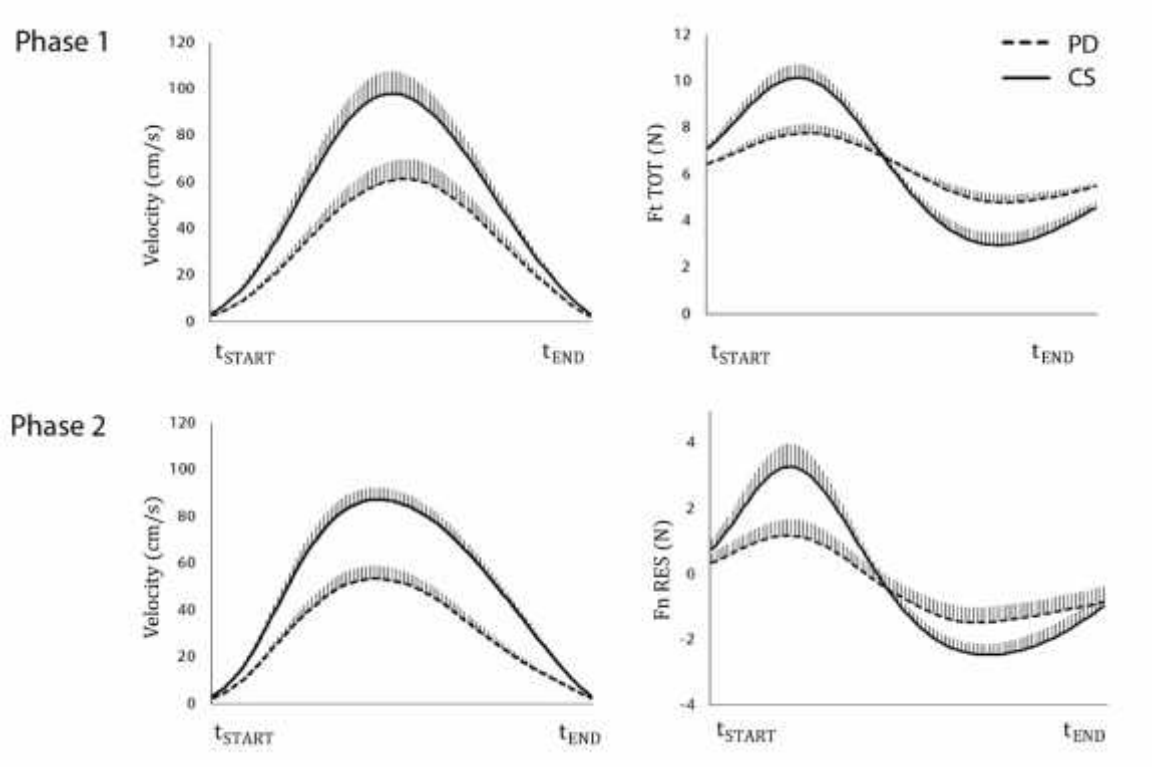

Figure 5-2. Time profiles of movement velocity, sum of tangential forces (Ft TOT) in phase 1, and resultant force (Fn RES) in phase 2. Averaged values across subjects for the PD and CS groups are presented with standard error shades from the initiation (t_{START}) to the termination (t_{END}) of movement in each phase. The data between t_{START} and t_{END} were re-sampled to 100 points.

During steady states, magnitude of grip force (F_G, estimated as the normal force produced by the thumb; ΔF_T^N) was slightly higher in PD. For phase 1, F_G was 14.8 ± 1.1 N in the PD group and 13.7 ± 1.6 N in the CS group. For phase 2, F_G was 16.6 ± 1.3 N in the PD group and 15 ± 1.7 N in the CS group. These differences, however, were not statistically significant. Modulation of F_G during movements (ΔF_G) was significantly smaller in the PD group as compared to the CS group (Figure 5-3). The modulation was quantified using peak-to-peak change of F_G during the movement in phases 1 and 2 for each trial. These observations were supported by a two-way significant main effects of *Group* [$F_{[1,14]} = 5.25$, $p < 0.05$] and *Phase* [$F_{[1,14]} = 19.89$, $p < 0.05$] without a significant interaction.

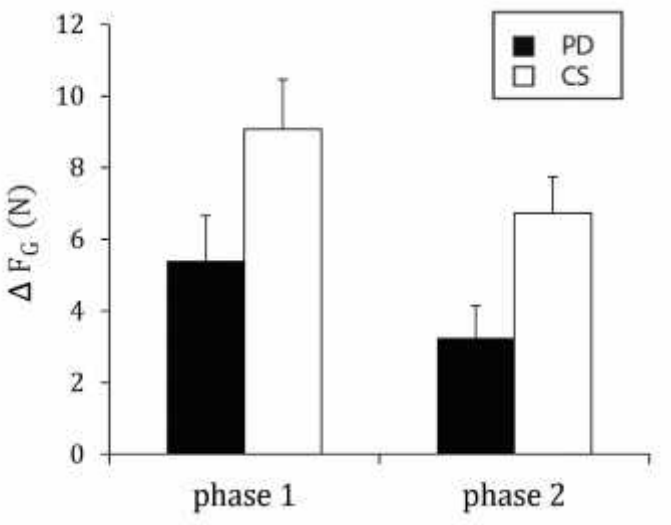

Figure 5-3. Peak-to-peak grip force during the movement (ΔF_G) for phases 1 and 2 in control (CS, white bars) and Parkinson's disease (PD, black bars) groups. Group means are shown with standard errors.

Further, we explored the relationship between ΔF_G and modulation of the thumb tangential force (ΔF^T) in the two groups. Phase 1 data averaged across trials within a subject were used for linear regression analysis. There was a significant correlation between ΔF_G and ΔF^T in each of the groups. The linear regression equations are shown with coefficients of determination in Figure 5-4. Both slopes and intercepts of the regression lines were significantly different between the groups ($p < 0.05$).

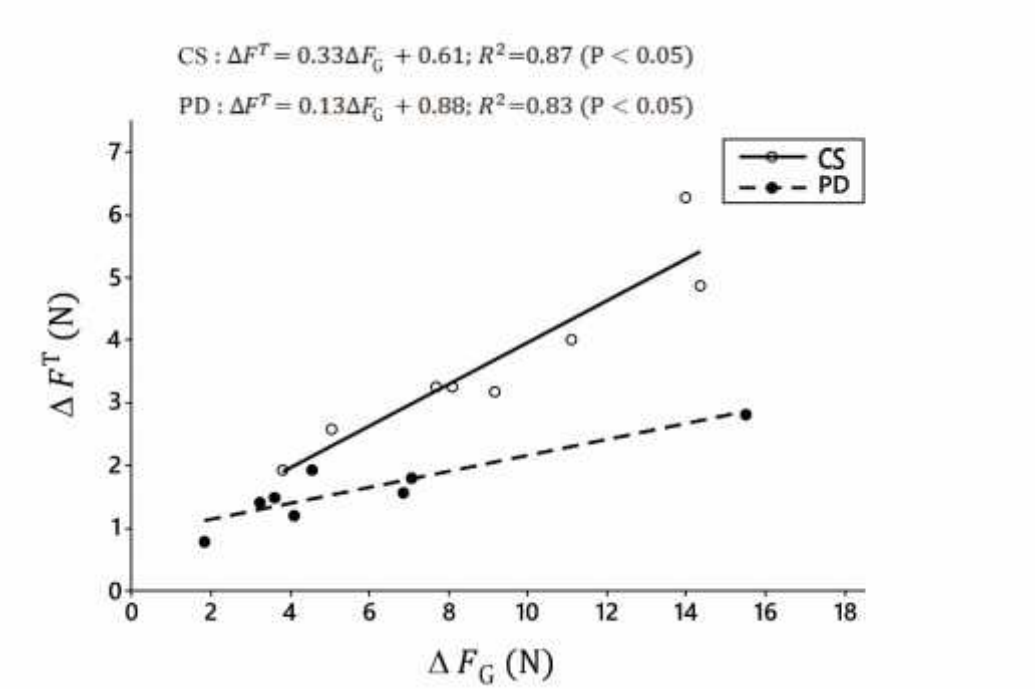

Figure 5-4. The relationship between the changes in the grip force (ΔF_G) and thumb tangential force (ΔF^T) during phase 1 for the two groups, control (CS) and Parkinson's disease (PD). Each point represents the averaged value across trials within each subject. Linear regression equations are shown for the PD and CS groups separately, along with the coefficients of determination (R^2). repeated measures ANOVA with factors *Group* and *Phase* (phases 1 and 2), which showed

- Safety margin

Local safety margin for the thumb (SM_{TH}) was computed for each subject, each trial, and at each time sample of phases 1 and 2. During SS1, the PD group showed overall higher SM_{TH} values as compared to the CS group. During the movement, however, the PD group showed a smaller modulation of SM_{TH} and, as a result, the peak SM_{TH} values were lower in PD subjects. The averaged across subjects time profiles of SM_{TH} for phase 1 are presented in Figure 5-5. The magnitude of change in SM_{TH} (ΔSM_{TH}) was computed within each phase; ΔSM_{TH} in the PD group was lower by 71% in phase 1 and by 69% in phase 2. These findings were supported by a two-way repeated measures ANOVA on ΔSM_{TH} with factors *Group* and *Phase* (phases 1 and 2), which showed a significant main effect of *Group* [$F_{[1,14]} = 13.85$, $p < 0.05$] without other effects.

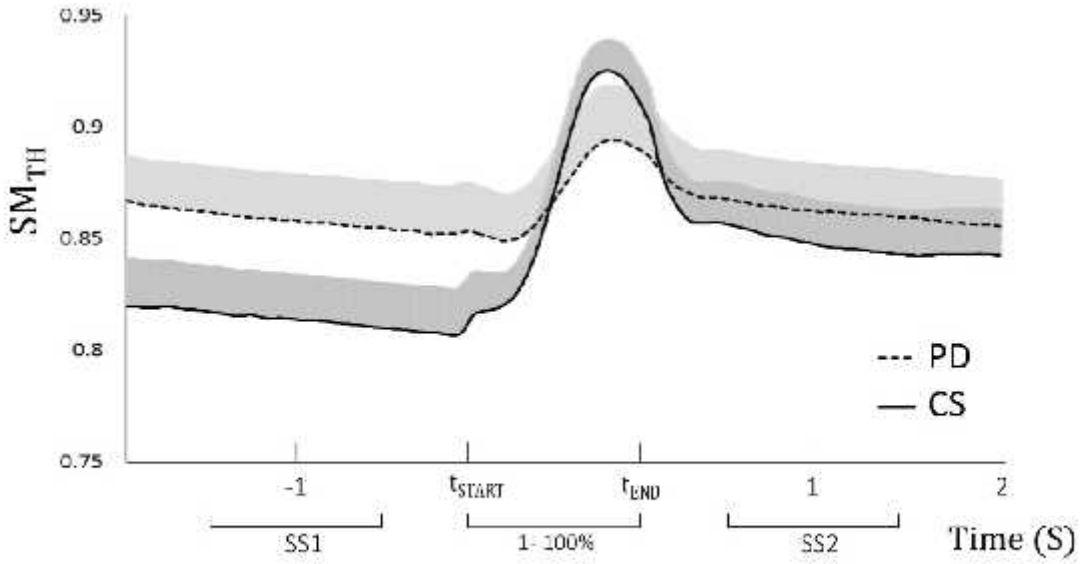

Figure 5-5. Safety margin for the thumb plotted against time for the control (CS) and Parkinson's disease (PD) groups. Averaged values across subjects within each group are presented with standard error shades over the first steady state (SS1), between the initiation of movement (t_{START}) and the termination of movement (t_{END}) re-sampled to 100 points, and over the second steady state (SS2). Note the higher SM values and smaller magnitude of modulation in the PD group.

- Multi-digit synergies and anticipatory synergy adjustments

Multi-digit synergies were quantified using an index (ΔV_Z) that was computed at each of two levels of hierarchy, the VF-TH and IF levels, for three performance variables, normal force ($\Delta V_Z F^N$), tangential force ($\Delta V_Z F^T$), and total moment of force ($\Delta V_Z M_{TOT}$). The mean ΔV_Z values of two steady- states averaged across subjects within each group are shown in Figure 5-6.

At the VF-TH level, the log-transformed synergy indices were positive for all three variables during steady states in all phases and in both groups. These indices were smaller in the PD group compared with the CS group, with particularly larger differences in $\Delta V_Z F^N$ and $\Delta V_Z F^T$. These findings were confirmed by a significant effect of *Group* in a two-way ANOVA on $\Delta V_Z F^N$ [$F_{[1,14]} = 7.34$, $p < 0.05$] and on $\Delta V_Z F^T$ [$F_{[1,14]} = 7.16$, $p < 0.05$]. The effects of *Phase* also were significant for both indices, [$F_{[2,13]} = 26.1$, $p < 0.001$] and [$F_{[2,13]} = 85.73$, $p < 0.001$], respectively. There were no interaction effects.

At the IF level, $\Delta V_Z F^T$ and $\Delta V_Z M_{TOT}$ were consistently positive, whereas there were some negative values for $\Delta V_Z F^N$ in both groups. The $\Delta V_Z F^T$ and $\Delta V_Z M_{TOT}$ indices in the PD group were smaller compared with the CS group, although $\Delta V_Z F^N$ was larger in PD subjects. ANOVAs showed a significant effect of *Group* only for $\Delta V_Z M_{TOT}$ [$F_{[1,14]} = 6.72$, $p < 0.05$]. The effects of *Phase* were significant for all variables; $\Delta V_Z F^N$ [$F_{[2.13]} = 9.07$, $p < 0.05$], $\Delta V_Z F^T$ [$F_{[2.13]} = 7.25$, $p < 0.05$], and $\Delta V_Z M_{TOT}$ [$F_{[2,13]} = 5.34$, $p < 0.05$]. There were no interaction effects.

The PD group showed signs of an impaired ability to adjust synergies in preparation to a quick action (ASA). For phase 1, the magnitude of drop in ΔV_Z before the vertical movement initiation ($\Delta\Delta V_Z$, see Methods) was quantified for F^T at the VF-TH level. This index was lower in the PD group compared to the CS group by 59% (0.40 ± 0.11 in PD; 0.97 ± 0.20 in CS, $p < 0.05$, *t*-test). We also found a significant negative correlation between *MT* of phase 1 and $\Delta\Delta V_Z$ across all subjects ($r = - 0.68$, $p < 0.05$).

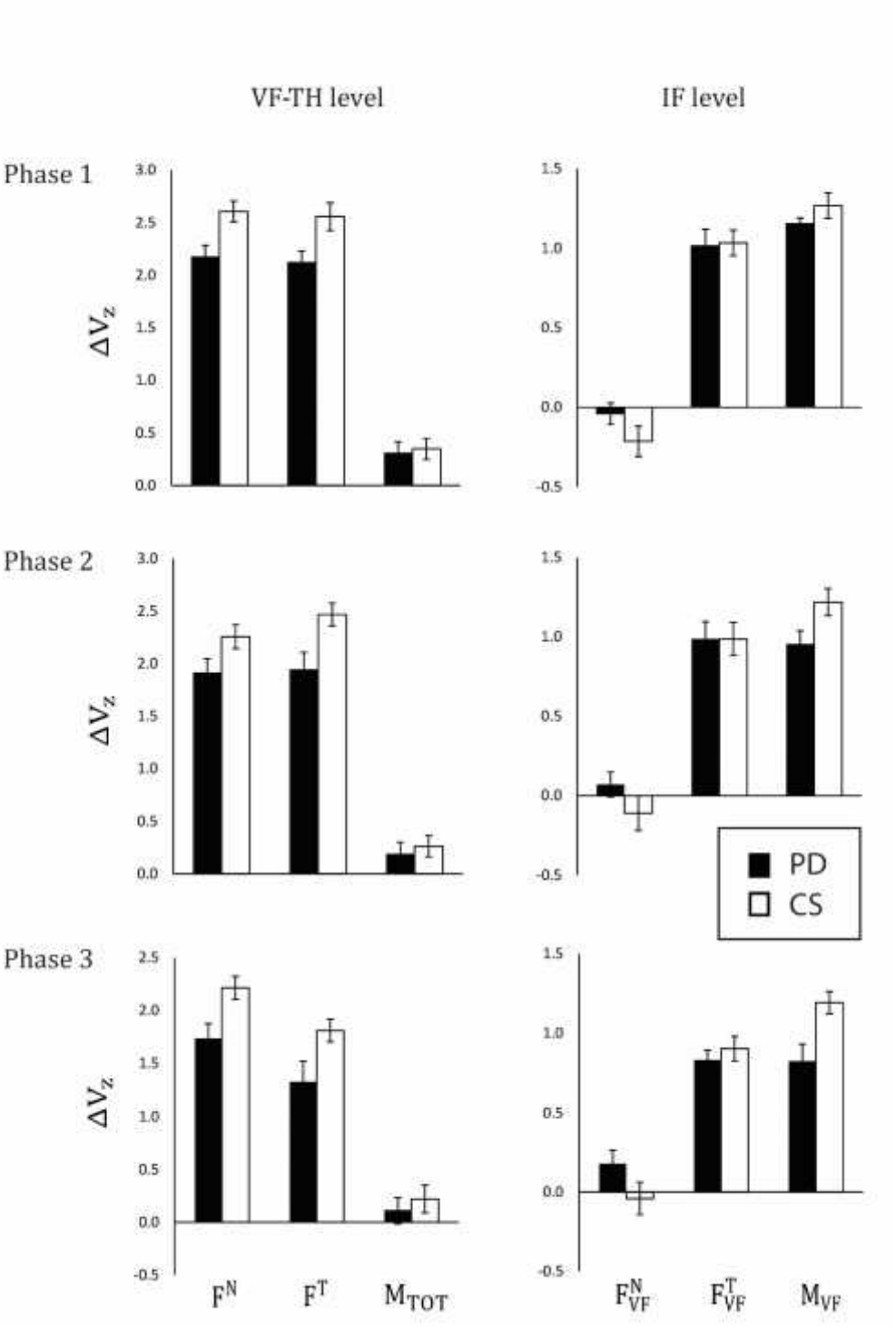

Figure 5-6. The synergy index (ΔV_Z) during the steady states averaged across subjects within each group (CS – control subjects; PD – Parkinson's disease) at each of the two levels of hierarchy, the VF-TH level and IF level, for three performance variables: normal force (F^N), tangential force (F^T), and total moment of force (M_{TOT} and M_{VF}). Group means with standard error bars are shown.

When synergy indices were compared between the pressing and prehension tasks, significant correlations were observed only between the indices in the pressing task computed for the normal finger force and in the prehension task for the tangential force ($\Delta V_Z F^T$). In particular, ΔV_Z in the pressing task showed positive correlations with $\Delta V_Z F^T$ computed at the VF-TH level in all three movement phases ($0.53 < r < 0.63$, $p < 0.05$). In contrast, when $\Delta V_Z F^T$ was computed at the IF level, the correlations with ΔV_Z in the pressing task were similar in absolute magnitude but negative. No significant correlation between ΔV_Z in the pressing task and ΔV_Z indices computed for the normal force and moment of force in the prehension task were observed.

Glass-with-water test

Movement time in the glass-with-water test was longer in PD subjects compared to CS (16.5 ± 0.7 s and 13.0 ± 4.2 s, respectively), with the difference approaching significance ($p < 0.06$); the amount of water spilled was similar between the two groups, although slightly higher in PD (13.8 ± 1.0 ml) compared to the CS group (13.3 ± 5.9 ml). When movement time was normalized by the amount of water that was not spilled, the resulting index (normalized movement time, MT_{WATER}) was significantly longer in PD subjects (28.4 ± 1.1) compared to CS (23.9 ± 1.7, $p < 0.05$). There were significant correlations between MT_{WATER} and movement times recorded during the prehensile handle manipulation test. This was true for MT indices over all three phases: phase 1 (MT_{P1}) ($r = 0.80$, $p < 0.001$), phase 2 (MT_{P2}) ($r = 0.71$, $p < 0.05$), and phase 3 (MT_{P3}) ($r = 0.55$, $p < 0.05$). An example of this correlation is presented in Figure 5-7A. Note that whereas the data for all subjects fit the same regression line, the PD group data show consistently longer *MT* values.

MT_{WATER} also correlated negatively with synergy indices computed for the pressing task. In particular, significant correlations were observed between MT_{WATER} and the synergy index

during steady state prior to force pulse production (ΔV_{SS}; illustrated in Figure 5-7B; r = - 0.74, p < 0.05) and with the overall drop in the synergy index during ASA ($\Delta V_{SS\text{-}t0}$; r = - 0.56, p < 0.05). Whereas the indices of performance and synergy indices showed significant correlations, the UPDRS scores failed to show significant correlations with any of the measured and computed indices (p > 0.3).

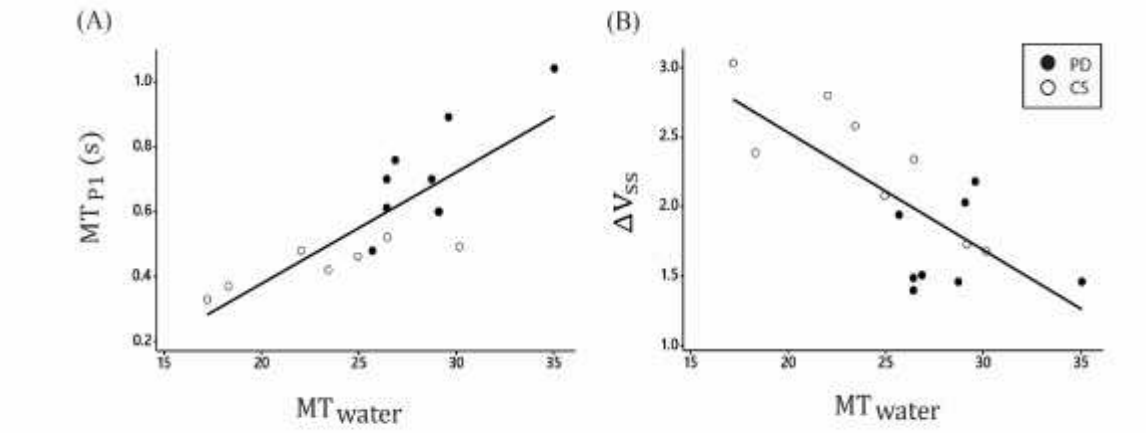

Figure 5-7. The correlations between normalized movement time during the "glass-and-water" test (MT_{water}) and movement time during phase 1 (MT_{P1}) in the prehension task (panel A, r = 0.80, p < 0.001), and also with the synergy index at the steady state (ΔV_{SS}) in the pressing task (r = - 0.74, p < 0.05). The correlations were computed over all subjects from both groups, controls (CS) and Parkinson's disease (PD).

Discussion

The data provide support for most of the hypotheses formulated in the Introduction. In particular, patients with PD moved slower than the controls in the prehension test (the "glass-with-water" test produced results just under the significance level), reflecting bradykinesia typical of PD. The patients also showed lower finger force (MVC) and higher indices of enslaving, indicating impaired individualized control of fingers (similar to the results of Park et al., 2012). Taken together, these findings support our Hypothesis 1. The patients showed lower synergy

indices during steady states in the pressing task and also for most analyses performed during the prehension task in support of Hypothesis 2. These differences were seen at both levels of the assumed hierarchy controlling the hand action (Arbib, 1985; Zatsiorsky & Latash, 2008) and with respect to both forces and moments applied to the handle.

Whereas anticipatory synergy adjustments (ASAs, Olafsdottir et al., 2005) were significantly delayed and reduced in the PD group in the pressing task, as expected based on earlier studies (Park et al., 2012; Park et al., 2014), the findings in the prehension task were less consistent. Only one variable, the tangential force, showed significantly reduced ASAs in the PD group, whereas analysis with respect to other variables showed no clear ASAs in either group. As a result, Hypothesis 3 has been supported in data from the pressing task, whereas the prehension task produced ambiguous findings.

Synergy indices correlated between the pressing and prehension tasks, as predicted by Hypothesis 4. The pattern of these correlations was unusual such that F^N in pressing correlated with F^T in prehension, although the correlation was positive at the task VH-TF level and negative at the IF level. We are encouraged particularly by the correlations between synergy indices in the pressing task with performance indices in both the prehension task (movement time) and the functional "glass-with-water" test (normalized movement time). These correlations suggest that a simple test of a multi-finger synergy in a constrained task and associated ASAs predict changes in hand performance in object manipulation tasks. These results are in contrast to the lack of significant correlations of any of our indices with UPDRS scores.

Changes in motor synergies in PD

A number of studies on PD patients have reported impaired motor coordination in early PD, with some of the changes reflecting more general signs such as bradykinesia and tremor

(Bertram et al., 2005; Fradet et al., 2009; Brown & Almeida, 2011). One of the main goals of our line of research has been to introduce an objective, quantitative method for measuring impaired motor coordination. Based on recent data (Park et al., 2012; Park et al., 2013a; Park et al., 2014) and this work, we are confident that the analysis of motor synergies is such a method that is highly sensitive to effects of PD, even at its early stages and when the patients are on their prescribed medication.

The word *synergy* has been used in the movement science literature in at least three different ways. First, in clinical studies, particularly those of patients after stroke, synergy commonly means a stereotypical pattern of muscle activation (such as, flexor synergy and extensor synergy) interfering with the production of functional movements (Bobath, 1978; Dewald et al., 1995). Second, frequently, this term implies groups of variables, kinematic, kinetic, or electromyographic, that show parallel changes over the task execution or over changes in task parameters (d'Avella et al., 2003; Ivanenko et al., 2004; Ting & Macpherson, 2005). The organization of large sets of variables into synergies has been assumed to reduce the number of variables manipulated by the central nervous system and to alleviate the problem of motor redundancy (Bernstein, 1967). Our third definition implies that synergy represents a neural organization providing for task-specific stability of actions by multi-element systems. Stability is paramount for everyday functional movements given that the external conditions of movement execution are never the same and frequently unpredictable. Hence, having appropriate synergies stabilizing salient performance variables is a prerequisite for successful movements (reviewed in Latash, 2008b).

Studies on the structure of variance in a redundant space of elemental variables (e.g., joint angles, digit forces, etc.) over repetitions of a motor task have been used to quantify synergies. This method, based on the uncontrolled manifold (UCM) hypothesis (Scholz &

Schöner, 1999) has been able to detect changes in motor synergies with atypical development, healthy aging, fatigue, and exercise (reviewed in Latash et al., 2007; Latash, 2008b).

A number of studies have linked PD to changes in movement variability and stability. In particular, the magnitudes of the variability measures were significantly correlated with the severity of PD in reach-to-grasp movements (Albert et al., 2010; Rand et al., 2014). Our earlier studies have shown that changes in the magnitude of variability in PD are associated with significant changes in the structure of variance during a relatively artificial, constrained pressing task (Park et al., 2012; Park et al., 2013a; Park et al., 2013b). The current study for the first time extends these findings to a less constrained object manipulation task designed to simulate motion of a hand-held object (e.g., a glass with water). The new task was associated with expanding the analysis to more performance variables (normal force, tangential force, and moment of force) and also to two levels of analysis (VF-TH and IF levels) assumed based on earlier studies of the hand (reviewed in Arbib, 1985; Zatsiorsky & Latash, 2008). Most of the analyses showed multi-digit synergies stabilizing relevant performance variables that were weaker in PD compared to control subjects. This was reflected in the smaller synergy indices (ΔV) computed for the performance variables.

Another major difference between the two subject groups was seen in task phases, which required the subjects to produce a quick action associated with a quick change in some of the performance variables. During the pressing task, a drop in the synergy index stabilizing total force was seen prior to the first detectable change in the force (ASA, Olafsdottir et al., 2005). This was true for both groups, but control subjects showed significantly earlier ASAs compared to the PD group (as in Park et al., 2012). In addition, the magnitude of the drop in the synergy index was larger in the control group. A similar group difference was seen in the prehension task but only for one of the three performance variables (tangential force) analyzed at the upper level of the assumed hierarchy (the VF-TH level). Other variables showed no clearly identifiable ASAs,

possibly because the actions were not associated with fast enough changes in those variables. Note that the assumed function of ASA is to phase out synergies stabilizing a variable in preparation to its quick change (Zhou et al., 2013); ASAs may not be needed if the variable does not change quickly.

The two main findings may be viewed as reflections of two components of the impaired control of stability in PD, weaker synergies reflecting lower stability of performance variables and delayed (also reduced) adjustments in preparation to a quick action. Qualitatively similar (and, in some comparisons, correlated) findings in the pressing and prehensile tests suggest a general impairment that may be expected to lead to behavioral consequences across a range of motor tasks. Note that low postural stability is one of the cardinal features of PD and low movement stability also has been reported (Oates et al., 2013).

ASAs represent a specific example of feed-forward motor control. There have been reports on impaired feed-forward control in PD, including reduced anticipatory postural adjustments in postural tasks and during gait (Traub et al., 1980; Fernandez et al., 2013; Pieruccini-Faria et al., 2013) and reduced grip force adjustments in preparation to an action involving a quick motion of a hand-held object (Gordon et al., 1997; Muratori et al., 2008). Significantly reduced ASAs in PD may have strong implications for some of the disabling features of this disease. For example, making a step requires destabilization of posture associated with a specific pattern of motion related to the center of pressure (Crenna & Frigo, 1991). This loss of postural stability may be reflected formally in ASAs computed with respect to synergies stabilizing the center of pressure coordinate during quiet standing (Klous et al., 2011; Krishnan et al., 2011). Hence, reduced ASAs may lead to problems with step initiation reflected in episodes of freezing of gait typical of PD (Giladi et al., 1992). Note that “postural inflexibility” has been recently invoked as a possible contributor to freezing of gait (Smulders et al., 2014). *Inflexibility* in our framework implies reduced use of flexible involvement of the elements to perform the task

and may be reflected in lower amounts of variance within the corresponding uncontrolled manifold (V_{UCM}) leading to lower synergy indices. As a result, both lowered synergy indices and reduced ASAs may be viewed as potential markers for episodes of freezing in PD (*vide infra*).

Neurophysiology of synergies is all but unknown. Several studies have emphasized the importance of subcortical structures in motor synergies, in particular of the loops involving the basal ganglia and cerebellum (reviewed in Wu & Hallett, 2013) as well as of the brain stem (Hacker et al., 2012). Several recent brain-imaging studies have suggested cerebellar involvement in PD (Yu et al., 2007; Wu et al., 2011), as well as involvement of other brain structures including cortical areas (Planetta et al., 2014). In particular, weakened striatum-cerebellar connections have been documented (Wu et al., 2011), possibly related to problems with action initiation. It has been suggested that the cerebellum may play a compensatory role following primary basal ganglia dysfunction (Lewis et al., 2007; Sen et al., 2010). Consistent with this view, we found that patients with MSA-P (Park et al., 2013b) also display a significant reduction in synergy indices. Sensitivity of synergy indices to dopaminergic drugs (Park et al., 2014) supports the importance of cortico-striato-thalamo-cortical pathways in motor synergies. Our observations are compatible with the general view that PD leads to changes in the functioning of several loops involving subcortical structures, all contributing to loss of stability of motor actions.

Multi-digit synergy indices and the hand function

A number of changes in the indices of motor performance in our tasks may be viewed as potential contributors to the changed hand function. As in earlier studies (Park et al., 2012; Park et al., 2013a; Park et al., 2014), we saw decreased maximal finger forces and larger indices of unintentional force production in PD (larger enslaving, Zatsiorsky et al., 2000). Bradykinesia typical of PD (cf. Teo et al., 2013) was reflected in slower performance in both the prehension

task and the “glass-with-water” test. In addition, our subjects showed a change in their use of grip force and its adjustments during object manipulation. These changes involved higher grip force and its poor modulation (cf. Gordon et al., 1997; Gorniak et al., 2013).

Whereas the mentioned changes may be specific to the pressing task and, by themselves, not limiting performance in everyday functional tasks, changes in the synergy indices observed in both pressing and prehension tasks potentially may reflect a global impairment within the central nervous system affecting a range of hand actions and potentially affecting performance of other tasks that do not rely on the hand function.

The first study reporting impaired multi-finger synergies in PD failed to find significant correlations between the indices of synergies, such as ΔV and indices of ASAs, and UPDRS scores. A later study of a group of patients with a mixture of parkinsonian and cerebellar signs (MSA-P) found rather strong correlations between the synergy indices and UPDRS scores (Park et al., 2013b), possibly due to the much broader range of UPDRS scores in these patients. It is also possible that involvement of cerebellar circuitry contributed to the significant correlations in that study. Our current study also used patients at a relatively early stage of PD (stage I-II according to the Hoehn and Yahr scale) tested on their optimal medications. Once again, we failed to detect any significant correlations between our outcome indices (both behavioral and synergic) and UPDRS scores. This may be due in part to the narrow range of UPDRS scores and mild nature of motor disability in the study subjects, similar to our previous study (Park et al., 2012). In addition, UPDRS is a composite of several subjective evaluations of motor functions (from finger to whole body movements). Objective functional hands tests may be more relevant to our synergy indices.

Whereas there are several broadly used functional hand tests, these typically are sensitive to more serious impairment of hand function (such as the Jebsen-Taylor test) or reflect the ability to perform precision manipulations (such as the Pegboard test). We decided to introduce a test

that would have several important features. First, we wanted it to reflect hand function in a typical everyday motion. Second, we designed the test to require stability of hand performance. Third, we intended it to be natural, easy to perform, and easy to quantify. Based on these requirements, we came up with the "glass-with-water" test. Note that this test requires stabilization of the glass in a vertical orientation at all times. Indeed, the performance index in this test (normalized movement time) correlated significantly with both performance indices in the tests (e.g., MT in the prehensile task) and the synergy and ASA indices (such as ΔV_Z and $\Delta\Delta Vz$) in the pressing task. We conclude that synergy and ASA indices are linked to changes in hand functional performance. This conclusion has to be viewed as tentative, until a broader range of tasks are studied.

Changes in multi-digit synergies as a potential biomarker of subcortical disorders

As mentioned in the Introduction, changes in hand function are among the relatively early symptoms of PD (Viviani et al., 2009). Our previous studies showed significant changes in multi-finger synergy indices and ASAs during pressing tasks even in patients at stage-I PD (Park et al., 2012; Park et al., 2014). In those patients, no clinical signs of PD could be identified on one side of the body during a clinical examination. The cited studies showed, however, significant changes in multi-finger synergies in the apparently unimpaired hand suggesting that indices of motor synergies may turn out to be highly sensitive, early behavioral biomarkers of PD.

In the current study, we also tested PD patients at stage-II (bilateral involvement). Overall, our data support using synergy indices as sensitive biomarkers of PD motor disability. In fact, the indices obtained in the constrained pressing task showed the most reproducible and significant group differences and correlations with performance indices in the other two tasks,

prehensile and “glass-with-water.” The constrained nature of the pressing task contributes to less within-subject variability, which could be the cause of more reproducible findings.

An important issue is whether the synergy changes are specific to PD or can be seen in other neurological disorders. So far, there is no unambiguous answer. One of our earlier studies of patients with multi-system brain atrophy with cerebellar involvement (Park et al., 2013b) documented changes in multi-finger synergies that were qualitatively similar to those observed in PD. Along similar lines, a recent study of hand force control deficits in individuals with various subcortical disorders including PD, multiple systems atrophy, and progressive supranuclear palsy has documented many similarities across these different patient populations (Neely et al., 2013). Taken together, these studies suggest that by itself changes in finger coordination (including those reflected in synergy indices) may be a common feature of subcortical disorders. The limited available reports of synergies after stroke suggest that, despite major changes in motor performance, synergy indices may remain unchanged (Reisman & Scholz, 2003).

Searching for biomarkers of early PD has been a very active field of research. Indices based on mechanical (e.g., based on derivative of acceleration, Teulings et al., 1997; Dounskaia et al., 2009) and electromyographic variables (e.g., during writing movements – Rupasov et al., 2012; or during sleep – Chahine et al., 2014) have been explored as possible early signs of PD. We believe that our approach has certain advantages such as the strong theoretical foundation (the theory of synergies), direct links to such a vitally important feature of movement as its stability, and the demonstrated sensitivity of the outcome measures to early-stage PD and dopamine-replacement therapy (Park et al., 2014). As a result, we remain optimistic that our method can be developed into a valuable tool for early detection of PD, despite the mentioned concerns about the specificity of the method to PD.

Concluding Comments

We would like to acknowledge a number of limitations regarding the current study. We tested the patients in the on-medication state only. This was done on purpose, to focus on the differences between the indices of digit coordination and hand function that can be detected even when the patients were on their optimal medication. On the other hand, this could contribute to the lack of correlations between our outcome measures and UPDRS scores. Another limitation is using the same task order across all subjects. This was done to minimize spurious effects that could be induced by chance by different test orders in the two groups. On the other hand, this increased the chance that accumulation of fatigue could affect performance in later tests, such as the "glass-with-water" test. We would like to note, however, that all the pressing and handle-motion tests were not fatiguing, and the subjects always had plenty of rest in-between tests. The "glass-with-water" test included only one trial involving three revolutions over the four targets. This was done for practical reasons, to limit the total testing time. More reliable results could be expected with multiple trials.

5.2. Effects of deep brain stimulation on synergies in patients with Parkinson's disease

Over the last few decades, deep brain stimulation (DBS) has been shown to provide a safe therapeutic effect on PD. DBS has become important for patients in the more advanced stages of the disease, in particular those associated with drug-induced motor fluctuations and dyskinesia. Currently, two targets have been mainly used in PD patients for the implantation of stimulators; the globus pallidus internal (GPi) and subthalamic nucleus (STN). Although its exact mechanism of action is still unknown, DBS of these regions has been highly effective for the cardinal motor features of PD including tremor, rigidity, and bradykinesia as well as drug-induced complications without causing obvious impairment of voluntary movement (Marsden & Obeso, 1994; Wichmann & Delong, 2011).

One study investigated movement speed along with the amplitude and temporal features of EMG activity to determine how these parameters are changed by DBS and medication (Villancourt et al., 2004). Medication and DBS had similar effects in that both treatments increased movement speed, increased the amplitude of the first agonist burst, increased burst duration, and reduced co-contraction. When DBS and medication were combined, only temporal measures of burst duration and the number of agonist bursts were different from the medication alone condition.

In previous studies, we have applied the theory of synergies (Latash et al., 2007) and the framework of the uncontrolled manifold hypothesis (Scholz & Schöner, 1999) to explore the changes in finger coordination in patients with PD. This theory assumes that the central nervous system organizes important sets of effectors (muscles, joints, digits, etc.) to stabilize important performance variables in a task-specific way. Recent studies has shown that early-stage PD is associated with significantly reduced indices of multi-finger and multi-muscle synergies and

impaired ability to modify the synergies in preparation to a quick action (Park et al., 2012; Jo et al., 2015; Falaki et al., 2016). The latter aspect, anticipatory synergy adjustments (ASAs), represents the ability to purposefully decrease the stability of a performance variable that the person plans to change. This set of synergy indices has also shown to be sensitive to dopamine-replacement medication during multi-finger tasks; synergy index was weaker during steady-state and ASA were delayed and reduced off-drug compared to on-drug condition (Park et al., 2014).

In this study, we explored whether indices of synergies in PD are sensitive to DBS. We have recruited PD patients with positive DBS effect on their motor symptoms and quantified synergy indices both during steady-state tasks and ASAs. We expected that patients would show higher synergy indices during steady state and larger and earlier ASAs on-DBS as compared to off-DBS.

Methods

Subjects

Six male patients with PD (aged 58.2 ± 9.6 years) with implanted DBS stimulators participated in this study. DBS surgical sites were either bilateral GPi or bilateral STN and all participants had a history of positive response to DBS surgery. All patients were tested while on their prescribed anti-parkinsonian medication. The levodopa equivalent daily dose (LEDD) was estimated according to a published formula (Tomlinson et al., 2010). Unified PD Rating Scale part III-motor scores under on- and off-DBS conditions had a mean ± SE of 26.5 ± 4.7 and 37.0 ± 6.6, respectively. Descriptive data of patients are presented in more detail in Table 5-3. The study protocol was approved by the Pennsylvania State University-Hershey Medical Center Institutional Review Board. Written consent was obtained from all subjects.

Apparatus and procedures

Details on the apparatus were described previously in chapter 4. Subjects were tested twice, in the on-DBS and off-DBS conditions. Within each condition, both hands were tested in a random order for MVC, single-finger ramp tasks, and quick force pulse production tasks (see chapter 4). The order of on- and off-DBS conditions was also randomized. For off-DBS condition, the tests started 1-2 minutes after turning the DBS off.

Table 5-3. Description of the patients.

	Sex	Age, yr	Handedness	Side of symptom onset	Disease duration, yr	Medication	Total LEDD, mg
1	M	74	R	L	9.1	On	650
2	M	48	R	Both	12.1	On	767.5
3	M	55	R	L	16.3	On	200
4	M	58	R	R	8.4	On	1200
5	M	50	R	L	3.1	On	1250
6	M	64	R	R	9.1	On	292.5

	DBS surgical site	Time since surgery, yr	HY stage On-DBS	HY stage Off-DBS	UPDRS motor On-DBS	UPDRS motor Off-DBS
1	GPi	2.5	II	II	17	26
2	STN	0.3	II	II	15	16
3	STN	1.7	III	III	19	59
4	GPi	0.4	II	II	38	49
5	STN	0.6	II	II	42	44
6	-	4.0	III	III	28	28

Abbreviations: M, male; R/L, right/left; HY, Hoehn and Yahr; UPDRS, Unified Parkinson's Disease Rating Scale; Med, medication; LEDD, levodopa equivalent daily dose.

Data analysis

The force data were digitally low-pass filtered with a zero-lag, fourth-order Butterworth filter. The cutoff frequency was set to 4 Hz to filter out the tremor. Two of the patients showed tremor in their OFF-DBS condition. The data processing was done using a customized Matlab code. Indices of enslaving and synergy were quantified as described in chapter 4.

Statistics

Standard descriptive statistics and two-way ANOVAs with repeated measures were used with the factors *DBS* (on- and off-DBS conditions) and *HAND* (right and left). Variables with computational boundaries were transformed using adjusted Fisher's transformation to ensure normality prior to comparisons. The level of significance was set at $p < 0.05$.

Results

Performance indices

Subjects showed similar MVC forces under the two, on-DBS and off-DBS, conditions (Table 5-4). During the single-finger ramp tasks, non-task fingers produced substantial finger forces in all conditions. Whereas the index of enslaving was consistently larger in left hand for both on- and off-DBS conditions (Table 5-4), there was no significant difference between the hands and no significant differences between the on- and off-DBS conditions. Two-way ANOVAs *DBS*×*HAND* on MVC and enslaving revealed no significant effects.

Subjects performed the quick force pulse task with comparable accuracy during the on- and off-DBS conditions. The percentage of trials rejected was slightly larger for the off-DBS

condition (on-DBS: 29.4 ± 3.6; off-DBS: 37.0 ± 1.5) but this difference was not statistically significant. The average number of accepted trials was 18.8 ± 2.0 trials. The average time to peak force (t_{peak}) was 0.24 ± 0.01 s on average without significant differences between the hands or DBS conditions (Table 5-4).

Table 5-4. Performance characteristics and main outcome variables

		MVC (N)		Enslaving		T_{peak} (s)	
		on	off	on	off	on	off
Right hand	Mean	68.8	68.7	0.28	0.29	0.23	0.24
	SE	10.6	9.0	0.04	0.03	0.02	0.01
Left hand	Mean	65.7	66.5	0.33	0.34	0.22	0.26
	SE	9.2	8.9	0.06	0.07	0.03	0.03
		ΔV_{SS}		ΔV_{SS-t0}		t_{ASA} (s)	
		on	off	on	off	on	off
Right hand	Mean	2.45	2.26	0.47	0.16	-0.34	-0.04
	SE	0.09	0.17	0.07	0.08	0.09	0.02
Left hand	Mean	2.81	2.77	0.52	0.35	-0.16	-0.05
	SE	0.22	0.28	0.09	0.14	0.03	0.03

Means and standard errors (SE) of maximal voluntary force (MVC), enslaving index, the average time to reach force peak (t_{peak}), synergy index at steady-state (ΔV_{SS}), magnitude (ΔV_{SS-t0}) and time (t_{ASA}) of anticipatory synergy adjustments are presented. R/L, right/left hand; on/off, on-/off-DBS condition.

Synergy and ASA

During steady-state of the force production task, subjects demonstrated covariation among the elemental variables (finger modes) across repetitive trials to stabilize the total force level. This was reflected in positive synergy indices (ΔV_{SS}) in both the on-DBS and off-DBS conditions. The magnitude of ΔV_{SS} was higher in the left hand as compared to the right hand without a significant effect of DBS (slightly higher on-DBS as compared to the off-DBS

condition; Table 5-4). A two-way ANOVA *DBS*×*HAND* on ΔV_{SS} showed a significant main effect of *HAND* [$F_{[1,5]} = 7.09$, $p < 0.05$] without other effects.

The synergy index showed a drop prior to the force pulse initiation (t_0). These anticipatory synergy adjustments (ASAs) started earlier and were of a larger magnitude in the on-DBS condition than in the off-DBS condition. These findings were supported by two-way ANOVAs *DBS*×*HAND* on the magnitude and timing indices, ΔV_{SS-t0} and t_{ASA}, which showed a significant main effect of *DBS* [$F_{[1,5]} = 13.3$, $p < 0.05$ for ΔV_{SS-t0}; $F_{[1,5]} = 12.56$, $p < 0.05$ for t_{ASA}]. Additionally, ANOVA on t_{ASA} showed a significant main effect of *HAND* [$F_{[1,5]} = 6.81$, $p < 0.05$].

Discussion

This study is the first to demonstrate the effects of DBS on finger coordination in PD patients using the indices of synergy. We observed significant effects of DBS on anticipatory synergy adjustments (ASAs) prior to a force pulse that started earlier and were larger in magnitude in the on-DBS condition compared to the off-DBS condition. In contrast, no effects of DBS were seen on general indices of performance and finger interaction (MVC, enslaving, and force pulse characteristics) and on the index of a multi-finger synergy stabilizing total force during steady-state accurate force production. Taken together, the findings suggest that DBS in PD patients may have different effects on different components of motor coordination.

The most prominent changes with DBS were shown in the aspect of feed-forward control of the stability of multi-finger actions, reflected in ASAs indices. The purpose of ASAs has been assumed to gradually destabilize a salient performance variable to facilitate a quick change of that variable. Accordingly, an impairment of ASAs can lead to difficulties with quick actions and potentially to the movement initiation problems that are common in later stages of PD (Latash &

Huang, 2015). Indeed, studies have shown that DBS improves gait initiation (Liu et al., 2006) and alleviates freezing of gait in PD (Moreau et al., 2008; Moreau et al., 2009) and, although speculative, modulation of ASAs could be related causally to those changes.

It is noteworthy that the difference in synergy index during steady-state did not reach significance because it remained relatively high in both the off-DBS and on-DBS conditions. Compared to the data of healthy controls of our previous studies using the same protocol, the patients' synergy indices (ΔV_{SS}) are very similar to those of controls even in the off-DBS condition. It is possible that the combination of drugs and DBS allowed preventing the drop in the synergy index documented during steady-state force production in several earlier studies (Park et al. 2012, 2014; Jo et al. 2015). These effects are likely long lasting with no immediate changes after turning the DBS off. The continued action of the drugs could play a major role in the continued high magnitudes of the ΔV_{SS} index.

Recent studies have shown that the signs and symptoms of PD respond to DBS with different time course (Temperli et al., 2003; Herrington et al., 2016). Those signs that respond rapidly to DBS such as tremor, rigidity, and bradykinesia may be mediated by ongoing network activity, whereas signs like axial symptoms that respond after longer delay at least in part result from synaptic plasticity with gradual reshaping of synaptic activity (Agnesi et al., 2013; Wichmann & DeLong, 2016). In this context, our results suggest that DBS may act by different mechanisms on two different aspects of synergic control; an ability to modulate ASAs is mediated by rapidly reversible DBS mechanisms whereas synergies are associated with longer-term mechanisms. Further studies with different time intervals after turning DBS on and off could provide a better understanding of these.

5.3. Finger force changes in the absence of visual feedback in patients with PD

Stability of action is paramount given the unpredictable external conditions typical of natural everyday motor behavior. The idea of task-specific stability (Schöner, 1995b) implies that the central nervous system (CNS) is able to organize redundant (actually, abundant, Latash, 2012a) sets of elements taking part in all natural movements into groups (synergies, Latash et al., 2007; Latash, 2008b) that provide stability with respect to salient, task-specific variables. Analysis of inter-trial variance within the space of elemental variables has been used to provide a quantitative index of stability: Assuming that individual trials start from somewhat different internal states, variance in directions of low-stability is expected to be large whereas variance in directions of high stability is expected to be low. Within the uncontrolled manifold (UCM) hypothesis (Scholz & Schöner, 1999), the difference between the former (variance within the UCM, V_{UCM}) and the latter (variance orthogonal to the UCM, V_{ORT}) has been used as an index of synergy (ΔV) stabilizing the corresponding performance variable.

Problems with stability of posture and movement are among the most common consequences of Parkinson's disease (PD), and postural instability is one of the cardinal features of PD (Fahn et al., 2007). In a recent series of studies, we used the framework of the UCM hypothesis to quantify stability of multi-finger pressing and prehensile actions (Park et al., 2012; Park et al., 2013a; Jo et al., 2015). Across tasks and analyses, patients with early-stage PD showed significantly lower synergy indices, ΔV, stabilizing the multi-finger steady-state actions compared to controls.

Recently, a complementary mechanism of ensuring stability of action has been hypothesized based on the observations of unintentional changes in the motor output when subjects were instructed to keep the output constant (Vaillancourt & Russell, 2002; Zhou et al.,

2014; Ambike et al., 2015). In particular, when a healthy person is asked to press with a finger and maintain constant force, turning the visual feedback off leads to a slow drop in the produced force, up to 40% of the initial force level over 20 s (Slifkin et al., 2000; Vaillancourt & Russell, 2002; Shapkova et al., 2008; Ambike et al., 2015). Active force production may be viewed as a consequence of a discrepancy between the actual (AC) and referent (RC) coordinates of the finger multiplied by a gain (apparent stiffness, cf. Latash & Zatsiorsky, 1993). Within this view, the unintentional force drop reflects a slow drift of RC towards AC, which is fixed in isometric conditions. This drift reduces the difference between the AC and RC and hence moves the effector closer to the minimum of its potential energy (reached when AC = RC), which is also a state of high stability.

A recent study explored accurate total force production by the two index fingers pressing simultaneously while the shares of the total force produced by the two fingers varied across trials within a broad range (Ambike et al., 2015). Turning the visual feedback off led to two phenomena: The aforementioned drift of the total force was accompanied by a drift in the sharing pattern towards more equal force distribution between the two fingers. The time profiles of the two drifts were similar leading to a conclusion that they reflected a single neurophysiological mechanism.

In this study, we explored the unintentional force drift during accurate force production without visual feedback in patients in early-stage PD. Our main hypothesis was that PD patients could use an adaptive strategy to compensate, at least partially, for their loss of stability reflected in the reduced synergy index (Park et al., 2013a; Park et al., 2014). Hence, we expected the patients to show a stronger coupling between the AC and RC of the fingers resulting in a faster unintentional drop in the finger force when the visual feedback was turned off (cf. Vaillancourt et al., 2001). We also explored the effects of varying the initial sharing pattern of force between the two fingers based on the mentioned observations that the sharing drifts towards a preferred

pattern, close to 50:50 (Ambike et al., 2015). In that study, Ambike and colleagues suggested that a single neurophysiological process could be responsible for the observed drifts of finger forces to lower values and sharing towards a preferred pattern. Both were supposed to reflect a drift within the UCM, which also affected total force because of the coupling between the UCM and orthogonal to the UCM sub-spaces. Therefore, our second hypothesis for the present study was that the adaptive changes leading to a faster drop in forces in PD patients (as in the first specific hypothesis) would also lead to a faster drift in the sharing pattern.

Methods

Subjects

Ten patients with PD (aged 63.1 ± 4.6 years; 6 males) and 10 age-matched control subjects (CS; aged 63.3 ± 3.1 years; 7 males) were tested. The participants were selected from a larger pool of subjects of an ongoing clinical and neuroimaging correlation study in which all PD subjects were recruited from a movement disorder clinic and diagnosed by movement disorder specialists. CS were recruited from spouses and friends of the patients, as well as through flyers posted in the local community. All participants were right-handed according to their preferential hand use during writing and eating. None of the CS had any known neurological disorders or arthritis in their upper extremities.

Descriptive data for all subjects are presented in Table 5-5. For PD subjects, Unified PD Rating Scale part III – motor scores (UPDRS- III) was assessed on the day of testing by clinical specialists and it ranged between 3 and 24. The median duration of illness since diagnosis was 2.2 years (ranging from 0.1 to 8.1 years); none of the patients showed postural instability and/or signs of drug-induced dyskinesia. PD subjects were tested while on their prescribed anti-parkinsonian medication. The levodopa equivalent daily dose (LEDD) was estimated for PD subjects according

to a published formula (Tomlinson et al., 2010). The study protocol followed the Helsinki principles and was reviewed and approved by the Pennsylvania State University-Hershey Medical Center Institutional Review Board. Written informed consent was obtained from all subjects.

Table 5-5. Description of study participants

	Sex M/F	Age yr	Handed-ness R/L	Symptom Onset	Years Since Diagnosis	HY Stage	UPDRS motor score	Med On/Off	Total LEDD mg
PD group									
1	M	49	R	R	4.9	II	10	On	300
2	F	72	R	R	4.1	II	11	On	400
3	F	47	R	Both	0.9	II	12	On	160
4	M	76	R	Both	1.0	II	24	On	350
5	F	48	R	L	1.7	I	10	On	380
6	F	79	R	L	2.0	I	16	On	250
7	M	43	R	R	0.1	I	12	Off	0
8	M	67	R	L	8.1	I	3	On	737.5
9	M	79	R	R	2.3	II	8	On	500
10	M	71	R	R	3.2	II	21	On	400
CS group									
1	F	59	R						
2	M	47	R						
3	F	77	R						
4	M	56	R						
5	F	54	R						
6	M	69	R						
7	M	64	R						
8	M	77	R						
9	M	70	R						
10	M	60	R						

Abbreviations: M/F, male/female; R/L, right/left; HY, Hoehn and Yahr stage defined in the "on-drug" stage; UPDRS, Unified Parkinson's Disease Rating Scale; Med, medication; LEDD, levodopa equivalent daily dose.

Apparatus and procedure

Subjects were seated comfortably in a chair with their forearms resting on top of a table and facing a 19-in. computer monitor positioned at eye level. They performed a set of tasks with two fingers pressing on individual force sensors (1) right and left index fingers (*BOTH* condition); (2) right index and middle fingers (*RIGHT* condition); and (3) left index and middle fingers (*LEFT* condition). Two piezoelectric force sensors (model 208A03; PCB Piezotronics, Depew, NY) were used to measure the vertical forces produced by the fingers. Each sensor was covered with sandpaper (100-grit) to increase the friction between the fingertips and the top surface of the sensors. Prior to each trial, all sensor signals were set to zero when subjects placed their fingertips on the sensor centers and relaxed their hands. As a result, the sensors measured only active downward forces. A customized LabVIEW program was used for the data acquisition at 100 Hz with 16-bit resolution and for subject feedback.

For the *BOTH* condition, subjects' shoulders were flexed at approximately 30°, abducted at approximately 30° and internally rotated approximately 45° with the elbows flexed approximately at 90° (Figure 5-8A). The mid-point between the two sensors was aligned with the midline of the body, and the distance between the midpoints of the two sensors was 3 cm. For the *RIGHT* and *LEFT* conditions, the configuration of the corresponding upper limb was similar to that in the *BOTH* condition. The position of the sensor for the middle finger was adjusted in the anterior-posterior direction according to each subject's individual hand and finger anatomy in order to achieve a comfortable hand posture.

Within each of the three conditions described above, subjects performed a maximum voluntary contraction (MVC) task and the main, accurate force production task. In the MVC task, subjects were instructed to press on the sensors as hard as possible using both task fingers simultaneously to achieve maximal total force level within 8 s. They were instructed to relax

immediately after reaching maximal force. Feedback presented to the subjects showed the sum of the forces from both fingers. Each subject performed two consecutive attempts and the trial with the higher MVC was selected to set the main task.

Figure 5-8B shows the visual feedback screen provided to the subject during the main task. As the subject pressed on the two sensors, real time feedback on finger force appeared on the screen as a black line. The total force was depicted as the length of the line. One end of the line was always in the center of the X-axis and the angle of the line with the X-axis reflected the force-sharing ratio of the two fingers. For example, the line would be vertical when the finger forces were equal (the sharing ratio was 1:1); it tilted towards the left or right side of the screen when the corresponding finger force share was larger. The task was to reach a red target with the far end of the force line, which could be accomplished by applying the prescribed amount of total force with the prescribed force sharing between the two fingers. The subjects had 10 s to reach the target point. Time was represented on the screen with a blue bar, with the 10-s point clearly marked. The force line showing the subject's force level and sharing ratio disappeared after 10 s. The subjects were instructed to "continue producing the same finger forces" for an additional 20 s without visual feedback. Thus, each trial duration was 30 s.

There were six target points (all six points are shown in Figure 5-8B) and only one was shown on the screen for each trial. The six target points were combinations of two total force levels (15% and 25% MVC) and three sharing ratios between the left and right task fingers (1:3, 1:1, and 3:1). The sharing ratio corresponds to the fraction of total force produced by the left-most task finger: left index finger in the *BOTH* condition, the middle finger in the *LEFT* condition, and the index finger in the *RIGHT* condition. The visual locations of the targets on the screen were the same for all subjects and all conditions, although the actual amount of force needed to reach each target was scaled to the subject's MVC. Subjects performed two consecutive trials for each target. Each subject performed 36 trials (3 hand conditions × 2 force

levels × 3 sharing ratios × 2 repetitions) in total. The three hand conditions (*BOTH*, *RIGHT*, and *LEFT*) were randomized. The order of six targets for each hand condition also was randomized. Subjects had 1-2 practice trials before each condition. The interval between trials was about 10-15 s and there were 5-min breaks between conditions. Subjects were offered rest at any time if they felt fatigued during testing. The entire experiment lasted ~1 h.

Two subjects in each group performed additional pilot trials for the *RIGHT* hand condition to explore possible memory effects. Subjects were instructed to reach the 25% MVC target with the 1:1 sharing ratio for the first 10 s with visual feedback. To test memory effects (Vaillancourt & Russell, 2002), subjects were asked to relax for the following 10 s and then to reproduce the initial target level of force for the last 10 s without visual feedback. Each subject performed five consecutive trials with 10 s intervals between trials.

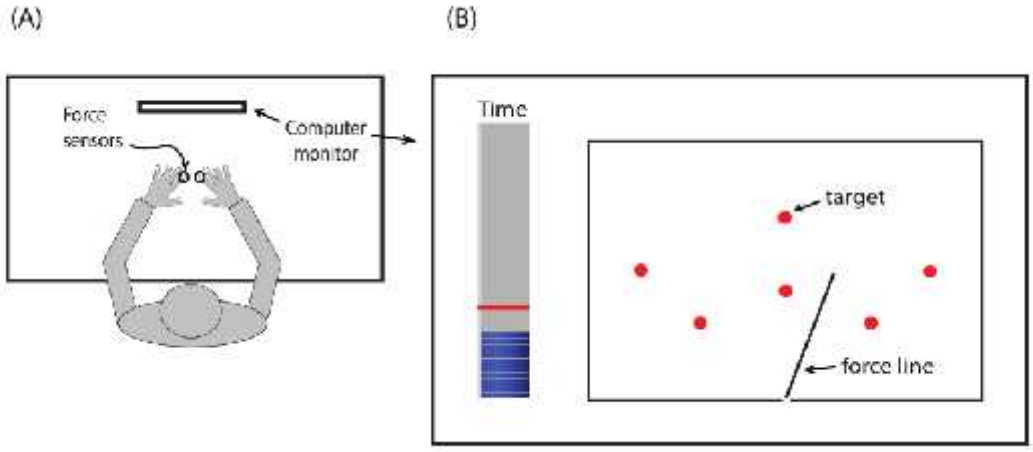

Figure 5-8. (A) Experimental setup (for *BOTH* hands condition). (B) Visual feedback provided to the subject. Only one of the red targets was shown on the screen for each trial. The six target points are combinations of two force levels (15% and 25% MVC) and three sharing ratios of the left and right fingers (1:3, 1:1, and 3:1). The blue bar represents time, and takes 30 s to reach the top. The red line indicates the 10-s point, when the visual feedback (force line) disappears.

Data analysis

Force data were digitally low-pass filtered with a zero-lag, fourth-order Butterworth filter at 5 Hz. Data processing was performed using a customized MATLAB code. Two repetitions for each target were averaged for further analysis. The task variables, normalized total force (F_T) and force sharing (F_S), were computed from the finger forces for each hand condition as follows:

BOTH condition:	$F_T = (F_{RI} + F_{LI}) / \mathrm{MVC}_{BOTH} \times 100$	$F_S = F_{LI} / (F_{RI} + F_{LI})$
RIGHT condition:	$F_T = (F_{RI} + F_{RM}) / \mathrm{MVC}_{RIGHT} \times 100$	$F_S = F_{RI} / (F_{RI} + F_{RM})$
LEFT condition:	$F_T = (F_{LI} + F_{LM}) / \mathrm{MVC}_{LEFT} \times 100$	$F_S = F_{LM} / (F_{LI} + F_{LM})$

The subscripts of the force variables (F) refer to the following: *RI*, right index finger; *RM*, right middle finger; *LI*, left index finger; *LM*, left middle finger. Total force was normalized using the corresponding MVC value for comparisons across subjects. The variables for the left fingers were selected as the numerator in F_S computations in each hand condition for consistency.

The change in total force (ΔF_T) was calculated for the 20 s period without visual feedback. The first and last 0.5-s intervals were averaged and used as initial ($F_{T,\mathrm{initial}}$) and final ($F_{T,\mathrm{final}}$) values to compute ΔF_T.

$$\Delta F_T = F_{T,\mathrm{initial}} - F_{T,\mathrm{final}}$$

The magnitude of the force change was re-calculated separately for two time intervals to compare the rate of force change. The changes in force during the first 10-s interval ($\Delta F_{0\text{-}10}$) and during the second 10-s interval ($\Delta F_{10\text{-}20}$) were quantified. The first and last 0.5-s intervals were used for computing averages as in the computation of ΔF_T.

The change in force sharing (ΔF_S) was calculated for the 20-s period without visual feedback. The first and last 0.5-s intervals were averaged and used as initial ($F_{S\,\text{initial}}$) and final ($F_{S\,\text{final}}$) values. For F_S starting at 0.75 (3:1 *Sharing* condition), ΔF_S was defined as

$$\Delta F_{S\_0.75} = F_{S,\text{initial}} - F_{S,\text{final}}$$

and for F_S starting at 0.25 (1:3 *Sharing* condition), ΔF_S was defined as

$$\Delta F_{S\_0.25} = F_{S,\text{final}} - F_{S,\text{initial.}}$$

This method of computation was based on the general observation that the sharing tended to drift towards 50% across all conditions. Thus, the method yields positive values for initial conditions, 3:1 and 1:3. Data averaged across subjects also were fit with exponential functions for each group and each condition separately.

Statistics

Standard descriptive statistics were used and the data are presented as means and standard errors (SE). Mixed-design ANOVAs with repeated measures were used to explore how outcome variables (ΔF_T, $\Delta F_{0\text{-}10}$, $\Delta F_{10\text{-}20}$ and ΔF_S) were affected by factors *Group* (PD and CS), *Hand* (*BOTH*, *RIGHT* and *LEFT*), *Force* (15% and 25% MVC), *Sharing* (1:3, 1:1, and 3:1 for ΔF_T comparisons; 1:3 and 3:1 for ΔF_S comparison) and *Time* (0-10 s and 10-20 s). The data were checked for violations of sphericity and Greenhouse-Geisser criterion was used to adjust the degrees-of-freedom when necessary. Pair-wise comparisons were performed with Bonferroni corrections to explore significant effects of ANOVAs. Pearson correlation coefficients were used to determine significant relationships between variables. All statistical tests were performed with SPSS 19.0 (SPSS Inc, Chicago, IL, USA).

Results

Magnitude of drop in the total force

The two groups did not differ significantly in the maximal voluntary contraction (MVC) force; on average, the MVC force was 55.8±16.8 N for the PD group and 55.0±14.2 N for the control group. During the accurate force production trials, after the visual feedback disappeared, all subjects showed a drop in total force across all finger conditions and sharing ratios. This force drop was consistently larger in the PD group. Since this was true across the three sharing patterns, we illustrate the result with the time profiles of normalized total force (F_T) averaged across the sharing conditions and subjects (Figure 5-9). Note that PD subjects (dashed lines) showed a faster drop in F_T compared to CS (solid lines).

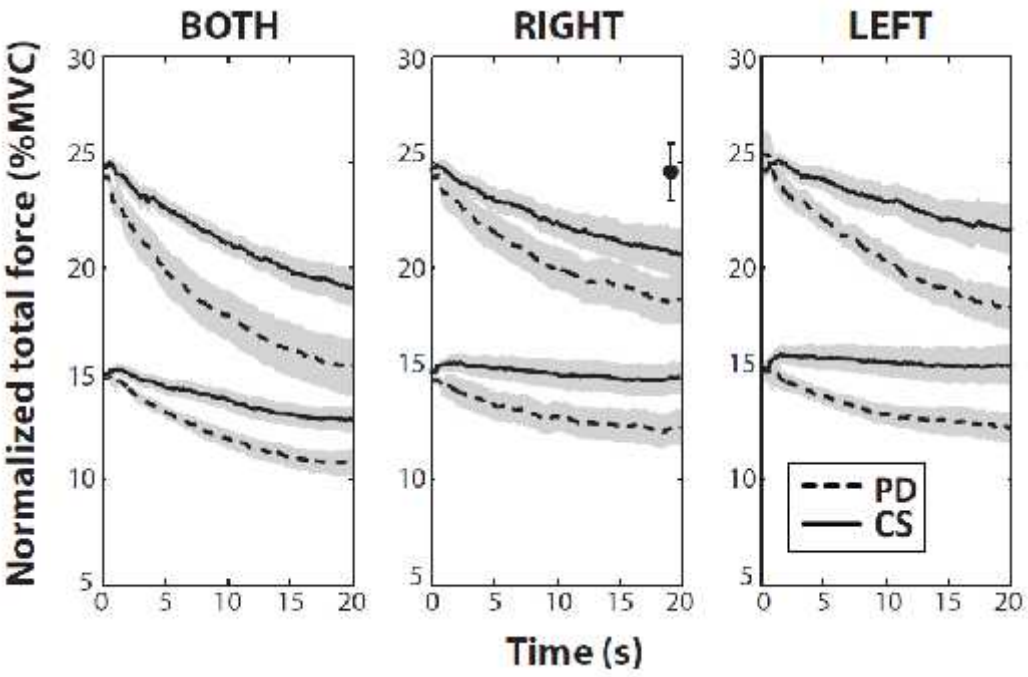

Figure 5-9. The across-subject means of the total force (F_T) trajectory are presented with SE shades. The traces are for the 20 s without visual feedback. Three sharing ratios (1:3, 1:1, and 3:1) are averaged within subjects at each force level to show the overall trend of change in force. For the memory pilot trials, the average value of total force across four subjects is shown with SE bars in the middle panel.

The curves shown in Figure 5-9 suggest an exponential force drop with time for the 25%MVC task and also for the 15%MVC task performed by the PD group (less so for the CS). The exponential function regression, $F(t) = a \times \exp(t/b) + c$, where a, b, and c are constants, accounted for over 99% of the total variance for the 25%MVC task in both groups and all three conditions. For the 15%MVC task, the regressions accounted for over 98% of the variance for the PD group, whereas the fit was poor for the CS group in the RIGHT and LEFT conditions. Across all regression analyses, there was a relatively small group difference between the a parameters (6.2 vs. 6.6 for PD and CS) and between the c parameters (13.7 vs. 16.0 for PD and CS), whereas the difference between the b parameters was more than two-fold (9.9 vs. 21.6 for PD and CS). This difference suggests a much faster drop in force in the PD group, which was explored quantitatively using another method (see below).

We tried running similar analyses on individual trials but, in some cases, very small force changes resulted in unrealistically large exponential time constants. The resulting distributions of the outcome variables were very far from normal, and this prevented us from using across-subjects ANOVA.

The magnitude of force drop (ΔF_T) is shown in Figure 5-10. In the *BOTH* condition, ΔF_T was significantly larger in the PD group. This was confirmed by a three-way ANOVA on ΔF_T with factors *Group*, *Force*, and *Sharing*. There was a significant effect of *Group* [$F_{[1,18]} = 6.55$, $p < 0.05$]. There also were significant effects of *Force* [$F_{[1,18]} = 70.71$, $p < 0.001$] and *Sharing* [$F_{[2,17]} = 8.02$, $p < 0.05$] with no interaction effects. The effect of *Force* reflected the larger magnitudes of ΔF_T for the higher initial force level (25%MVC). Post-hoc analysis for *Sharing* revealed that 1:3, 3:1 > 1:1.

Although ΔF_T showed a similar pattern in the *RIGHT* and *LEFT* conditions to that in the *BOTH* condition, the effect of *Group* on ΔF_T was significant in the *LEFT* condition [$F_{[1,18]} = 4.74$, $p < 0.05$] but did not reach significance in the *RIGHT* condition [$F_{[1,18]} = 2.35$, $p = 0.14$]. The

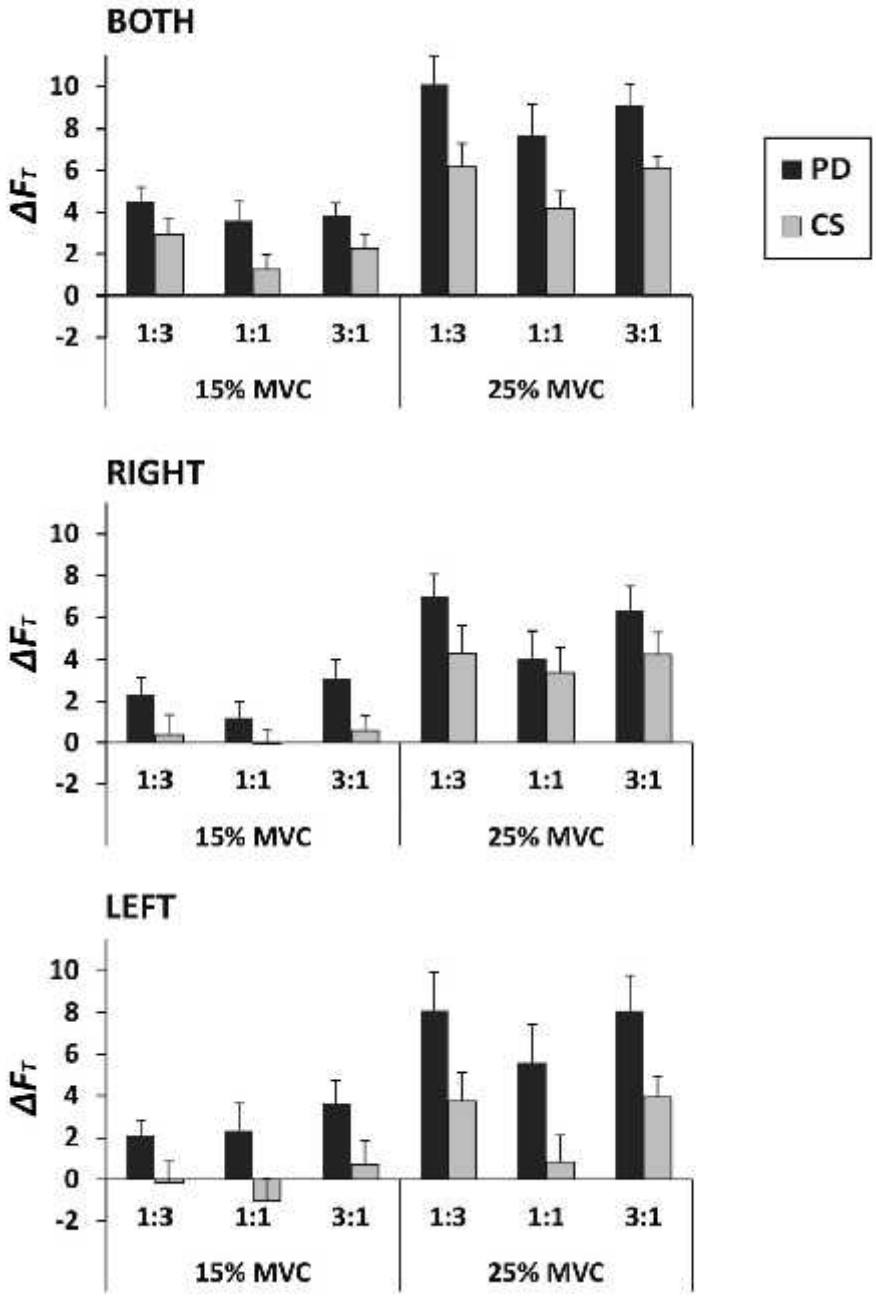

Figure 5-10. The change in total force (ΔF_T) was calculated at the end of the 20-s time interval without visual feedback. The across-subject means for each group, force level, and sharing pattern are presented with SE bars. Note the consistently larger ΔF_T for the PD group.

effects of *Force* [$F_{[1,18]} > 52.0$, $p < 0.001$] and *Sharing* [$F_{[2,17]} > 6.45$, $p < 0.05$] were significant in the LEFT and RIGHT conditions, reflecting the same differences as those described earlier for the *BOTH* condition. For the *LEFT* condition, there also was a significant *Force* × *Sharing* interaction [$F_{[2,17]} = 5.23$, $p < 0.05$] indicating the lack of a difference between the 1:3 and 1:1 sharing conditions at the low force level that was present at the high force level.

To explore the effect of *Hand* in ΔF_T, we averaged 12 trials (2 Force levels × 3 Sharing ratios × 2 repetitions) within each *Hand* condition for each subject. Two-way ANOVA showed significant effects of *Group* [$F_{[1,18]} = 6.19$, $p < 0.05$] and *Hand* [$F_{[2,17]} = 11.49$, $p < 0.05$] with no interactions. Post-hoc analysis for *Hand* revealed that *BOTH* > *RIGHT*, *LEFT*.

Pilot trials for the memory effect showed no trend for a drop in total force. The average value of the four subjects (24.58 ± 1.35 %MVC) is shown in Figure 5-9 as a large dot with standard error bars in the bottom middle panel.

Rate of force drop

To explore the rate of drop in total force, $\Delta F_{0\text{-}10}$ and $\Delta F_{10\text{-}20}$ were compared (Figure 5-11). Overall, the PD group showed a faster rate of force drop reflected in the larger differences between $\Delta F_{0\text{-}10}$ and $\Delta F_{10\text{-}20}$ compared to the CS group. For the *BOTH* condition, two-way ANOVA showed significant effects of *Group* [$F_{[1,18]} = 6.16$, $p < 0.05$], *Time* [$F_{[1,18]} = 23.69$, $p < 0.001$] and an interaction of *Group* × *Time* [$F_{[1,18]} = 5.81$, $p < 0.05$]. For the *RIGHT* condition, only *Time* [$F_{[1,18]} = 11.07$, $p < 0.05$] showed a significant effect (for *Group*, $p = 0.149$; for *Group* × *Time*, p=0.098). For the *LEFT* condition, the factors *Group* [$F_{[1,18]} = 4.94$, $p < 0.05$] and *Time* [$F_{[1,18]} = 5.04$, $p < 0.05$] were significant. There also was an interaction of *Group* × *Time* [$F_{[1,18]} = 5.65$, $p < 0.05$]. The significant interactions for the *BOTH* and *LEFT* conditions reflected the larger differences between $\Delta F_{0\text{-}10}$ and $\Delta F_{10\text{-}20}$, i.e., the faster drop of F_T, in the PD group.

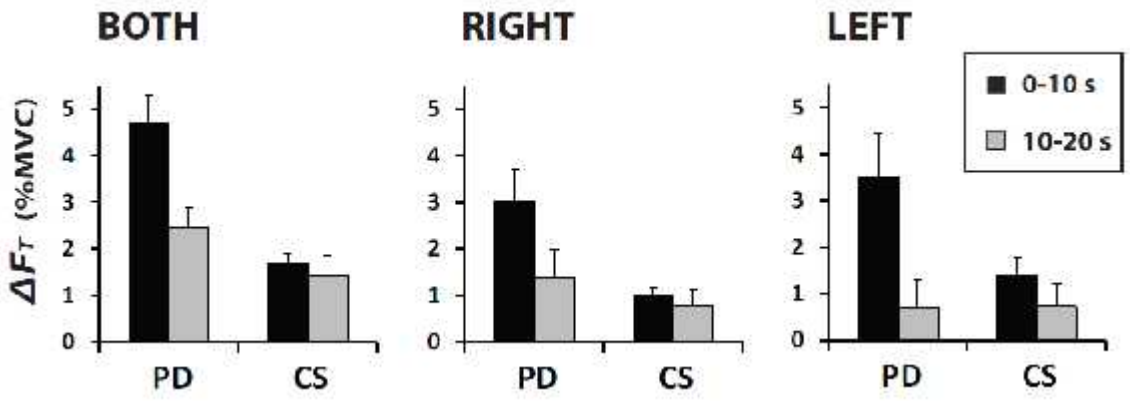

Figure 5-11. The across-subject means of the change in total force (ΔF_T) for the two time intervals (0-10 s and 10-20 s) are presented with SE bars. The data represent averages across the three sharing ratios (1:3, 1:1, and 3:1) and two force levels (15% and 25% MVC).

Changes in individual finger forces for the first 10-s and the second 10-s intervals were consistent with the total force changes. Three-way ANOVA (*Group* × *Time* × *Finger*) for each hand condition showed similar statistical effects as the above two-way ANOVA (*Group* × *Time*). The effect of *Finger* was significant only in the *BOTH* condition [$F_{[1,18]} = 16.83$, $p < 0.05$], reflecting $\Delta F_{LI} > \Delta F_{RI}$, with no other effects.

There were no significant correlations between the UPDRS motor score and any of ΔF values. Also no correlations were seen between ΔF values and LEDD as well as between ΔF values and disease duration (see the data in Table 5-5).

Force sharing

There was a clear trend of the two finger shares towards more equal values over the 20-s time interval when the subjects produced force without visual feedback. This trend was present across conditions in both groups, with ΔF_S values significantly larger than zero ($p < 0.001$). A three-way ANOVA (*Hand* × *Force* × *Sharing*), however, showed no significant effects in either

group. Hence, the data for the three *Hand* conditions and two *Force* levels were averaged within a subject to compare $\Delta F_{S\_0.25}$ and $\Delta F_{S\_0.75}$ between the two groups (Figure 5-12). A two-way ANOVA (*Group* × *Sharing*) revealed no significant effects. On average, $\Delta F_{S\_0.75}$ was 0.102 ± 0.016 and $\Delta F_{S\_0.25}$ was 0.086 ± 0.016 (p = 0.217) over the 20-s without visual feedback.

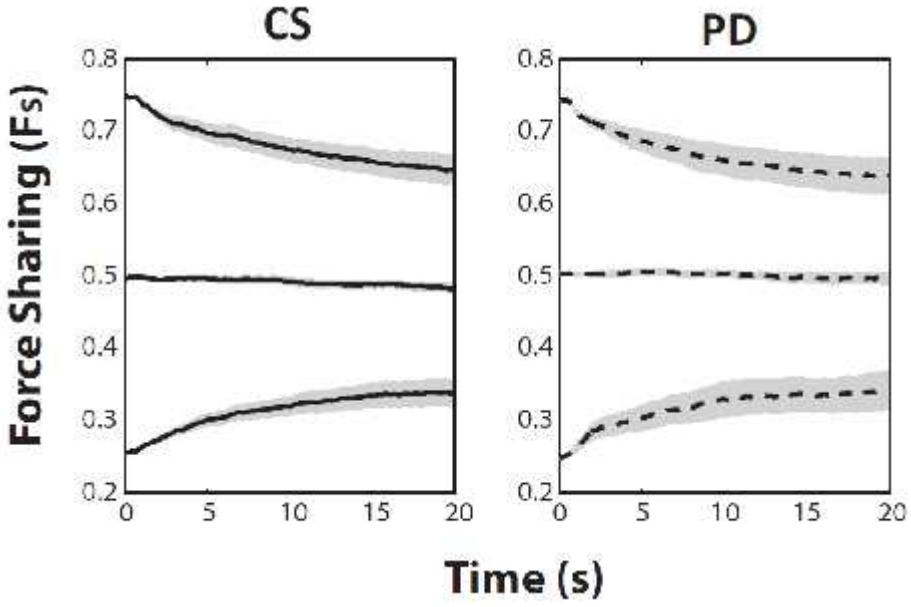

Figure 5-12. The across-subject means of the force sharing (F_S) are presented with SE shades for the control (left, CS) and PD (right) groups. The traces are shown for the 20-s time interval without visual feedback. Three *Hand* conditions and two *Force* levels were averaged within a subject. Three lines within each group for each graph represent the three sharing ratios (3:1, 1:1 and 1:3).

Discussion

The results provided support for our main hypothesis formulated in the Introduction. Indeed, while both subject groups showed an unintentional drop in the finger force after the visual feedback had been turned off, the PD patients showed a significantly faster force drop (as in Vaillancourt et al., 2001). This was a robust result that was true across different finger combinations, involving fingers of one hand at a time or of both hands, and for both initial force

magnitudes. Further, we offer and develop an interpretation of the observed unintentional finger force drop based on the idea that isometric force production is associated with setting a referent coordinate (RC) for the effector (cf. the referent configuration hypothesis, Feldman, 2009). Within this interpretation, a faster force drop is associated with a faster RC drift that moves the system to a minimum of its potential energy. The faster RC drift in PD may be viewed as an adaptive strategy to compensate, at least partially, for the loss of stability documented for multi-finger force production and prehensile tasks in PD (Park et al., 2013a; Park et al., 2014; Jo et al., 2015).

The second hypothesis has been falsified. We expected the group differences in the total force drift (faster force drop for PD subjects) to be reflected in similar differences in the sharing pattern drift (faster drift towards 50:50) based on the interpretation that the drifts in total force and in sharing represent two peripheral outcomes of a single neurophysiological mechanism (Ambike et al., 2015). As in the previous study (Ambike et al., 2015), both groups showed a drift in the force sharing towards 50:50 in trials that had started with a significantly different sharing pattern. Contrary to our expectation, however, there were no group differences in the sharing drift speed. This result suggests that independent neurophysiological processes may be responsible for changes in total force and changes in sharing.

Stability of steady-state actions by abundant systems

Stability is a crucial feature of functional movements in the everyday environment with its unpredictable and variable forces. One of the central features of natural movements is their task-specific stability (Schöner, 1995). This term means that the same abundant set of elements (joints, digits, muscles, etc.) can be organized by the CNS to ensure stability of different performance variables depending on the task and intention of the actor.

An unexpected observation has been made in experiments with similar transient perturbations involving a time interval between the perturbation application and removal (dwell time): An increase in the dwell time led to larger violations of equifinality with respect to the performance variable (Zhou et al., 2015a). These unintentional changes in the performance variable were observed despite the explicit instruction to the subjects "not to react to the perturbations." These observations have been interpreted as the consequence of a drift in the RC for the performance variable towards the actual coordinate (AC) for this variable. Note that the difference between AC and RC for a variable results in active force production directed towards moving the variable closer to RC due to the length-dependence of muscle forces, both peripheral and reflex-based (Feldman, 1986; Feldman & Levin, 1995). In other words, all effectors at all times exist in elastic force fields produced by all of the participating muscles. For a given effector, a minimum of potential energy in such a field is reached when AC = RC. Hence, a drift in RC towards AC may be viewed as a natural behavior of the system moving towards a minimum of potential energy, which also is a state of high stability.

Thus, we conclude that two factors define stability of a motor system. The first is typical of abundant systems and reflects the task-specific neural organization stabilizing salient performance variables. A number of mechanisms have been suggested for this mechanism, from back-coupling loops within the CNS (Latash et al., 2005) and from peripheral receptors (Martin et al., 2009) to optimal feedback control schemes (Todorov & Jordan, 2002). The second factor acts in both single-element and multi-element systems. Its neurophysiological origin is unknown, although its physical origin seems to be straightforward: It reflects the natural tendency of any physical system to move to a minimum of its potential energy reflected in the motion of RC to AC.

Potential origins and causes of unintentional force changes

The hypothesis that RC may drift naturally towards AC also can be used to account for other phenomena. In particular, it has been known for years that turning visual feedback off during an isometric force production task leads to an unintentional drop in the force (Slifkin et al., 2000; Vaillancourt & Russell, 2002). This drop may be rather large, up to 40% of the initial force level, without the subject being aware that the performance has changed.

In the original papers (Slifkin et al., 2000; Vaillancourt & Russell, 2002), a hypothesis was offered that the unintentional force drop had been due to the limited capacity of working memory. Our observations of the faster force drift in the PD group seem to provide indirect support for this hypothesis. Indeed, PD is known to be associated with working memory dysfunction (Sagar et al., 1988; Sullivan & Sagar, 1991; Lee et al., 2010). We believe, however, that these results may have a different origin.

The working memory hypothesis has obvious limitations. In particular, forgetting the initial force level may be expected to lead to a force drift in both directions, up and down, whereas typically the force drops consistently. An increase in the force has been documented only for very low initial force levels (Ambike et al., 2015), interpreted as a reflection of adaptation of pressure-sensitive receptors in the fingertips. This observed increase also was consistent across trials and subjects, something not expected from working memory problems that are more likely to lead to high inter-trial variance and not a consistent force drift. In our experiment, only a few subjects performed the pilot trials designed to check whether memory played a significant role in force drift. In those trials, subjects were asked to stop producing force for a time interval sufficient to observe a force drop and then to reproduce the memorized force. If memory was involved, a comparable drift of the force level would be expected. This did not happen, however: The mixed group of subjects, two CS and two patients with PD, showed no visible force drift,

suggesting that their memory on the initial force level did not drift to lower levels (see Figure 5-9).

The hypothesis that the unintentional force drop reflects a drift of the corresponding RC towards the unchanging AC (fingertip coordinates that stay the same throughout the trial) offers a different explanation for the finding of the faster force drift in PD. This explanation is based on two important concepts: First, the loss of stability of multi-element action in PD, and second, the idea of neural adaptations to primary motor impairments leading to non-trivial behavioral consequences.

Recently, the concept of '*slacking*' has been suggested (Reinkensmeyer et al., 2009; Secoli et al., 2011) as the property of the human motor system to decrease levels of muscle activation when movement error is small. In particular, slacking was observed during practicing movements with robotic assistance after neurologic injury: Subjects sometimes reduced their effort in response to external assistance. Slacking and RC-back-coupling seem to be related; perhaps slacking is a manifestation of RC-back-coupling in the robot-assisted-rehabilitation setting.

Effects of Parkinson's disease on stability of action

Loss of postural stability commonly is mentioned as one of the cardinal features of PD (Fahn et al., 2007). It is not observed, however, in PD patients with Hoehn-Yahr stage II. A series of recent studies have documented that such patients demonstrate a significant drop in synergy indices during multi-finger accurate force production and prehensile tasks (Park et al., 2012; Park et al., 2014; Jo et al., 2015). Moreover, patients with Hoehn-Yahr stage I that have clinical signs limited to only one half of the body, showed comparable synergy indices to those in PD patients with bilateral involvement. Given that synergy indices reflect stability of the performance

variable (reviewed in Latash et al., 2007), these studies have demonstrated that stability loss of multi-finger action may be one of the earliest, even pre-clinical, signs of PD motor dysfunction.

In addition to low synergy indices during steady-state tasks, PD patients also show delayed and reduced adjustments in those synergies in preparation to a quick action (Park et al., 2012; Jo et al., 2015). Such adjustments (anticipatory synergy adjustments, ASAs, Olafsdottir et al., 2005; Shim et al., 2005) are functionally important as they destabilize the salient variable in preparation to a quick action. Without ASAs, the action would have to fight the pre-existing synergies. Taken together, PD subjects demonstrate impaired control of action stability that is seen early in the disease and involves two components: Low synergy indices and small ASAs.

Adaptive motor strategies to impaired stability of action

Neural adaptations to a variety of neurological disorders have been documented. Such adaptations commonly lead to motor patterns that look different from those seen in unimpaired persons. For example, persons with atypical development, healthy older persons, and persons with neurological disorders commonly show patterns of muscle activation characterized by increased co-contraction of agonist-antagonist muscle pairs (Woollacott & Shumway-Cook, 1990; Aruin & Almeida, 1997; Carpenter et al., 2004). These differences, however, still may be compatible with optimal motor function given the actual state of the body (Latash & Anson, 1996; 2006).

Loss of stability of movement patterns is one of the least explored aspects of motor disorders (although see a review by Stergiou & Decker, 2011) even though it is expected to render actions associated with many everyday tasks unstable and, therefore, useless. The current study may be viewed as the first one providing evidence for an adaptive reaction to loss of action stability. Indeed, the documented impaired stability of action in PD is expected to make many

hand actions within the everyday repertoire subjected to major disturbances from the natural variability in external forces and internal body states.

It is natural to expect the CNS of PD patients to search for alternative and/or complementary strategies to ensure action stability. One such strategy would be to facilitate motion of the involved motor system towards its most stable state, which is achieved when AC = RC. This can be done by an increase in the gain in hypothetical neural loops involved in the naturally occurring drift of motor systems to their respective RCs. Our observations of the accelerated force drop in PD corroborate this hypothesis.

More than one drift process during multi-finger force production

In an earlier study, two drifts were documented during two-finger accurate force production tasks without visual feedback (Ambike et al., 2015). First, in tasks with moderate force levels (between 7% and 30% MVC), the total force drifted to lower values. Second, the sharing pattern drifted towards a more equal force distribution between the fingers (close to 50:50) in trials that had started with significantly different proportions of the total force produced by the two fingers. Both drifts were fit with exponential functions with similar time constants, close to 15 s. The similarity of the time constants suggested a common source for these changes. This expectation also follows the fact that changes in the sharing are unambiguously related to changes in the finger forces (See Section 7.1.3). Indeed, the finger that started a trial with a higher force level was expected to show a larger force drop as compared with a finger that started the trial with a lower initial force level. This could lead to an effect on the sharing pattern drawing the two force magnitudes closer to each other.

In our current experiment, however, this interpretation failed to receive support. The significantly faster total force drift in the PD group (Figure 5-9) was not accompanied by a faster

sharing pattern drift (Figure 5-11). In fact, no differences between the two groups in the sharing pattern drift were seen. These observations cast doubt on the hypothesis that a common neurophysiological mechanism generates the two drifts and suggest that the drift in the sharing pattern was a reflection of another mechanism, apparently unchanged in PD. At this time, we cannot offer a physiological mechanism that could bring about the sharing pattern drift, but such a mechanism is likely immune to PD-associated changes in the dopaminergic projections in the basal ganglia and to possible secondary (adaptive) changes.

Concluding comments

We would like to emphasize two potentially important findings. The first is the accelerated decline of the total force in PD, which is likely not related to problems with working memory. We offer an interpretation of this phenomenon based on the idea of RC-back-coupling and hypothetical adjustments within the central nervous system of PD patients possibly adaptive to the documented loss of action stability in PD. The second is the significant group differences in the force drift while no such differences were seen in the sharing drift. These results suggest that the two drifts, while similar in their timing characteristics for healthy individuals, are likely to reflect different physiological mechanisms. It is important to state that the findings were consistent across force levels and finger combinations.

As any study, ours is not without weaknesses. The first is the inclusion of only early-stage PD patients. Indeed, if the hypothesis on an adaptive origin of the accelerated force drift in PD is correct, one can expect stronger effects in PD patients at later stages of the disease that allow more time for development of adaptive reactions. Such a study is in our plans. The second is the pilot nature of the working memory tests. Partly, this was done to reduce the testing time for the participants. We offered this test only to a few participants who were not time constrained

and willing to prolong the testing session. These results have to be confirmed in a larger cohort that would allow proper statistical analysis of the data.

5.4. Synergy as a new and sensitive marker of basal ganglia dysfunction: A study of asymptomatic welders

Since all natural human movements are performed in a poorly predictable environment and involve varying internal states, movement stability is crucial for successful everyday motor performance. For example, holding a cup of water steady requires stability of the integrated contribution of the many involved joints and muscles, all of which may vary their state. It is important to note that stability is not always desirable. If a person wants to change a variable quickly from a steady state, high stability would resist this intentional change. We address the ability to modify steady states in preparation to a quick action as agility. Loss of stability of motor performance may cause spills, falls (balance problems), dropped objects, illegible writing, stuttering, etc, whereas loss of the agility may cause difficulty in motor initiation (such as freezing of gait). These examples are extreme and obvious; but loss of movement stability also may be subtle and not observable with the naked eye.

Until recently, no method could quantify movement stability of motor function across the repertoire of everyday actions that involve multi-digit object manipulation, multi-joint reaching, and whole-body actions [although important advances have been made in the field of non-linear time series analysis, see (Stergiou et al., 2004)]. Based on two theoretical constructs, the principle of abundance (Gelfand & Latash, 1998; Latash, 2012) and the uncontrolled manifold hypothesis (Scholz & Schoner, 1999), we have developed an index of motor synergies ensuring action stability. We define synergies as task-specific organizations of redundant (abundant, Latash, 2012) sets of elements. If a person performs several task trials, trajectories in the space of elemental variables (those produced by the effectors, e.g., individual finger forces) are expected to diverge in less stable directions and converge in more stable directions. As a result, stabilizing a particular salient performance variable (e.g., total force) leads to relatively high variance of elemental

variables (e.g., individual finger forces) within the sub-space where the performance variable does not change (its uncontrolled manifold, UCM; Scholz & Schoner, 1999) compared to variance orthogonal to the UCM direction, ORT. Variance along the UCM (VUCM) has no effect on the performance variable, as it reflects flexible use of varying solutions to ensure the same performance with varying effector contributions. Variance along the ORT (VORT) reflects accuracy of performance. The normalized difference between VUCM and VORT has been defined as a synergy index (ΔV; reviewed in Latash et al., 2002; 2007). Prior to a quick change in the corresponding performance variable, a drop in an index of stability was observed in young, healthy persons 200-300 ms prior to the initiation of a quick action from steady state (Olafsdottir et al. 2005). We defined this phenomenon as anticipatory synergy adjustments (ASAs), which reflect the ability to modify steady state called agility in experimental studies.

Recently, we demonstrated that perturbation of the basal ganglia in Parkinson's and parkinsonism patients leads to a significant decrease in synergy indices and ASAs (Park et al., 2012; Park et al., 2013b; Jo et al., 2015), suggesting impairments both in creating task-specific stability of salient variables (cf. Schöner, 1995a) and adjusting it in anticipation of a quick action. Most importantly, we found synergy changes in early-stage Parkinson's patients, even in the asymptomatic limb. Together, these data suggested that multi-digit synergies might capture subclinical basal ganglia dysfunction. Testing this hypothesis is important because many neurodegenerative disorders have a long pre-clinical period (Sandberg et al., 2001; Mandel & Korczyn, 2011; Eisen et al., 2014) and developing tests that sensitively detect preclinical signs may also help develop neuroprotective methods.

Asymptomatic welders with relatively low exposure levels may serve as a human model of subclinical basal ganglia dysfunction based on the following knowledge: 1) High-exposure welding causes a clinical syndrome similar to Parkinson's disease (manganese-induced parkinsonism or manganism) such as slowness of movements, tremor, and balance problems.

Their symptoms, however, are probably related to excessive exposure to manganese (Mn) (Huang et al., 1993; Hauser et al., 1996; Mergler & Baldwin, 1997; Pal et al., 1999; Guilarte, 2013). 3) Many studies have documented subclinical symptoms that do not meet criteria for occupational manganism (Bowler et al., 2006a; Bowler et al., 2006b; Bowler et al., 2007a; Bowler et al., 2007c; Ellingsen et al., 2008; Chang et al., 2009; Cowan et al., 2009a; Cowan et al., 2009b; Simon-Sanchez et al., 2009). Although manganism can be differentiated from PD by the lack of L-dopa response (Ostiguy et al., 2006), they share the common feature of basal ganglia dysfunction. In Parkinson's, the basal ganglia dysfunction arises from dopaminergic cell loss in the substantia nigra, whereas in manganism it may be related to Mn accumulation in the basal ganglia, especially in the globus pallidus (Kim et al., 1999, Dorman et al., 2006, Criswell et al., 2012, Lee et al., 2015). Thus, asymptomatic welders with relatively low exposure levels may represent a transitional group that allows us to determine if synergy metrics can serve as a sensitive measurement for preclinical basal ganglia dysfunction.

In this study, we tested the following two hypotheses: 1) multi-digit synergy and ASA indices in welders are reduced compared to controls; 2) reduced synergy metrics in welders are associated with exposure measurements (welding-related metal accumulation and/or microstructural changes) in the BG.

Methods

Subjects

Twenty welders and 13 matched controls were selected from a larger cohort of subjects in an exposure and neuroimaging study. The original cohort was recruited from regional union meetings in central PA, USA, and from the community around the Penn State Hershey Medical Center (PHMC; Lee et al., 2015). Welders were defined as subjects who had welded at any point in their lifetime and controls as those who did not have any history of welding. Subjects selected

for this study were all male, right-handed according to their preferred hand during writing and eating, and answered negatively for past diagnosis of neurological disorders. As part of the screening visit, detailed demographic information was obtained from all subjects. All welders underwent an orbital radiograph to rule out any metal fragments around the eye prior to brain MRI. Written informed consent was obtained from all subjects in accordance with the Declaration of Helsinki and approved by the PHMC Internal Review Board/Human Subjects Protection Office.

All subjects were examined and ascertained to be free of any obvious neurological and movement deficits using the Unified Parkinson's Disease Rating Scale-motor scores (UPDRS-III) with a threshold score of <15 indicating lack of parkinsonian motor symptoms as defined by a previous welder study (Lee et al., 2015). Subjects also completed sections I (a non-motor-related functional questionnaire) and II (a motor-related functional questionnaire) of the UPDRS. None of the control subjects had any arthritis in their upper extremities. Descriptive data for all subjects are presented in Table 5-6.

Experimental design

All subjects were assigned a study identification number (study ID) upon enrollment. This study ID then was used during data analysis so that analyses could be carried out in a blinded fashion. Subjects were not randomly assigned to a group, as group assignment was dictated by previous welding history.

Exposure assessment

Exposure first was assessed by the work history (WH) questionnaire that collected job information over the individual's working lifetime, emphasizing welding and other jobs

Table 5-6. Demographic, exposure, and MRI metrics for welders and controls.

	Controls (N=13)	Welders (N=20)	p-values
Age (years)	41.9 ± 10.8	47.1 ± 12.9	0.239
Education (years)	16.3 ± 2.0	13.3 ± 2.2	< 0.001
ALT[1] (IU/L)	37.1 ± 16.7	45.1 ± 19.9	0.24
BMI (kg/m^2)	25.1 ± 3.2	29.4 ± 5.9	0.02
HrsW (hours)	0 ± 0 (0)	162 ± 140	< 0.001
YrsW (years)	0 ± 0 (0)	24.7 ± 12.3	< 0.001
MRI metrics			
PI	108.9±1.3	109.2±1.8	0.436
R1			
Caudate	0.670±0.058	0.676±0.091	0.854
Putamen	0.712±0.064	0.701±0.046	0.552
Globus pallidus	0.889±0.081	0.867±0.039	0.161
R2*			
Caudate	21.5±1.9	23.6±3.0	0.080
Putamen	25.9±2.7	27.2±3.7	0.472
Globus pallidus	34.5±5.4	37.8±5.2	0.826
FA			
Caudate	0.166±0.014	0.176±0.018	0.220
Putamen	0.211±0.029	0.237±0.030	0.280
Globus pallidus	0.349±0.034	0.358±0.027	0.649
MD			
Caudate	7.80×10^{-4}	7.66×10^{-4}	0.110
Putamen	7.35×10^{-4}	7.45×10^{-4}	0.618
Globus pallidus	7.73×10^{-4}	7.58×10^{-4}	0.282

All data represent the mean±SD, unless otherwise indicated. Data were analyzed using ANCOVA except for gender and handedness, which were analyzed using Fisher's Exact test. Abbreviations: ALT, alanine aminotransferase; BMI, body mass index; FA, fractional anisotropy; HrsW, hours welding in the 90 days prior to study visit; MD, mean diffusivity; PI, pallidal index; YrsW, total years welding.

associated with welding exposure. Responses on the WH enabled an estimate of cumulative lifetime years welding (YrsW). An additional supplementary exposure questionnaire (SEQ; Lee et al., 2015) focused on the 90-day period prior to the MRI and determined the time spent welding, type of metal welded, and various types of welding performed. The exposure metrics derived from the SEQ were: hours welding, brazing, or soldering [HrsW = (weeks worked) * (h/week) * (fraction of time worked related directly to welding)] in the 90-day period preceding the MRI (Lee et al., 2015).

Apparatus and procedures

- Pressing tasks

Multi-digit pressing setup and procedures used in this study were described in more detail in chapter 4. Briefly, the experiment comprised three tasks: 1) MVC tasks, 2) single-finger ramp tasks, and 3) quick force pulse production tasks. The subjects performed all three tasks in the above order with both hand. The entire experiment lasted ~1 h.

- Grooved Pegboard Test

The *Grooved Pegboard Test* (Lafayette Instrument Company, Lafayette, Indiana) is a conventional neurobehavioral assessment to measure fine motor dexterity and used widely in patient populations (reviewed in Causby et al., 2014). This test contains 25 holes with randomly positioned slots and pegs that have a key along one side. Subjects were asked to rotate the pegs to match the hole before it could be inserted. Subjects were instructed to place all pegs into the 25 holes, picking up one at a time, and using just one hand. They completed the test first using their dominant and then their non-dominant hand. Total completion time was measured using a stopwatch. Average scores for the dominant or non-dominant hands in each group were

calculated. The scores then were transformed to z-scores based on age- and education-adjusted norm scores (Ruff & Parker, 1993).

- MRI data acquisition

All images were acquired using a Siemens 3 T scanner (Magnetom Trio, Siemens Medical Solutions, Erlangen, Germany) with an 8-channel head coil. High-resolution T1-weighted (T1W) and T2-weighted (T2W) images were acquired for anatomical segmentation. T1W images were collected using an MPRAGE sequence with Repetition Time (TR)=1540 ms, Echo Time (TE)=2.3 ms, FoV=256×256 mm, matrix=256×256 mm, slice thickness=1 mm, slice number=176 (with no gap), and voxel spacing 1x1x1 mm. T2W images were acquired using a fast-spin-echo sequence with TR/TE=2500/316, and the same spatial resolution as the T1W images.

For whole brain fast T1 mapping, images were acquired using a spoiled gradient recalled echo (SPGR) with two flip angles and transmit field (B1) correction. Image acquisition parameters for the T1 mapping were as follows: TR=15 ms, TE=1.45 ms, flip angles=4/25, FoV=250×250 mm, matrix=160×60, slice thickness=1 mm, slice number=192 50% overlap, and voxel spacing=1.56×1.56 x 1 mm; and for the B1 field mapping: TR=1000 ms, TE=14 ms, flip angles=45/60/90/120/135, FoV=250×250 mm, matrix=32×32, slice thickness=5 mm, and slice number=22.

For R2*, five echoes with TE ranging from 8-40 ms and an interval of 8 ms were acquired with TR=51 ms, flip angle=15°, FoV=230 mm×230 mm, matrix=256×256, slice thickness=1.6 mm, and slice number=88. For R1, parameters were TR=15 ms, TE=1.45 ms, flip angles=4/25, FoV=250×250 mm, matrix=160×160, slice thickness=1 mm, slice number=192, and voxel spacing=1.56×1.56×1 mm.

For DTI, TR/TE=8300/82 ms, b value=1000 s/mm^2, diffusion gradient directions=42 and 7 b=0 scans, FOV=256×256 mm, matrix=128×128, slice thickness=2 mm (with no gap), and slice number=65 were used.

Data Analysis

- Finger force data analysis for index of enslaving and synergies are explained in chapter 4.
- Defining brain regions of interest

Bilateral basal ganglia structures (putamen, caudate, and globus pallidus) were defined for each subject using automatic segmentation software (AutoSeg; Joshi et al., 2004; Gouttard et al., 2007) as regions of interests (ROIs) and then eroded by 1 voxel using a morphological operation in order to ensure the segmented ROIs were within the anatomical ROIs based on the T1W image. The quality of the segmentation then was confirmed visually for all subjects by a reviewer blinded to group assignment. Bilateral ROIs were analyzed separately (please see Statistical analysis section below).

- Estimations of brain MRI measurements

R1 values: R1 values in each ROI were calculated as 1/T1 in each voxel and averaged over the entire ROI as previously described (Lee et al., 2015).

Pallidal index*:* The PI was derived from the ratio of globus pallidus T1W intensity to frontal white matter intensity [PI = (globus pallidus/FWM) x 100] (Krieger et al., 1995) as previously described (Lee et al., 2015).

***R2*values*:** R2* values in each ROI were calculated as 1/T2* in each voxel and averaged over the entire ROI as previously described (Lee et al., 2016).

DTI values: Two DTI values [fractional anisotropy (FA) and mean diffusivity (MD)] were calculated out of three diffusivity eigenvalues (λ1, λ2, λ3; Le Bihan et al., 2001). FA is a

weighted average of pairwise differences of the three eigenvalues and may represent the degree of diffusion anisotropy.

$$FA = \sqrt{\frac{1}{2}}\frac{\sqrt{(\lambda_1-\lambda_2)^2+(\lambda_2-\lambda_3)^2+(\lambda_3-\lambda_1)^2}}{\sqrt{(\lambda_1^2+\lambda_2^2+\lambda_3^2)}}$$

MD is an average of the three eigenvalues and provides information regarding the magnitude of the diffusion. (Le Bihan et al., 2001; Du et al., 2014).

Statistical analysis

Group comparisons were conducted using one-way ANOVAs. For motor tasks of synergy data [*MVC, EN,* and outcome variables of the quick force pulse production task (t_{Ftot}, $\Delta V_{SS,}$ $\Delta\Delta V_{Z,}$ and t_{ASA})] and Grooved Pegboard, analysis of covariance (ANCOVA) was used with adjustments for age and education level. For MRI DTI (FA and MD), R1, R2*, and PI data, ANCOVA was used with adjustments for age, body mass index (BMI), and respirator use.

Spearman partial correlation analyses were conducted between motor tasks which showed significant group difference and welding-related exposure measurements (exposure metrics and MRI markers) after adjusting for age for welders. The imaging data for one welder was excluded due to poor quality, resulting in 19 welders included in the imaging and correlation analyses.

Since there were several subtests for the synergy task and multiple basal ganglia regions for the MRI markers to be compared, the group comparisons of motor tasks (synergy data), MRI markers, and the correlation analyses were corrected for multiple comparisons using the Stepdown Bonferroni method (Holm, 1979) to control the familywise error rate (*FWER*) at p=0.05. All statistical tests were two-tailed.

Results

Demographic

There were no group differences in age or ALT (Table 5-6). Control subjects had significantly more years of education than welders ($p<0.001$). The BMI was significantly higher in welders compared to controls ($p=0.020$).

- Exposure metrics: HrsW ($p<0.001$) and YrsW ($p<0.001$) measures were significantly higher in welders compared to controls (Table 5-6).
- MRI markers: There were no group differences in any welding-related MRI markers in any ROI either using the combined or separate measures for each hemisphere after adjustment for age, BMI, and respirator use (ps>0.079; Table 5-6). Please note that the study is powered to detect group difference for synergy indices, not MRI markers.

Motor tasks

- UPDRS and Grooved Pegboard scores

As seen in Table 5-7, there were no significant differences in the UPDRS total score or the motor (sections II and III) and non-motor (section I) sub-scores. Welders, on average, performed slower than controls on the Grooved Pegboard task using their left or right hands, but the differences did not reach statistical significance (ps>0.128; Table 5-7).

- Maximal voluntary contraction (MVC) and enslaving (EN)

Maximal force values (*MVC*) produced by welders were similar to those produced by controls (ps>0.05, Table 2). Both groups showed substantial force production by the non-task fingers during single-finger ramp force production tasks. The enslaving index (*EN*) in both groups was similar in each hand (Table 5-7). Time to peak force (t_{Ftot}) also did not differ between the groups (ps> 0.91).

Table 5-7. Performance characteristics for motor measurements

	Controls	Welders	P values
UPDRS subscores			
I	3.8 ± 3.3	4.5 ± 3.4	0.549
II	0.62 ± 1.4	0.80 ± 1.3	0.703
III	1.6 ± 2.8	2.7 ± 2.9	0.461
Total	6.0± 5.2	8.0± 4.8	0.278
Grooved Pegboard Tests			
Right hand	-0.127±0.871	0.458±1.300	0.135
Left hand	-0.189±1.036	0.312±1.270	0.183
Finger test measures			
Maximal voluntary contraction (N)			
Right hand	89.5 ± 31.9	86.2 ± 26.7	0.796
Left hand	90.0 ± 29.2	82.2 ± 27.2	0.698
Enslaving indices			
Right hand	0.690±0.217	0.673±0.222	0.658
Left hand	0.831±0.402	0.700±0.293	0.175
Time to peak force (s)			
Right hand	0.146±0.023	0.146±0.038	0.909
Left hand	0.141±0.024	0.143±0.035	0.940
Synergy measures			
Overall steady-state synergy index, ΔV_{SS}			
Right hand	2.257±0.253	2.040±0.425	0.160
Left hand	2.615±0.392	2.213±0.275	**0.004***
Time of anticipatory synergy adjustment (s)			
Right hand	-0.176±0.140	-0.162±0.118	0.692
Left hand	-0.152±0.093	-0.187±0.131	0.292
Synergy index change during ASA, $\Delta\Delta V_Z$			
Right hand	-0.475±0.345	-0.407±0.221	0.870
Left hand	-0.524±0.336	-0.390±0.237	0.231

Data represent the means ± the standard deviation (SD). For the Grooved Pegboard data are presented as the mean±SD and represent the z-transformed time needed to complete the task. Data were analyzed using analysis of covariance (ANCOVA) with adjustment for age and education level. *Represents associations that survived adjustment for multiple comparisons. All the ΔV indices were log-transformed. Abbreviations: UPDRS, Unified Parkinson's Disease Rating Scale.

- Multi-finger synergies and ASA measures

All subjects showed much higher inter-trial variance of commands to fingers (force modes) compatible with an unchanged value of total force (V_{UCM}) compared to the variance that

changed total force (V_{ORT}). This was reflected in consistently positive synergy indices quantified over the steady-state accurate force production, ΔV_{SS} (Table 5-7). Welders had a significantly lower steady-state synergy index (ΔV_{SS}) of the left hand compared to controls (p=0.004, Table 5-7), which remained significant after correction for multiple comparisons, whereas the difference did not reach statistical significance in the right hand (p=0.160). Thus, we focused on synergy indices on the left hand for the correlation analyses in the next section.

Prior to the force pulse initiation, both groups showed a consistent drop in ΔV, which started on average ~170 ms prior to the first detectable change in total force. Figure 5-13 illustrates a typical performance by one of the welder subjects. Note the drop in the synergy index ΔV_Z (black line) prior to the time of force pulse initiation (t_0). The initiation time of the ΔV drop (t_{ASA}) and the change in the synergy index during ASA ($\Delta\Delta V_Z$) were not significantly different between the two groups in either hand (ps>0.231; Table 5-7).

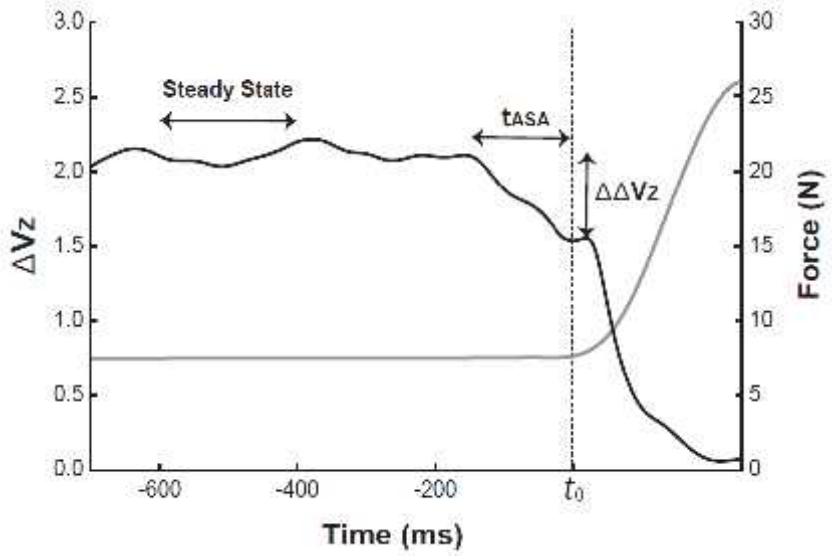

Figure 5-13. Total force (gray line) and index of synergy (ΔVZ, black line) during the force pulse production task by a representative welder subject. Note the drop in ΔVZ starting prior to the force pulse initiation (t0). The figure also shows the time (tASA) and magnitude (ΔΔVZ) of the anticipatory synergy adjustment.

Synergy associations with exposure and imaging measures

Since the left steady-state synergy index (ΔV_{SSL}) was the only synergy metric significantly different between welders and controls, this metric was used in the exposure and imaging correlation analyses.

- Exposure measurements

The synergy index of the left hand (ΔV_{SSL}) correlated negatively with HrsW (r=-0.477, p=0.039) and YrsW at a trend level (r=-0.448, p=0.055) in welders. The significant relationship between ΔV_{SSL} and HrsW, however, did not survive correction for multiple comparisons.

- R1, R2*, and PI measurements

There were no significant associations between the left synergy index (ΔV_{SSL}) and any of the MRI measurements for Mn (R1 or PI) or iron (R2*) accumulation (Table 5-8) in welders.

Table 5-8. Imaging and synergy (ΔVSS-L) correlations among welders.

	Brain regions of interests					
MRI modality	**CN_L**	**CN_R**	**PUT_L**	**PUT_R**	**GP_L**	**GP_R**
R1	0.244 (0.314)	0.149 (0.541)	0.126 (0.607)	-0.092 (0.708)	0.204 (0.402)	0.045 (0.856)
PI	n.a.	n.a	n.a.	n.a.	-0.252 (0.429)	-0.251 (0.432)
R2*	0.173 (0.507)	0.024 (0.927)	0.223 (0.389)	-0.006 (0.981)	0.134 (0.606)	-0.150 (0.566)
FA	0.451 (0.061)	***0.486 (0.041)***	0.096 (0.706)	0.292 (0.239)	***0.731* (<0.001)***	0.346 (0.160)
MD	-0.534 (0.831)	-0.279 (0.263)	0.130 (0.608)	-0.233 (0.352)	-0.376 (0.124)	-0.498 (0.068)

Data represent the Spearman correlation coefficient and the associated p value (in parentheses). Regions of interest are listed individually (left or right). Significant correlations are indicated in bold italics, whereas trend associations are in italics. *Represents associations that survived adjustment for multiple comparisons. Abbreviations: CN, caudate nucleus; FA, fractional anisotropy; GP, globus pallidus; MD, mean diffusivity; PI, pallidal index; PUT, putamen; ROI, region of interest.

- FA and MD measurements

The synergy index of the left hand (ΔV_{SSL}) was correlated positively with FA values in the left globus pallidus in welders (r=0.731, p=0.0006, Table 5-8 and Figure 5-14), which remained significant after correction for multiple comparisons. The relationship was lacking in controls (see Figure 5-14). ΔV_{SSL} also was correlated positively with FA values in the right caudate (r=0.486, p=0.041), but the association did not survive correction for multiple comparisons. ΔV_{SSL} was not correlated with MD in any ROI (ps>0.068).

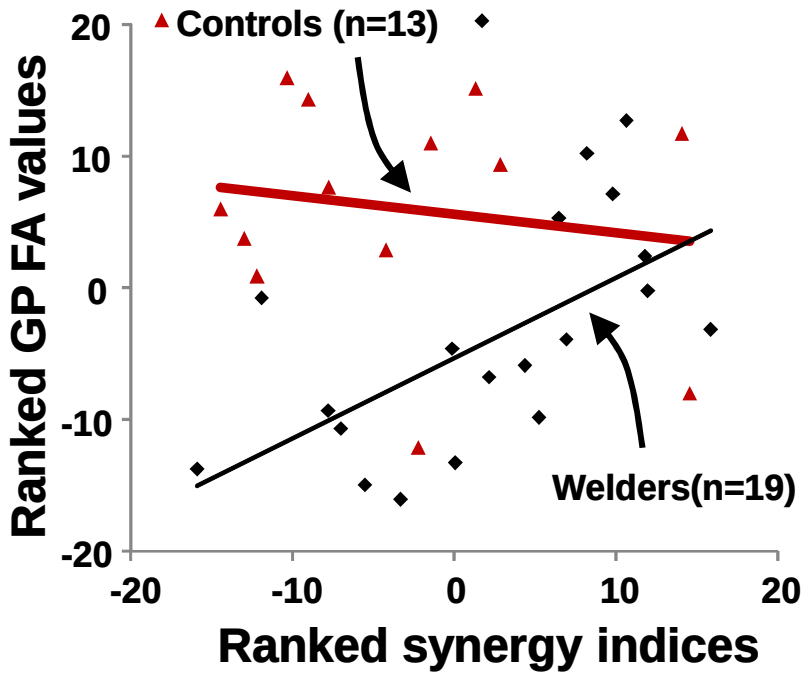

Figure 5-14. Synergy-GP FA correlations in welders and controls. Welders (black line) demonstrated a strong and significant correlation between the synergy index and GP FA values, whereas controls (red line) showed no significant relationship between the two measures. GP FA values and synergy indices were ranked due to non-normal distributions.

Discussion

This is the first study to examine whether multi-digit synergies may capture subclinical basal ganglia dysfunction in asymptomatic welders. The results confirmed the hypotheses formulated in the Introduction: 1) welders had a decreased synergy index compared to control subjects, particularly for the left hand; and 2) the synergy index was correlated with welding-related imaging metrics reflecting microstructural changes in the basal ganglia of welders. The results, however, do not support that synergy measurements correlated with measures of Mn or Fe metal accumulation per se. Together, these data suggest that multi-digit synergy metrics may serve as preclinical markers for basal ganglia dysfunction in welders and, potentially, other populations at risk for basal ganglia dysfunction. The findings may have important clinical, scientific, and public/occupational health implications as we discuss below.

Synergy studies as a tool to measure impaired motor stability in welders

A series of studies have shown that impaired control of action stability happens with healthy aging (Shinohara et al., 2004; Olafsdottir et al., 2007a; Olafsdottir et al., 2007b). Those studies tested healthy elderly subjects (70–85 years of age) and documented a reduction in the synergy index in multi-digit pressing and prehensile tasks. Two studies have shown that exercise may lead to a significant improvement in the synergy index in older adults (Olafsdottir et al., 2008b; Wu & Hallett, 2013). Recently, our group has demonstrated synergy changes in patients with basal ganglia dysfunction (Parkinson's and parkinsonism; Park et al., 2013b; Jo et al., 2015).

This study is the first to investigate multi-finger synergies in asymptomatic welders who are often associated with Mn-induced Parkinsonism. The finding of a decreased synergy index, a metric for movement stability, in asymptomatic welders is consistent with the involvement of the

basal ganglia, which is vulnerable to welding-related damage due to higher metal accumulation (Kim et al., 1999; Dorman et al., 2006; Criswell et al., 2012; Lee et al., 2015; Lee et al., 2016). In addition, this finding also is consistent with previous literature that welders have issues with balance and tasks requiring maintaining stability (Mergler et al., 1994; Bouchard et al., 2007; Bowler et al., 2007b; Zoni et al., 2007; Ellingsen et al., 2008).

Welders generally hold a torch or electrode and repeat a very precise motion with their dominant (e.g., right) hand, while using their non-dominant (left) hand to guide and stabilize the object. Several recent studies have shown that multi-digit synergies are stronger in the non-dominant hand during steady-state tasks (Park et al., 2012; Jo et al., 2015). This observation fits well with the dynamic dominance hypothesis (Sainburg, 2002; Sainburg, 2014), which suggests that the non-dominant hand has an advantage during positional tasks. We observed significant group differences in the left hand synergy index during steady-state accurate force production, whereas the differences were non-significant in the dominant right hand. This is an intriguing result. Asymptomatic active welders are able to remain in their regular welding job that requires tremendous accuracy and agility (Ellingsen et al., 2008; Baker et al., 2015). In fact, welders may have superior motor function, especially in their dominant hand, compared to other manual workers not exposed to welding fumes, and be able to mask subtle welding-induced changes in motor functions when the exposure level is relatively low ("skilled-worker" phenomena). This may have contributed to the lack of significant motor deficits in the dominant hand. Nevertheless, we did observe a trend in the right hand and increasing the sample size might reveal this difference. It would be interesting in future studies to obtain synergy metrics for tasks not involving hands, such as postural tasks, that may help test effector-specific vs. systemic effects on motor stability.

Synergy as a sensitive a marker of basal ganglia dysfunction

As a new concept (Latash & Huang, 2015), the syndrome of impaired control of stability has not been mentioned in clinics or human health-related research. Currently, the main test of basal ganglia dysfunction in a clinical setting is the UPDRS Scale. The scale is subjective, offers little insight into motor coordination, and is not useful in asymptomatic populations with subclinical basal ganglia dysfunction. The Grooved Pegboard test also has been used for gauging fine motor dysfunction (reviewed in Ruff & Parker, 1993; Causby et al., 2014). This test may be useful and sensitive to detect definite declines in fine motor skills for patient populations (Lee et al., 2013) but may not be sensitive to detect subtle motor function changes in subclinical populations (Ellingsen et al., 2008). Consistent with this notion, the pegboard test in the current study failed to detect significant differences between the groups, whereas the multi-finger synergy index succeeded in detecting these differences.

Several recent studies from our group have shown that impaired motor synergies during multi-finger action may be one of the earliest detectable motor dysfunctions in Parkinson's, even in the apparently unaffected (subclinical) side (Park et al., 2012; Park et al., 2013a; Park et al., 2014). Welders tested in the current study had no parkinsonian signs. In addition, their fine motor skills were comparable with those of controls and they showed no difference from controls in the ability to perform quick force pulses. The fact that we captured reduced synergy indices in this group of welders is consistent with the hypothesis that synergy changes may provide the earliest behavioral markers for basal ganglia dysfunction.

The synergy index was more specific to subcortical dysfunction and relatively preserved in cortical dysfunction (Reisman & Scholz, 2003; Reisman & Scholz, 2006; Jo et al., 2016), whereas ASA changes have been observed in both Parkinson's and cortical stroke patients (Jo et al., 2016). It is interesting to note that our welders showed reduced synergy indices during steady-state tasks, whereas the ASAs were unchanged. This result suggests that synergy index changes

during steady-state tasks may be specific to subclinical changes in the basal ganglia while ASA changes may emerge later in progressive disorders when more diffuse neural networks are involved. It would be very interesting in future studies to see if ASA change occurs in clinical, symptomatic welders (manganism) and can be used to gauge the extent and severity of the associated neurodegenerative process.

Biological relevance of synergy-brain microstructural associations in understanding Mn-related neurotoxicity

Overt Mn neurotoxicity is known to have similarities to Parkinson's disease (Cersosimo & Koller, 2006; Bowler et al., 2007a). The neurotoxic effects of chronic and lower-level Mn exposure, at the level most relevant to occupational and public health, however, are less clear. Past studies of "asymptomatic" welders support an association between exposure to Mn-containing welding fumes and subclinical neural deficits (Ellingsen et al., 2008; Chang et al., 2009), but the conclusion was marred by the lack of an objective in vivo marker(s) to sensitively reflect Mn at the brain tissue level, the absence of accounting for co-exposed metal (i.e., iron) accumulation in brain tissue, and little investigation of their structural and functional consequences. In the current study, we leveraged the most recent advances in MRI to reflect basal ganglia metal (Mn and iron) accumulation and microstructural changes to address this gap.

The synergy index was not correlated with the metrics for Mn accumulation (R1 and the PI). This is not surprising because although these metrics (R1 and PI) may reflect sensitively current or ongoing brain Mn exposure, it may not capture long-term lingering effects of Mn on brain tissues or function, particularly when the levels of exposure are low (Han et al., 2008; Baker et al., 2015; Lee et al., 2016).

The finding of a strong and significant association between the synergy index and globus pallidus FA values, the region known to have highest susceptibility for Mn accumulation, is very encouraging and suggests that the decline in motor stability is not only measurable, but also related to Mn-induced microstructural changes in the globus pallidus (Lee et al, 2016). Indeed, in a previous study we found reduction in GP FA in asymptomatic welders which whosed a robust association between globus pallidus FA values and the PI (a traditional measure for Mn accumulation in the globus pallidus) but not with R2* values (Lee et al., 2016). In contrast to MRI metrics for Mn accumulation which may be more sensitive to short-term dynamics of Mn-exposure, Mn-induced microstructural changes probably are related more to long-term, cumulative neurotoxic effects resulting from multiple transient exposures. In line with this notion, we recently discovered that globus pallidus FA changes, not Mn brain accumulation (particularly R1), are correlated with long-term Mn exposure metrics (Lee, under review).

Hemispheric control of motor function

Although motor function primarily is controlled by the contralateral hemisphere, previous work demonstrated significant and important ipsilateral hemisphere involvement in unimanual hand tasks (Davare et al., 2007), particularly when the task is complex (Singh et al., 1998; Haaland et al., 2004a) or requires increased force (Hess et al., 1986; Muellbacher et al., 2000). Ipsilateral control of motor function is most evident in the left (dominant) hemisphere, as right-handed subjects more strongly activate the left motor cortex during left-handed tasks than the right motor cortex during right-handed tasks (Kim et al., 1993; Kobayashi et al., 2003). Virtual lesion studies confirm these imaging findings (Chen et al., 1997). Patients with stroke often have contralateral hemiparesis (Bourbonnais & Vanden Noven, 1989; Levin, 1996) but motor deficits ipsilateral to the lesion also are observed (Haaland & Harrington, 1996; Sunderland, 2000). Our

finding of the strong relationship between left hand synergies and FA values in the left globus pallidus support important ipsilateral control in motor tasks. In addition, the association may reflect left (dominant) hemisphere specialization on multi-finger synergies to ensure stability of motor performance. Further studies are warranted to confirm these findings and elucidate the underlying mechanisms.

Limitations and Summary

Although the results reported are intriguing and robust, the sample size is relatively small. The findings need to be replicated in a larger cohort, preferably with a longitudinal component, to determine whether these changes persist or evolve, and tasks not involving hands need to be tested to sort out effector vs. systemic effects. Nevertheless, our data suggested that the multi-digit synergy index can capture early and subclinical motor changes in asymptomatic welders and may serve as a preclinical marker for basal ganglia dysfunction in welders and other populations at risk for basal ganglia dysfunction.

Chapter 6 Effects of multiple sclerosis on multifinger synergies

6.1. Changes in multi-digit synergies and their feed-forward adjustments in MS

Many activities of daily living, such as eating, drinking, and brushing teeth rely on hand function. Poor hand performance, in particular in tasks requiring finger coordination, is commonly seen in multiple sclerosis (MS) (Shinohara et al., 2004; Ziemssen, 2011). Earlier studies have documented a range of MS effects on finger coordination in a variety of tasks. For example, MS patients show unusually high grip force magnitudes when manipulating a hand-held object (Iyengar et al., 2009) associated with an increase in grip force variability (Marwaha et al., 2006). Such tasks are also associated with poor coordination of the grip and manipulation forces seen in both unimanual (Krishnan et al., 2008; Krishnan & Jaric, 2008) and bimanual tasks (Gorniak et al., 2014).

Most of the earlier studies of the hand function in MS focused on the combined action of fingers on the hand-held object (for an exception see Bonzano et al., 2013). In this study, we focus on finger synergies defined as flexible patterns of finger involvement that ensure controlled stability of performance in multi-finger tasks (reviewed in Latash & Huang, 2015). A method to quantify synergies has been developed within the uncontrolled manifold (UCM) hypothesis (Scholz & Schöner, 1999; reviewed in Latash et al., 2007). The idea of the method is that, if a person performs several trials at a task using a redundant set of effectors, trajectories in the space of elemental variables (those produced by the individual effectors) are expected to diverge in less stable directions and converge in more stable directions. As a result, if a person stabilizes a particular salient performance variable, variance across trials is expected to be relatively high

within a sub-space that leads to no changes in that variable (UCM) as compared to variance in the orthogonal to UCM sub-space (ORT). The difference between the two variance indices, V_{UCM} and V_{ORT}, has been used as a synergy index (ΔV; reviewed in Latash et al., 2002b; 2007).

Several recent studies have shown that the synergy index in multi-finger accurate force production tasks is sensitive to a variety of states characterized by impaired hand function, from the healthy elderly (Shinohara et al., 2004), to persons with Down syndrome (Latash et al., 2002a; Scholz et al., 2003), Parkinson's disease (Park et al., 2012; Jo et al., 2015) and multiple-system atrophy (Park et al., 2013b). The main goal of this study has been to explore whether multi-finger synergies are affected in MS. Based on the earlier hypothesis that multi-finger synergies are highly sensitive to functioning of subcortical structures (Latash & Huang, 2015) where many MS lesions reside, our first hypothesis was that the synergy index would be significantly reduced in MS patients.

Ensuring stability of steady-state performance is only one of the components of controlled stability of performance. The other component is the ability to reduce stability of performance in anticipation of an action that requires a quick change in the salient variable. Such anticipatory synergy adjustments (ASAs, Olafsdottir et al., 2005) are seen in healthy young persons about 300 ms prior to the action initiation, but are reduced in both magnitude and duration in patients with subcortical disorders (Park et al., 2012; Park et al., 2013b; Jo et al., 2015). Since deficits in feed-forward control have been documented in MS (Jacobs & Kasser, 2012; Aruin et al., 2015), although in whole-body postural studies, our second hypothesis was that ASAs would be reduced in MS.

Methods

Subjects

Thirteen patients with MS (aged 47.1 ± 3.8; 3 males) and 13 healthy control subjects (CS; aged 46.5 ± 3.7; 4 males) were tested. None of the CS had any known neurological disorder or arthritis in their upper extremities. Descriptive data for the MS patients are presented in Tables 6-1 and 6-2. In this study, we purposefully selected patients with a relatively broad range of age (29 - 75), time since diagnosis (1.5 - 37.2 years), and the number and location of brain (from 3 to 50) and spinal (from 0 to 5) lesions to explore most general changes in multi-finger synergies with MS. Table 6-2 presents the results of the neurological examination of the hand function; about half of the patients showed no identifiable abnormalities; in other patients, most common abnormalities included mild tremor and dysmetria. The locations of the main lesions are also described in more detail in Table 6-2.

We did not perform disability testing with the Expanded Disability Status Scale (EDSS) as it is heavily biased by performance in locomotor tasks (Amato & Portaccio, 2007) and our study focuses on the hand function. The study protocol followed the Helsinki Declaration and was reviewed and approved by the Pennsylvania State University-Hershey Medical Center Institutional Review Board. Written informed consent was obtained from all subjects.

Apparatus and procedures

The pressing setup and tasks described in chapter 4 was used for this study. Briefly, the experiment involved three tasks: 1) Maximal voluntary contraction (MVC) task; 2) single-finger ramp tasks; and 3) quick force pulse production task (See chapter 4 for detailed description of each task). The subjects performed all three tasks with the left and right hands separately in a

Table 6-1. Descriptive data of MS patients

Subject	Sex, M/F	Age, yr	Handedness, R/L	Time since diagnosis, yr	Number of brain lesions	Number of spinal lesions
1	F	44	R	1.5	15	3-4
2	F	34	R	7.1	> 50	Unknown
3	M	49	L	8.2	> 30	Unknown
4	F	29	R	4.1	4	1
5	F	62	R	37.2	20-30	4
6	F	36	R	4.2	3	0
7	F	58	R	3.1	14	1
8	F	49	R	9.1	4	0
9	F	33	R	13.1	8	Unknown
10	M	52	R	3.0	6	3
11	M	34	R	5.3	30	0
12	F	57	R	3.4	> 30	4-5
13	F	75	R	24.2	Unknown	Unknown

Abbreviations: M/F, male/female; R/L, right/left.

Table 6-2. Hand function and location of brain lesions in MS patients

	Hand function	Lesion location
1	No clear abnormalities	Periventricular region; Lt peritrigonal area
2	No clear abnormalities	Supratentorial WM; corpus callosum; Rt frontal lobe
3	No clear abnormalities	Periventricular, pericallosal, infratentorial and periatrial regions; cerebellum
4	No clear abnormalities	Periventricular and pericallosal regions
5	No clear abnormalities	Periventricular, supratentorial and infratentorial regions
6	No clear abnormalities	Lt anterior periventricular WM; Lt frontal subcortical WM; Rt peritrigonal WM; Rt internal capsule
7	No clear abnormalities	Periventricular region; occipital and temporal lobes; callosal septal interface; Lt frontal juxtacortical WM
8	Rt decreased sensation	Lt centrum semiovale; basal ganglia
9	Rt dysmetria	Periventricular and pericallosal regions
10	Bilateral dysmetria	Rt frontal periventricular WM; occipital periventricular WM; subcortical WM; callososeptal interface; Lt thalamus; Lt caudate nucleus; Lt midbrain; pons; medulla
11	Mild bilateral tremor and numbness in fingertips	Periventricular regions; internal capsule; Lt temporal lobe; Lt thalamus; brainstem; brachium pontis
12	Mild bilateral dysmetria and decreased light touch	Periventricular, pericallosal and supratentorial regions; posterior parts of frontal lobes; Lt middle corona radiata
13	Mild bilateral dysmetria and tremor	Unknown

Abbreviations: Rt/Lt, right/left; WM, white matter.

balanced across subjects order. Subjects were given an instruction before each task and a few practice trials until they acquired a reasonable level of accuracy and consistency. Typically, 1-2 trials were given prior to the ramp task and 5-8 trials prior to the force pulse production task; only one practice trial was performed prior to the MVC task. There were 5-min breaks after testing one hand. Subjects were offered rest at any time if they felt fatigued. The entire experiment lasted ~1 h.

Data analysis

The data analysis for these tasks was previously described in chapter 4.

Statistics

Standard descriptive statistics were used, and the data are presented as means and standard errors (SE). Mixed-design ANOVAs with repeated measures were used to explore how outcome variables (*MVC*, *EN*, T_{peak}, V_{UCM}, V_{ORT}, ΔV_{SS}, ΔV_{SS-t0}, and t_{ASA}) were affected by factors *Group* (MS and CS), *Hand* (right and left) and *Finger* (I, M, R, and L). The data were checked for violations of sphericity and Greenhouse-Geisser criterion was used to adjust the degrees-of-freedom when necessary. Pair-wise comparisons with Bonferroni corrections were used to explore significant ANOVA effects. V_{UCM} and V_{ORT} were log-transformed for all comparisons to achieve a normal distribution (Shapiro-Wilk test, $p < 0.05$ level). Pearson correlation coefficients were used to determine significant relationships between variables. All statistical tests were performed with SPSS 19.0 (SPSS Inc, Chicago, IL, USA).

Results

Maximal force and enslaving

MS patients produced significantly lower peak forces in the MVC trials compared with CS. This was true for both hands. The average MVC of the MS group was only 62% of that of CS. The MVC values for the MS patients were 40.9 ± 5.5 and 41.5 ± 5.2 N for the right and left hand, respectively, whereas for the CS group these values were 69.5 ± 8.6 and 63.5 ± 7.7 N. A two-way ANOVA on *Group* and *Hand* showed a main effect of *Group* [$F_{[1,24]} = 7.05$; $p < 0.05$] without other effects.

During the single-finger ramp tasks, unintended force production by non-task fingers (enslaving, *EN*) was seen in both MS and CS groups. Whereas different fingers showed different amount of *EN*, for both groups, *EN* was largest in the ring finger task and smallest in the index finger task. Overall, the summed *EN* index over all trials (EN_{all}) was larger for MS than the CS group (for the right and left hand, 0.24 ± 0.03 and 0.29 ± 0.03 in CS; 0.34 ± 0.06 and 0.33 ± 0.04 in MS). A three-way ANOVA with factors *Hand, Finger* and *Group* showed significant main effect of *Finger* [$F_{[3,22]} = 40.1$; $p < 0.001$] without other effects. Pairwise comparisons confirmed that the $EN_I < EN_M$, $EN_L < EN_R$ ($p < 0.05$). The group difference in EN_{all} between groups was mainly in the lateral (index and little) finger tasks, with less of a difference in the medial (middle and ring) finger tasks. To test this effect, *EN* of the medial fingers (EN_{med}) and lateral fingers (EN_{lat}) was analyzed separately using a two-way ANOVAs *Group* × *Hand*. The ANOVA on EN_{lat} showed a main effect of *Group* [$F_{[1,24]} = 4.66$; $p < 0.05$] without other effects whereas the ANOVA for EN_{med} did not show any significant effects.

Performance in the force pulse task

During the steady-state phase of the quick force pulse task, both MS and CS groups demonstrated accurate task performance, with F_{TOT} close to the target level (8% of MVC_{TOT}) before the pulse initiation. Figure 6-1 shows the averaged across trials performance of representative subjects from each group for the quick force production. Note the slower force pulse in the MS subject. On average, MS patients were slower than CS in reaching the peak force. T_{peak} for the MS was 0.25 ± 0.03 and 0.22 ± 0.02 s, while T_{peak} for the CS was 0.19 ± 0.01 and 0.18 ± 0.01 s for the right and left hand, respectively. This difference approached significance (p = 0.09) according to a two-way ANOVA *Group* × *Hand*.

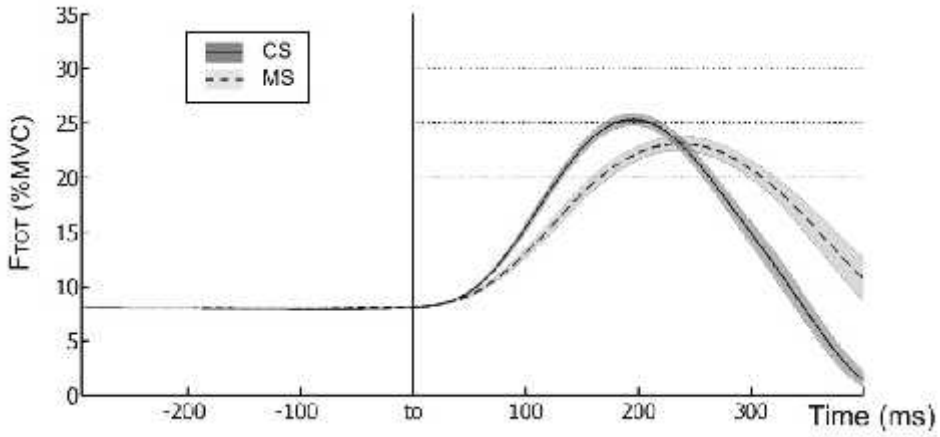

Figure 6-1. Time profiles of the averaged total force with SE shades computed across trials for typical subjects of each group during the quick force pulse task. The trials were aligned by the initiation of the force pulse (t_0). The dashed line shows the data for the right hand of a MS subject (T_{peak} = 0.255 s) and the solid line shows the data for the right hand of a CS (T_{peak} = 0.197 s).

Indices of multi-finger synergies

Both groups showed consistently positive synergy indices (ΔV_{SS}) during the steady state prior to the force pulse initiation. The large positive values of ΔV_{SS} reflected the large amounts of variance (V_{UCM}) in the space of commands to fingers that kept F_{TOT} unchanged. In Figure 6-2A, the time profiles of the two variance components, V_{UCM} and V_{ORT}, are presented for both groups. Note the twice as large V_{UCM} values in CS compared to MS, while V_{ORT} was relatively similar in the two groups leading to higher synergy index (ΔV_Z, Figure 6-2B) in CS. These results were supported by *Group* × *Hand* ANOVAs on V_{UCM}, V_{ORT}, and ΔV_{SS}, which showed significant main effects of *Group* for V_{UCM} [$F_{[1,24]} = 5.21$, $p < 0.05$] and ΔV_{SS} [$F_{[1,24]} = 7.75$, $p < 0.05$] without other effects.

Anticipatory synergy adjustments

Before the initiation of the force pulse, there was a drop ($\Delta\Delta V_Z$) in the synergy index in both groups (Figure 6-2B). The initiation of the ΔV_Z drop was delayed in MS, on average by 43%, and the magnitude of the drop was smaller in MS by 37% (Table 6-3). These results were supported by two-way ANOVAs *Group* × *Hand* on ΔV_{SS-t0} and t_{ASA} [main effect of *Group*: $F_{[1,24]} = 7.38$, $p < 0.05$ for ΔV_{SS-t0}; $F_{[1,24]} = 13.44$, $p < 0.05$ for t_{ASA}]. There were no other effects. Figure 6-2 suggests that the longer and larger ASAs were primarily due to the drop in V_{UCM} in CS without any visible changes in V_{UCM} in MS.

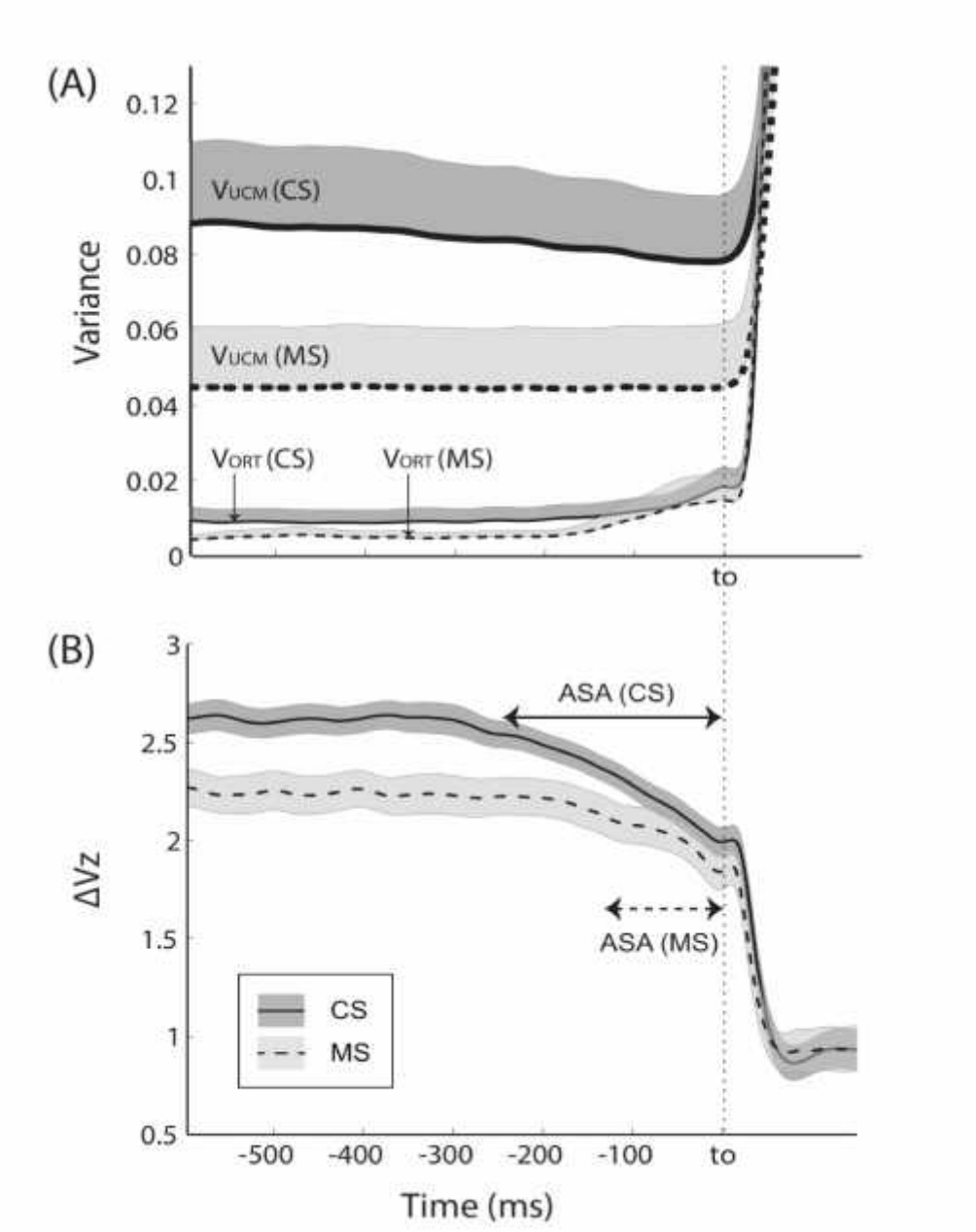

Figure 6-2. (A) Two variance components (V_{UCM} and V_{ORT}) and (B) the synergy index (ΔV_Z) during the quick force pulse production tasks for the MS patients and CS. Averages across subjects within each group are presented with standard errors shades. Average data across both hands were used for each subject. Note the difference in ASA between MS and CS groups before the initiation of the force pulse (t_0).

Table 6-3. Synergy indices for the quick force production task

		V_{UCM}	V_{ORT}	ΔV_{SS}	ΔV_{SS-t0}	t_{ASA} (s)
MS	R	0.044 ± 0.015	0.005 ± 0.002	2.23 ± 0.14	0.43 ± 0.07	-0.13 ± 0.03
	L	0.046 ± 0.018	0.005 ± 0.002	2.25 ± 0.13	0.37 ± 0.06	-0.13 ± 0.03
CS	R	0.083 ± 0.020	0.007 ± 0.003	2.55 ± 0.10	0.64 ± 0.07	-0.22 ± 0.02
	L	0.095 ± 0.027	0.011 ± 0.005	2.68 ± 0.10	0.62 ± 0.09	-0.25 ± 0.02

Means ± SE of variance indices at steady-state (V_{UCM}, V_{ORT}, and ΔV_{SS}), magnitude (ΔV_{SS-t0}) and time of anticipatory synergy adjustments (t_{ASA}) are presented for MS patients and CS. Abbreviations: R/L, right/left hand.

Discussion

Both hypotheses formulated in the Introduction have been confirmed in the experiment. Indeed, as predicted by Hypothesis 1, we observed lower synergy indices in MS during steady-state force production. Hypothesis 2 predicted decreased anticipatory synergy adjustments (APAs) in MS. The experiment showed significantly reduced duration and magnitude of ASAs in the MS group. There were also effects of MS on general indices of performance and on indices of finger individuation (enslaving, Zatsiorsky et al., 2000).

Finger enslaving and its changes in MS

Enslaving (lack of individuation) has been discussed as reflecting both peripheral and central factors including passive links among fingers, multi-tendon, multi-finger extrinsic hand muscles, and overlapping cortical representations (reviewed in Schieber and Santello, 2004). Changes in enslaving indices are typical across various groups with mildly impaired coordination including the healthy elderly (Shinohara et al., 2003; Shinohara et al., 2004; Park et al., 2012). Sometimes, these changes are counter-intuitive. In particular, healthy older adults show decreased

indices of enslaving (better finger individuation) while their overall performance in hand tasks and indices of multi-digit synergies are impaired (Shim et al., 2004; Olafsdottir et al., 2007a; Olafsdottir et al., 2008a). Several earlier studies reported positive correlation between MVC and EN indices, i.e., lower enslaving in weaker persons (elderly vs. young and females vs. males, Shinohara et al., 2003; Shinohara et al., 2004). Our study showed a different result: MS patients were weaker than controls, and their EN indices were larger for the lateral fingers (index and little) without significant differences for the medial (middle and ring) fingers. These results suggest a change in enslaving specific to MS, which is not linked to the reduced ability to produce high forces.

The larger effect of MS on the lateral fingers, which typically show lower EN indices (Zatsiorsky et al., 2000), is an intriguing result. It suggests that MS leads to less differentiation across fingers compared to controls. Also noted was the trend towards higher EN and lower MVC in the left hands of controls (similar to earlier reports, Shinohara et al., 2003), while both indices were nearly identical for the two hands in MS. Whether one of the consequences of MS is indeed loss of differentiation across digits and hands deserves further investigation.

MS effects of synergic control

MS is characterized by a variety of clinical presentations depending on specific pathways within the CNS affected by the demyelinating process. As a result, motor deficits in MS can involve symptoms typical of damage to the corticospinal pathway, such as paresis and spasticity, as well as symptoms more typical of problems with subcortical loops, such as cerebellar symptoms (Tranchant et al., 1995). Recent studies have suggested that synergic mechanisms responsible for stable behavior in steady-state tasks show significant changes in subcortical disorders (such as Parkinson's disease and multiple system atrophy), but not necessarily

following cortical stroke (Reisman & Scholz, 2003; Park et al., 2012; reviewed in Latash & Huang, 2015).

In the current study, most of our subjects had subcortical lesions involving the periventricular region, internal capsule region, cerebellar and pontine lesions. Given that MS commonly affects subcortical pathways, we expected, on average, a drop in the synergy index. This was indeed observed. It is important to emphasize that the drop in ΔV was associated not with higher V_{ORT} (less accurate performance) but lower V_{UCM} (more stereotypical performance). An increase in V_{UCM} has been reported in recent studies of the effects of specialized practice on multi-finger synergies (Wu et al., 2012; Wu et al., 2013b). These observations bring an optimistic message that such practice schedules may have a beneficial effect for the synergic control of the hand in MS.

As emphasized in a recent review (Latash & Huang, 2015), neurological disorders involving the basal ganglia and cerebellum lead to impaired control of movement stability, which has two components. The first, lower stability of steady-state actions, is reflected in the lower ΔV index. The second may be addressed as loss of agility reflected in impaired destabilization of performance variables in preparation to actions that require a quick change in such variables. The documented decrease in the ability to attenuate a synergy stabilizing a salient performance variable in persons with MS may lead to problems with the ability to initiate movement quickly. Note that MS leads to an increase in preparation time across a range of motor tasks (Remelius et al., 2008; Stoquart-Elsankari et al., 2010), which may be particularly pronounced under fatigue (Morgante et al., 2011; Barr et al., 2014).

Clinical relevance of our finding

This is the first study of multi-finger synergies in MS. It can be viewed as a proof of concept that requires a follow-up with a much larger group exploring changes in synergy indices as a function of location of demyelinating lesions and correlating them with changes in functional hand tests. The relatively small and varied sample of the patients may be viewed as a limitation; however, the fact that significant changes in the synergy index and ASAs were observed in the study suggests that these effects are strong. Given that our MS group involved patients with a variety of clinical signs, including those typical of subcortical lesions, we expected, on average, a drop in the synergy index and in ASAs. These were indeed observed. It is important to emphasize that the drop in ΔV was associated not with higher V_{ORT} (less accurate performance) but lower V_{UCM} (more stereotypical performance).

Currently, the most commonly used disability scale in MS is the Expanded Disability Status Scale (EDSS). Though there is a motor functional system component, the scale is heavily weighted toward ambulation and a criticism of the scale is that it does not reflect well upon motor function in the upper extremities (Thompson & Hobart, 1998; Amato & Portaccio, 2007; Kragt et al., 2008; Cohen et al., 2012). Due to the limitations of the EDSS, the Multiple Sclerosis Functional Composite (MSFC) was conceived. This includes the Nine Hole Peg Test (9-HPT), which is a brief, standardized, quantitative test of upper extremity function. Though this test has good inter-rater and test-retest reliability and can be sensitive to detect minor impairments in hand function, the test is sensitive to practice effects and may not reflect changes when the level of impairment is severe (see the above references). We hope that the synergic changes may provide a more objective and sensitive description of MS-related changes in the upper extremities, which may be useful for clinical trials. Future studies will have to 1) explore in-depth possible links between changes in the synergic control and performance of functional tasks 2) investigate the potential of using synergic measurements as objective measures for functional disability. These studies may guide the future development of rehabilitation strategies in MS.

Chapter 7 Effects of cortical stroke on multifinger synergies

7.1. Effects of unilateral stroke on multi-finger synergies and their feed-forward adjustments

Sensorimotor impairment of the hand happens commonly after a unilateral cortical stroke affecting a range of activities of daily living. Typical consequences of stroke that affect the extremities contralateral to the lesion include weakness, predominance of fixed patterns of muscle activations (abnormal synergies, Bobath, 1978; Dewald et al., 1995), spasticity, and intersegmental coordination deficits (Wyke, 1967; Beer et al., 2000). In cases of mild stroke, impairments in the coordination among motor elements, such as arm joints and digits, become important factors affecting functional independence, even in the ipsilesional arm (Wetter et al., 2005; Rinehart et al., 2009; Schaefer et al., 2009).

Recently, an approach to the neural coordination of multiple effectors has been developed based on the principle of abundance (Gelfand & Latash, 1998; Latash, 2012a). According to this principle, the apparently redundant design of the human body is not a source of computational problems for the central nervous system (CNS), but a rich and flexible apparatus that allows the CNS to organize stable performance in the varying and unpredictable environment. Neural organizations that ensure stable performance by co-varied contributions of elements (muscles, joints, digits, etc.) have been referred to as synergies (Latash et al., 2007). This term has been used in the literature in different meanings. As mentioned, abnormal synergies describe stereotypic pattern of muscle activations that interfere with intentional movements (Brunnstrom, 1970; Shumway-Cook & Woollacott, 2012). This term has also been used to imply parallel

changes in variables produced by effectors, kinetic, kinematic, or electromyographic, across task parameters or over the time course of movement execution (d'Avella et al., 2003; Ivanenko et al., 2004; Ting & Macpherson, 2005). We use this term to reflect stability of natural movements with respect to salient variables, which is crucial for success given the natural variability in body states and unpredictable changes in external forces (reviewed in Latash et al., 2007; Latash, 2008b).

This important aspect of coordination can be quantified using a method that has been developed within the uncontrolled manifold (UCM) hypothesis (Scholz & Schöner, 1999). This analysis is based on the idea that repeating actions from slightly different initial conditions is expected to lead to diverging trajectories in unstable directions and converging trajectories in stable directions. Hence, analysis of inter-trial variance in different directions in the space of elemental variables (those produced by elements involved in the action) provides an index that can be used as a proxy of stability in those directions within the multi-dimensional space of elemental variables. The analysis quantifies inter-trial variance in directions that lead to no changes in a potentially important performance variable (along the UCM for that variable, V_{UCM}) and in directions orthogonal to the UCM (V_{ORT}). If $V_{UCM} > V_{ORT}$, quantified per degree of freedom in the corresponding sub-spaces, a conclusion is drawn that a synergy stabilizes that performance variable. A synergy index, ΔV, reflecting relative amount of V_{UCM} in total variance has been used as a metric reflecting stability of the performance variable (reviewed in Latash, 2008b). Recently, relations of the ΔV index to stability have been studied in a number of experiments with controlled perturbations of ongoing actions (Yang et al., 2007; Wilhelm et al., 2013; Reschechtko et al., 2014; Zhou et al., 2015b).

In more intuitive terms, this definition of synergy is related to inter-compensation of errors among the contributions of elements to a salient performance variable (cf. principle of error compensation, Latash et al., 1998). For example, carrying a cup of coffee while walking requires co-variation of joint rotations to keep the cup vertical. A strong joint configuration synergy

implies that spontaneous variations in joint angles or a perturbation applied to the arm would lead to changes in joint configuration primarily within the UCM for the vertical cup orientation, i.e., cup orientation would show dynamic stability. This is expected to lead to relatively high V_{UCM} values and positive ΔV values.

In patients with mild to severe contralesional impairment, deficits in intersegmental coordination during reaching movements of the contralesional arm have been documented (Beer et al., 2000), and have been shown to vary with the side of the lesion. In addition, coordination deficits in the ipsilesional arm have been documented as early as 1967 (Wyke, 1967), and have been shown to differ, depending on the side of the lesion (Winstein et al., 1999; Haaland et al., 2004b). While these studies have addressed the coordination of joint motions to produce a given trajectory within a reaching trial, they have not addressed the ability to stabilize performance as reflected in the two aforementioned indices of inter-trial variance, V_{UCM} and V_{ORT}, and in the synergy index ΔV.

Only one group has so far applied this method of analysis to arm movements of post-stroke patients (Reisman & Scholz, 2003; 2006). The results were surprising: While the patients displayed abnormal patterns of coordination in the contralesional arm that were notably more deficient than those of the ipsilesional arm, the synergy index computed in the joint configuration space was about the same in the contralesional and ipsilesional arms. Thus, there appears to be a striking difference in the effects of stroke on coordinating the various joints of the limb to achieve an action, which is seen in the averaged across-trial kinematics, and the ability to stabilize that action as reflected in covariation of joint motions across trials.

In contrast, studies of finger coordination in patients with subcortical disorders (Parkinson's disease, PD, and multi-system atrophy, Park et al., 2012, 2013a,b; Jo et al., 2015) have shown major changes in the synergy index during accurate multi-finger tasks. These changes were significant in both hands, even in patients with Hoehn-Yahr stage-I of PD who

showed clinical symptoms on one side of the body only. The contrast between the findings in PD and stroke patients suggests that subcortical loops, rather than cortical structures, might be crucial for synergic control. However, since the stroke study quantified arm reaching movements, and the PD studies quantified finger coordination, a comparison of the results cannot differentiate between the effect of the disorder (PD or Stroke) and the limb effectors (proximal joint coordination vs. finger coordination).

In order to directly address this ambiguity, we quantified multi-finger synergies in a group of stroke survivors with unilateral hemisphere damage and mild contralesional impairment, using the same procedure as that of several earlier studies of PD patients (Park et al., 2012, 2014). Based on the mentioned earlier study (Reisman & Scholz, 2003), we hypothesize that the stroke group should show differences from control subjects and between the ipsilesional and contralesional hands in overall performance indices, but not in the multi-finger synergy index computed with respect to the salient performance task variable, namely total force (Hypothesis-1). As in many earlier studies (Latash et al., 2001; Scholz et al., 2002; reviewed in Latash et al., 2007), we analyzed multi-finger synergies in the space of finger modes as elemental variables. Finger modes are defined as commands to individual fingers that can be modified by the subject one at a time; each mode, however, leads to force production by all the fingers of the hand because of the phenomenon of enslaving (Zatsiorsky et al., 2000; Danion et al., 2003b). Due to enslaving, finger forces are expected to co-vary across tasks, and the amount of co-variation may differ across groups. Therefore, analysis of synergies in a finger force space can potentially lead to false conclusions on stronger or weaker synergies stabilizing specific performance variables. Analysis in the mode space eliminates this confound.

We also explored feed-forward adjustment of synergies in preparation for quick action (anticipatory synergy adjustments, ASAs, Olafsdottir et al., 2005; Shim et al., 2005). ASAs reflect an important mechanism of gradually reducing stability of a variable in preparation to its

quick change. ASAs are delayed and decreased in magnitude in PD patients (Park et al., 2012; Jo et al., 2015). Following the prediction of no changes in synergies after stroke, we hypothesized that no changes in ASAs would take place (Hypothesis-2).

Methods

Subjects

Twelve patients with unilateral stoke (aged 64.58 ± 12.05; 10 males) and 12 healthy control subjects (CS; aged 62.18 ± 7.65; 9 males) were tested. All participants were right-handed according to their preferential hand use during writing and eating. None of the CS had any known neurological disorders or arthritis in their upper extremities. Descriptive data for stroke patients are presented in Table 7-1. Six patients with right-hemisphere damage (RHD) and 6 patients with left-hemisphere damage (LHD) were recruited. The median time since stroke was 3.5 years and patients were mildly impaired, with average Upper Limb Fugl-Meyer motor scores of 61.8 ± 4.3 (out of a possible 66 points). The hand Fugl-Meyer score was 14 out of 14 in all patients. Eight patients showed no sensory deficit in the hands (2 points out of 2), while three patients showed dysesthesia (1 out of 2 points), and one patient showed anesthesia (0 points) according to the Fulg-Meyer hand sensory score.

The lesion distribution of the patients is illustrated in Figure 7-1, which shows a multi-slice representation of the damaged areas manually traced by a trained technician on T1 or T2 weighted brain images using MRIcron (version 6 June 2013; Chris Rorden) software (Rorden & Brett, 2000). Unified segmentation and normalization routines found in the Clinical Toolbox in SPM8 were used to normalize the T1 or T2 images and corresponding lesion maps to a clinical template created specifically for older adults (Rorden et al., 2012). Binarized, warped, and smoothed lesion maps created from the normalization process were then overlaid onto a brain

template in MRIcron. While there was substantial variability among the patients in the lesion volume, no difference was seen between the RHD and LHD groups, 29.78 ± 37.13 and 42.73 ± 41.52 cm^3, respectively. One RHD patient had the lesion extended to subcortical regions, with involvement of the basal ganglia. The results were qualitatively similar with and without that patient's data. Hence, we present results across the whole stroke group.

Table 7-1. Descriptive data of stroke patients

	Sex, M/F	Age, yr	Handed-ness, R/L	Stroke side, R/L	Years post-stroke	UE FM score	FM-Hand	FM-Hand Sensory	Pegboard Ipsi/Contra (s)
1	F	73	R	R	1.0	61	14	2	54/46
2	M	80	R	L	1.2	61	14	2	48/48
3	M	66	R	L	4.5	62	14	2	14/14
4	M	75	R	R	3.6	62	14	1	49/45
5	M	56	R	R	3.8	56	14	1	35/12
6	M	69	R	L	1.2	66	14	2	62/62
7	M	75	R	R	3.5	60	14	2	55/50
8	M	50	R	L	2.4	66	14	2	36/36
9	F	54	R	L	2.5	65	14	2	44/44
10	M	56	R	R	18.9	53	14	1	30/dnc
11	M	77	R	R	1.6	65	14	2	57/51
12	M	44	R	L	5.1	65	14	0	27/27

Abbreviations: M/F - male/female; R/L - right/left, UE –upper extremity, FM – Fugl-Meyer, dnc – did not complete, the last column presents the data for the Grooved Pegboard test performed by the ipsilesional (Ispi) and contralesional (Contra) hands.

Figure 7-1. A multi-slice representation of the damaged areas manually traced by a trained technician on T1 or T2 weighted brain images.

The study protocol followed the Helsinki principles and was reviewed and approved by the Pennsylvania State University-Hershey Medical Center Institutional Review Board. Written informed consent was obtained from all subjects.

Apparatus and procedures

The pressing setup and procedures were identical to the MS study (See chapter 6). Clinical tests, including the Upper limb component of the Fugl-Meyer test Assessment and Grooved Pegboard test, were scored with standard procedures that had been tested earlier for reliability (Ruff & Parker, 1993). Raw scores (total time in sec) in the Grooved Pegboard test were converted to age-, education-, and gender-adjusted *T* scores using normative data from Halstead-Reitan battery (Heaton et al., 2004). All clinical tests were administered during a separate visit prior to the experiment.

Data analysis

The force data were digitally low-pass filtered with a zero-lag, fourth-order Butterworth filter at 10 Hz. The data processing was done using a customized Matlab code. The data analysis process for single-finger ramp tasks and quick force pulse production task was described in chapter 4.

Statistics

Standard descriptive statistics were used, and the data are presented as means and standard errors (SE). Mixed-design ANOVAs with repeated measures were used to explore how

outcome variables (*EN*, T_{peak}, ΔV_{SS}, ΔV_{SS-t0}, and t_{ASA}) were affected by factors *Group* (stroke and CS), *Finger* (I, M, R, and L), *Hand* (right and left), and *Stroke* (LHD and RHD). We also used the factor *Side* (affected and less-affected), which compared the data for the ipsilesional hands of both LHD and RHD patients (affected) to the data for the contralesional hands of both groups (less affected). The data were checked for violations of sphericity and Greenhouse-Geisser criterion was used to adjust the degrees-of-freedom when necessary. Pair-wise comparisons with Bonferroni corrections were used to explore significant ANOVA effects. Pearson correlation coefficients were used to determine significant relationships between variables. All statistical tests were performed with SPSS 19.0 (SPSS Inc, Chicago, IL, USA).

Results

Performance indices

Stroke patients produced significantly lower MVC forces with both hands compared to CS. The MVC values (mean ± SE) for the stroke patients were 60.9 ± 5.2, whereas for the CS group these values were 85.4 ± 8.1 N. A two-way repeated measures ANOVA on *Group* and *Hand* showed only a main effect of *Group* [$F_{[1,22]} = 7.29$, $p < 0.05$]. The comparison between the more affected, contralesional, and less-affected, ipsilesional, hands of the stoke patients showed that the MVC was significantly lower in the contralesional hand (paired t-test, $p < 0.05$). The values were 56.2 ± 5.6 N for the affected hand and 65.7 ± 4.8 N for the less-affected hand.

During the single-finger ramp force production tasks, unintended force production by non-task fingers (*EN*; enslaving) was seen in all subjects and the summed *EN* of all individual fingers (EN_{sum}) was not different between groups (0.30 ± 0.04 in CS; 0.29 ± 0.04 in stroke patients). Whereas different fingers showed different amount of enslaving, the overall pattern was similar in both groups; *EN* was smallest when index finger was the task finger, while the ring

finger caused the largest enslaving. A three-way *Group* × *Hand* × *Finger* ANOVA on *EN* showed a main effect of *Finger* [$F_{[3,66]} = 19.59$, $p < 0.001$] without other effects. Post hoc comparisons confirmed that $EN_I < EN_M < EN_L < EN_R$ ($p < 0.05$).

Further comparison within the stroke group showed that EN_{sum} was larger in the contralesional hand compared to the ipsilesional hand (0.35 ± 0.05 and 0.23 ± 0.02 for the affected and less-affected side, respectively) while *EN* indices for individual fingers showed similar overall patterns for the contralesional and ipsilesional hands (Figure 7-2). A two-way repeated measures ANOVA on *EN* with factors *Side* and *Finger* showed significant main effects for *Side* [$F_{[1,22]} = 4.93$, $p < 0.05$] and *Finger* [$F_{[3,66]} = 8.19$, $p < 0.001$] without an interaction. Post-hoc comparisons confirmed that $EN_I < EN_R$, EN_L ($p < 0.05$).

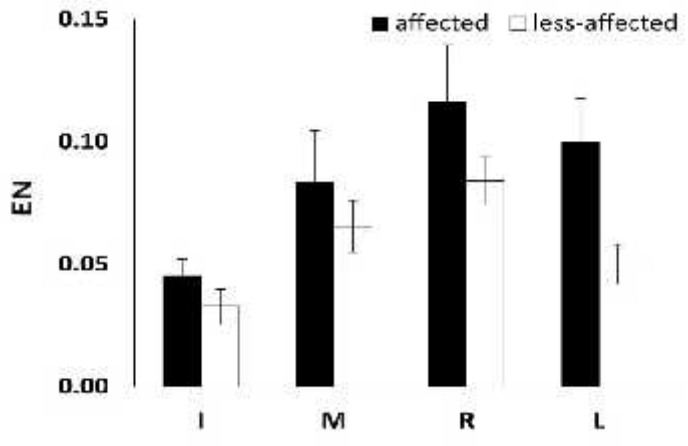

Figure 7-2. The enslaving indices (EN) for the index (I), middle (M), ring (R), and little (L) fingers of the affected (filled bars) and less-affected (open bars) hands for the stroke patients. Average values are presented with standard error bars. Note the larger enslaving in the affected (contralesional) hand.

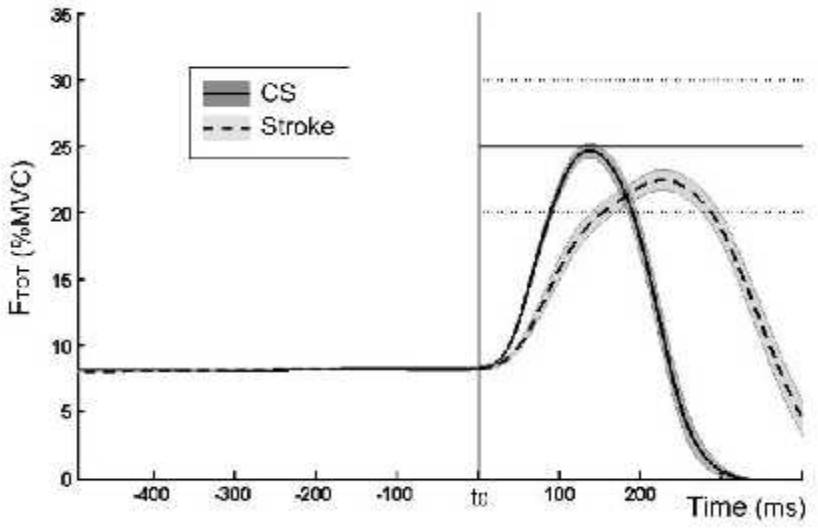

Figure 7-3. Time profiles of the averaged total force with SE shades computed across trials for typical subjects of each group during the quick force pulse task. The trials were aligned by the initiation of the force pulse (t_0). The dashed line shows the data for the left hand (affected side) of a stroke subject (T_{peak} = 0.22 s) and the solid line shows the data for the left hand of a CS (T_{peak} = 0.14 s).

Figure 7-3 shows the averaged performance of representative subjects from each group for the quick force pulse production. Stroke patients were slower than CS in reaching the force peak (T_{peak}; 0.21 s in the stroke patients and 0.15 s in the CS) but there were no noticeable differences between the hands. These results were supported by a two-way repeated-measures ANOVA on T_{peak} with factors *Group* and *Hand* which only showed significant main effect for *Group* [$F_{[1,22]} = 6.97$, $p < 0.05$]. There was no significant difference for T_{peak} between the ipsilesional and contralesional hands (Table 7-2).

Table 7-2. Performance and synergy indices for the quick force production test

		T_{Fpeak}	ΔV_{SS}	ΔV_{SS-t0}	t_{ASA} (s)
CS	Right	0.16 ± 0.02	2.22 ± 0.13	0.53 ± 0.08	-0.23 ± 0.03
(n=12)	Left	0.15 ± 0.01	2.63 ± 0.13	0.70 ± 0.14	-0.29 ± 0.03
Stroke	Contra	0.21 ± 0.02	2.43 ± 0.13	0.37 ± 0.09	-0.10 ± 0.03
(n=12)	Ipsi	0.21 ± 0.02	2.48 ± 0.15	0.45 ± 0.08	-0.17 ± 0.04

Means ± SE of time to force peak (T_{Fpeak}), variance indices at steady-state (ΔV_{SS}), magnitude (ΔV_{SS-t0}) and time of anticipatory synergy adjustments (t_{ASA}) are presented for stroke patients and CS. Abbreviations: Contra - contralesional side; Ipsi - ipsilesional side.

Multi-digit synergies and ASA in quick force pulse production

During the steady-state phase of the main task, both stroke and CS groups demonstrated stable task performance, which kept F_{TOT} close to the target level before the pulse initiation. This was reflected in consistently positive synergy indices during steady states (ΔV_{SS}) in both groups. These values reflected the larger amounts of inter-trial variance in the space of commands to fingers (modes, see Methods) that kept F_{TOT} unchanged. There was no significant group difference in ΔV_{SS}. These results were supported by a two-way *Group* × *Hand* ANOVA on ΔV_{SS} that showed a significant main effect of *Hand* [$F_{[1,22]} = 9.24$, $p < 0.05$] without other effects.

Before the initiation of the force pulse, there was a drop in the synergy index (ΔV_Z). The initiation of the ΔV_Z drop was delayed in stroke patients, on average by 48% for both hands. These results were supported by two-way repeated-measures ANOVA on t_{ASA} with factors *Group* [main effect: $F_{[1,22]} = 10.49$, $p < 0.05$ for t_{ASA}] and *Hand*. There were no interaction effects. The stroke group, on average, showed a smaller magnitude of the ΔV_Z drop (see Table 7-2 and Figure 7-4) but the group difference did not reach significance level.

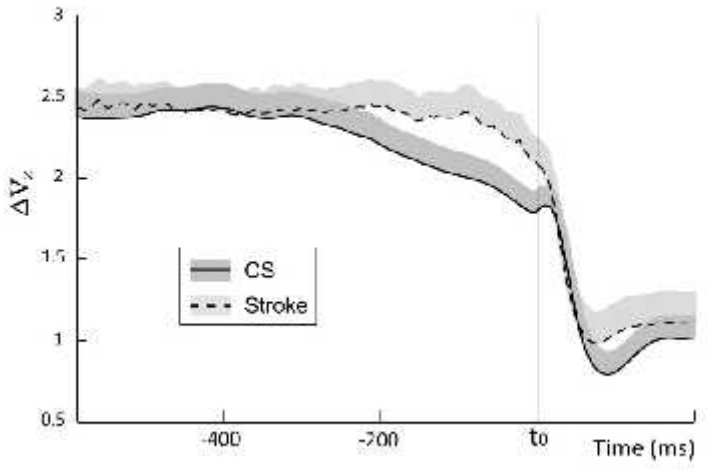

Figure 7-4. The average across subjects time profiles of the synergy index (z-transformed, ΔV_Z) with standard error shades. The data for the stroke group are shown with the dashed line and light shade; the data for the control group (CS) are shown with the solid line and darker shade. The data for the contralesional hand of the stroke patients and the average data across both hands of CS are presented. Note the very similar steady-state values and the much earlier drop in ΔV_Z in preparation to the force pulse.

All outcome variables from the synergy analysis are presented for each group in Table 7-2. When we compared the contralesional and ipsilesional hands of stroke patients, the delay in ASA was more prominent in the contralesional hand (Figure 7-4). The t_{ASA} values for the contralesional hands and ipsilesional hands in stroke patients and the average values between the right and left hands in CS were compared with one-way ANOVA. There was a significant difference among hands [$F = 6.03$, $p < 0.05$] and post-hoc comparisons confirmed that t_{ASA} was later (closer to t_0) in the contralesional hand of stroke patients than in CS ($p < 0.05$).

Lastly, we explored the correlations among the mentioned outcome variables from the synergy index and clinical test scores. The index of synergy (ΔV_{SS}) correlated positively with the Grooved Pegboard score in stroke patients when the Grooved Pegboard test was performed by the

left hand ($r = 0.68$; $p < 0.05$). The data for patient #10 were excluded because she was unable to perform the Pegboard test with the left hand. No other significant correlations were found.

Discussion

The main hypothesis of the study that stroke patients will show significant differences from the control group in indices of performance but not in synergy indices (Hypothesis-1) has been largely supported. Indeed, stroke patients differed significantly from the control group in such indices as MVC (lower in stroke) and time to peak force (longer in stroke). While group difference in the enslaving index was not significant, the index was significantly higher in the contralesional hand of the stroke patients compared to the ipsilesional hand. In addition, the contralesional hand showed lower MVC compared to the ipsilesional hand. In contrast, the synergy index during the steady-state phase of the task showed no effects of stroke and no difference between the ipsilesional and contralesional hands. Hypothesis-2, however, was not supported: Anticipatory synergy adjustments (ASAs) started significantly later in the stroke patients, and the delay in ASA was more prominent in the contralesional hand of the stroke patients. Our exploratory prediction was that LHD patients would show more problems with ASAs (preparation to a quick action), while RHD patients would more likely show impaired synergies during steady-state tasks. The results were in the predicted direction (on average, smaller magnitude of ΔV drop in LHD), but they did not reach significance level.

Effects of stroke on finger interdependence

When humans try to move a finger or press with a finger, other fingers of the hand move and press unintentionally (Kilbreath & Gandevia, 1994; Li et al., 1998; Lang & Schieber, 2003).

This phenomenon, addressed as lack of independence or enslaving (Zatsiorsky et al., 2000), is due to many factors including peripheral connective tissue links between fingers, multi-digit extrinsic hand muscles, and overlapping cortical representations of fingers (reviewed in Schieber & Santello, 2004). Studies with transcranial magnetic stimulation have suggested a substantial degree of physiological independence among the compartments of the external hand flexors (Danion et al., 2003a). In addition, experiments comparing the patterns of finger interdependence during pressing tasks with fingertips and with proximal phalanges showed similar patterns of enslaving in both conditions (Latash et al., 2002b). Note that pressing with proximal phalanges is produced by intrinsic hand flexors, which are finger-specific. Overall, these observations suggest that the patterns of finger enslaving are primarily defined by central, neural factors. This conclusion is also supported by the observations of strong and quick effects of practice on the enslaving indices (Wu et al., 2013a).

It is not surprising, therefore, that even mild cortical stroke has significant effects on finger individuation resulting in higher indices of finger enslaving (Li et al., 2003), likely with an important contribution from the lost cortico-spinal projections. Our experiment corroborated this conclusion by showing significantly higher enslaving indices in the contralesional hand of the stroke patients compared to the ipsilesional hand. The increased enslaving is likely to contribute to poor finger coordination and impaired hand function typical of stroke (cf. Schieber et al., 2009). We would like to emphasize, however, that relations between changes in enslaving and dexterity are not unambiguous. For example, healthy older adults show lower enslaving indices (Shinohara et al., 2003; Shinohara et al., 2004), while a drop in hand dexterity with advanced age is also well documented (Hackel et al., 1992; Hughes et al., 1997). It is possible that a certain amount of enslaving is optimal for performance of the typical range of everyday tasks given that enslaving contributes to stabilization of the total moment of force exerted on hand-held object (Zatsiorsky et al., 2000).

Note that the magnitude of enslaving is an important factor in the analysis of multi-finger synergies. High enslaving is expected to lead to predominantly positive co-variation among finger forces, which act to weaken synergies stabilizing total force. To remove these effects of enslaving, analysis of finger synergies is performed in the space of finger modes, hypothetical commands to individual fingers (Danion et al., 2003b). Each mode produces forces in all four fingers due to enslaving. Note that in persons with high enslaving, analysis in the finger mode space is more conservative: It leads to indices that are smaller than those in the force space. This means that low synergy indices in the finger mode space in persons/hands with higher enslaving imply even lower indices in the space of forces.

Finger synergies and their changes in neurological disorders

The definition of synergies accepted in this paper differs from two commonly used definitions. In clinics, abnormal synergy is a term used to describe stereotypical patterns of muscle activation interfering with intentional movements (Bobath, 1978; Dewald et al., 1995). In the motor control literature, synergies commonly mean proportional involvement of elemental variables, for example muscle activations, joint rotations, forces, etc. (d'Avella et al., 2003; Krishnamoorthy et al., 2003; Ivanenko et al., 2004; Ting & Macpherson, 2005). We link synergies to a crucial feature of all meaningful movements performed by redundant or more exactly abundant (Latash, 2012a) systems, that is, their stability. Two characteristics of synergies are usually studied, sharing and co-variation. The former reflects the average involvement of elements in a task; commonly, patterns of sharing are studied using optimization methods (Prilutsky & Zatsiorsky, 2002). The latter implies that, when one element in a particular trial deviates from its average trajectory, other elements are also likely to show deviations organized

to keep an important performance variable relatively unchanged. A method to study this feature quantitatively has been developed within the UCM hypothesis (reviewed in Latash et al., 2007).

Characteristics of synergies show significant changes in atypical development, fatigue, and healthy aging (reviewed in Latash, 2008b). Recently, significant changes in multi-digit synergies have been documented for patients with subcortical disorders such as Parkinson's disease and multi-system atrophy (Park et al., 2012; Park et al., 2013b). In particular, synergy changes in PD could be quantified even in patients who, according to the clinical evaluation, showed no signs of the disease in the studied extremities. Note that these patients were tested on their optimal medication and, as a result, they displayed minimal functional differences from healthy controls in overall characteristics of performance.

The only study of synergies in stroke survivors showed a qualitatively different picture: Overall patterns of reaching movements were affected in the patients, while the indices of kinematic synergies stabilizing the hand trajectory were unchanged (Reisman & Scholz, 2003; see also a follow-up in Reisman & Scholz, 2006). The contrast between these results and those in PD patients could be due to the difference in the task (multi-digit pressing and prehension in PD vs. multi-joint reaching in stroke) or to qualitatively different effects on synergies of a disorder in cortical vs. subcortical structures. The results from the current study favor the latter hypothesis. Indeed, we observed significant changes in performance variables in the stroke group and between the contralesional and ipsilesional hands while no changes in the synergy index could be seen during the steady-state force production. This conclusion fits well the hypothesis of Houk (2005) on the role of neural circuits involving the basal ganglia and the cerebellum in the so-called distributed processing modules, hypothetical neural operators that participate in the coordination of natural movements. Given that there have been so far only two studies exploring synergies after stroke and that they involved relatively small cohorts of patients (8 in the Reisman and Scholz study and 12 in the current study), these conclusions should be viewed as tentative.

Effects of stroke on feed-forward control of synergies

Anticipatory synergy adjustments (ASAs) represent a drop in a synergy index in anticipation of a quick change of the performance variable, for which the index has been computed (Olafsdottir et al., 2005; Shim et al., 2005). As a result, ASAs lead to relative loss of stability of the performance variable. ASAs functionally important because they allow the central nervous system to avoid fighting its own synergies. In fact, phenomena similar to ASAs can be observed in some of the everyday and athletic actions; consider, for example, the increased body sway of a tennis player who is getting ready for a fast serve by the opponent.

Earlier studies of various populations provided evidence for parallel changes in synergies and ASAs. In particular, synergy and ASA indices are both decreased in healthy elderly, in patients with PD, and in patients with multi-system atrophy (Shinohara et al., 2004; Olafsdottir et al., 2007a; Park et al., 2012; Park et al., 2013a; Park et al., 2013b). Taken together, these changes have been addressed as impaired control of stability of movement and posture (Latash & Huang, 2015). Our current study provides evidence for dissociation between changes in synergies and ASAs. Indeed, stroke patients showed no differences in the steady-state synergy index but significantly delayed ASAs (see Figure 7-4). These results suggest that while cortical structures may not be important to ensure the stability of performance (as reflected in synergy indices), they do contribute (at least in part) to agility of performance, as reflected in ASAs.

Problems with feed-forward movement control are well documented in patients with a variety of neurological disorders such as stroke, PD, cerebellar disorders, and even in healthy older adults (reviewed in Lemon & Griffiths, 2005; Latash & Huang, 2015). Examples include anticipatory postural adjustments (APAs, Massion, 1992) and grip adjustments to manipulation of a hand-held object: Both are reduced in all the mentioned populations as compared to control groups. Note that ASAs and APAs represent very different phenomena with respect to their

function (synergy adjustments vs. generation of net forces/moments) and timing (ASAs are seen 100-200 ms prior to the first signs of APAs). But they both are examples of feed-forward control, and it is possible that similar neural mechanisms are involved in these two phenomena.

The documented loss of ASAs may be causally related to the loss of hand dexterity after stroke (Hackel et al., 1992; Hughes et al., 1997), in particular in tasks that require quick finger actions. We would like to emphasize that the arm of our subjects was supported during the testing procedure so that possible abnormal upper-arm synergies were not expected to interfere with the required finger actions.

Concluding comments

Our study has a number of limitations. Among the obvious drawbacks is the relatively small cohort of subjects and the unbalanced male-female composition. Another problem typical of stroke studies is the diverse etiology and location of hemisphere lesions. Despite these drawbacks, the significant findings carry two strong messages. First, in contrast to patients with subcortical disorders, survivors of hemisphere stroke show relative unaffected synergies stabilizing steady-state performance, even though indices of performance are changed significantly. Second, feed-forward adjustments of synergies in hemisphere stroke patients suffer similar impairment as in patients with subcortical disorders.

Chapter 8 General Discussions and Conclusions

Since all natural human movements are performed in a poorly predictable environment and involve varying internal states, movement stability is crucial for successful everyday motor performance. For example, when a welder is involved in labor activity, the non-dominant hand typically ensures stability of the object of welding while the dominant hand controls the torch. To maintain stability, one should be able to flexibly use varying contributions of elements such as joints, digits, and muscles, rather than fixed, stereotypical patterns of their involvement. However, it is important to note that stability is not always desirable. If a person wants to change a variable quickly from a steady state, high stability would resist this intentional change.

In patients with neurological disorders, their impairments in motor function frequently involve loss of stability of motor performance that may cause spills, falls, dropped objects, illegible writing, stuttering and also loss of the agility of motor performance that may cause difficulty with quick change in performance variables or even with initiating the action, for example, freezing of gait (Latash & Huang, 2015). In this dissertation, a series of studies about synergies stabilizing the hand action in various populations are presented. Within the framework of synergic movement control, quantitative analysis of synergies in patient groups has allowed quantifying aspects of impairment related to movement stability and agility and also provided insights into understanding neural mechanisms of synergic control.

In the first study of PD, it has been confirmed that the impaired control of stability in patients with early-stage PD is reflected in the indices of synergy across different tasks. The problems with multi-finger synergies were not limited to pressing tasks that might be considered artificial and less relevant to daily activities but also present in more natural movements. A

prehensile task designed to simulate the movement of taking a sip from a glass demonstrated that there were low synergy indices among the fingers, as well as between the fingers and the thumb. ASAs were delayed and reduced in magnitude during both types of tasks.

The second study has shown that indices of synergies in PD are sensitive to DBS. The impairments in ASAs were rapidly reversed by DBS while synergy indices during steady-state force production did not show immediate changes after the DBS was turned off and on.

In the third study, PD patients have shown larger unintentional force drifts after the visual feedback was turned off. This has been interpreted as an adaptive strategy compensating for their loss of stability reflected in the reduced synergy and ASA indices.

The changes in synergies and ASAs have been demonstrated even in PD patients at earliest diagnosis (Park et al., 2012). Moreover, these indices have shown changes in people at high risk for Parkinsonism while tested at subclinical states. In the fourth study, apparently healthy professional welders, without obvious neurological deficits, were tested using the one-finger and four-finger pressing tasks. This population was chosen because the manganese (Mn) exposure makes welders susceptible to Mn toxicity, which manifests as a type of Parkinsonism and there was, indeed, a tendency of changes in synergy indices.

A study in patients with MS has shown similar results to those in the studies of PD patients. The synergy and ASA indices were significantly reduced in MS patients. On the other hand, patients after mild cortical stroke showed no differences in the synergy indices but did show significantly reduced and delayed ASAs. The results in the stroke group suggest the following important features of synergic control. First, it provides substantial support for the hypothesis that subcortical loops are crucial for high stability of task performance. Second, impairments in the control of stability have two components, low synergy indices and decreased

ASAs, which may have distinct neurophysiological mechanisms that could be selectively involved in different disorders.

Neurophysiological mechanisms of synergies

Although not directly targeted in the studies included in this dissertation, the cerebellum is a subcortical structure with potentially important role in synergic control. In one of the previous study, patients with multisystem atrophy with cerebellar involvement (known as olivo-ponto-cerebellar atrophy) showed changes in synergy indices similar to those in the PD patients (Park et al., 2013b). Clinically, these group of patients show a mixture of cerebellar and parkinsonian signs and symptoms reflecting the involvement of several subcortical loops. Taken together, the contrast between subcortical disorders versus cortical stroke survivors points at subcortical structures as being crucial for high stability of task performance.

In future, studies designed to refine the role of the basal ganglia and cerebellar circuits in synergic mechanisms are most warranted. Additionally, to further support this hypothetical role of subcortical structures in synergies, future studies on patients with amyotrophic lateral sclerosis (ALS) and spinal cord injury, where the function of subcortical structures are either mildly involved or intact, may be beneficial. Based on previous studies, no changes in the level of synergy indices could be expected in those patient populations. However, there could be differential effects of the two disorders depending on the involvement of cortical area; ASAs might be selectively deteriorated in patients with ALS similar to the observations in mild stroke patients.

According to the referent configuration hypothesis, the neural control of natural movements is based on specifying neural variables that lead to changes in a set of referent values

for salient, task-specific variables. Further, few-to-many mappings result in referent values for elemental variables that contribute to that salient variable. Those mappings may be organized in a synergic way, that is, they allow relatively large variations in the elemental variables as long as the referent value for the salient variable remains relatively unchanged. Adjustments in such mappings without a change in the referent value for the salient variable are plausible origins of ASAs (Latash, 2010b).

Another potentially important study design would be to compare sub-groups of cortical stroke patients with lesions in anterior regions vs. posterior regions. Considering that extensive body of literature has reported an important role of the primary motor cortex, several premotor areas, and supplementary motor area in motor preparation (Jacobs et al., 2009; Ng et al., 2011; Varghese et al., 2016), it would be worth using this protocol to explore effects of injuries to those two regions on ASAs.

Clinical utility of synergy indices

The methodology that was used to quantify synergies in the studies might provide a more objective tool for quantifying the impairments in the control of action stability in patients with various neurological diseases. The changes in synergy indices could be seen at early stages of the PD, even in the asymptomatic side (Park et al., 2012), which suggests that reduced motor stability (reduced synergy index) may precede the actual clinical detectable symptoms. Along the same lines, in asymptomatic welders without motor dysfunction, stability of hand action is reduced significantly compared to controls. The loss of movement stability in welders may be subtle and not observable with the naked eye and, possibly due to this reason, traditional fine motor tasks fail to detect any significant changes. These features potentially make synergy indices a powerful

tool to objectively quantify the impairments of motor symptoms and also a useful biomarker for early detection of motor changes in neurological patients.

Conclusions

The evidence presented in the dissertation has led to the following main conclusions. First, impaired control of movement stability is commonly seen in persons with impairments in subcortical brain structures. The impairments are seen as low synergy indices during steady states of performance and delayed/reduced drop in the synergy indices before quick action (low anticipatory synergy adjustments). Second, these two components of the impairments in the control of stability may have distinct neurophysiological mechanisms and they could be selectively involved in different disorders. The results consistently suggest subcortical loops as being crucial for high stability of task performance. Third, the changes in synergy indices could be seen at early stages of PD and even in subclinical stages of disorder involving the basal ganglia, when traditional clinical examination fails to show any impairment. Lastly, changes in motor synergies are sensitive to treatment in PD patients. These features potentially make synergy indices a powerful tool to objectively quantify the impairments of motor symptoms and also a useful biomarker for early detection of motor changes.

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Publications

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