IMPAIRED CONTROL OF MULTI-MUSCLE SYNERGIES
IN PARKINSON’S DISEASE

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by

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ABSTRACT

One of the main features of the human motor control system is its ability to control the stability of our actions, which involve multiple elements, such as digits, joints, and muscles. This is highly challenging given the poorly predictable environment and continuously changing intrinsic body states. Understanding the mechanisms of action stability and effects of neurological disorders on these mechanisms is, therefore, a highly important field of study. This dissertation quantifies changes in multi-muscle synergies that stabilize the vertical posture in Parkinson’s disease (PD), explore the relations between stability and agility of actions in PD, and try to link these effects to neural structures. Stability of the vertical posture is quantified using across-trials variance analysis in the space of hypothetical neural commands that form muscle groups with parallel modulation of their activation levels. This analysis quantifies the stability of the center of pressure coordinate and its changes in preparation to quick actions (agility). Early-stage PD patients with no clinically identifiable postural instability showed reduced indices of postural stability and an impairment in the ability to attenuate postural stability in preparation to a quick action. Indices of both stability and agility improve on dopamine-replacement drugs, and are getting worse by changes in the visual scene prior to step initiation. Comparing synergy indices across different multi-finger force production and multi-muscle whole body tasks suggests that synergy indices reflect systemic neural mechanisms shared across tasks and effectors. The contrasting effects of deep brain stimulation on indices of stability and agility suggest that these indices and their changes in PD reflect different functional neural subsystems. Analysis of multi-muscle synergies may provide a clinically sensitive biomarker for early diagnosis of PD and emergence of balance problems.
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<td>ANIO</td>
<td>Analytical Inverse Optimization</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of Variance</td>
</tr>
<tr>
<td>AP</td>
<td>Anterior-Posterior</td>
</tr>
<tr>
<td>APA</td>
<td>Anticipatory Postural Adjustment</td>
</tr>
<tr>
<td>ASA</td>
<td>Anticipatory Synergy Adjustment</td>
</tr>
<tr>
<td>CNS</td>
<td>Central Nervous System</td>
</tr>
<tr>
<td>cm</td>
<td>centimeters</td>
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<tr>
<td>COM</td>
<td>Center of Mass</td>
</tr>
<tr>
<td>COP</td>
<td>Center of Pressure</td>
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<tr>
<td>DBS</td>
<td>Deep Brain Stimulation</td>
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<td>DoF</td>
<td>Degrees of Freedom</td>
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<tr>
<td>DPM</td>
<td>Distributed Processing Modules</td>
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<tr>
<td>E</td>
<td>Enslaving Matrix</td>
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<tr>
<td>EMG</td>
<td>Electromyography</td>
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<tr>
<td>EP</td>
<td>Equilibrium Point</td>
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<tr>
<td>EPA</td>
<td>Early Postural Adjustment</td>
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<tr>
<td>EPH</td>
<td>Equilibrium Point Hypothesis</td>
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<tr>
<td>EV</td>
<td>Elemental Variable</td>
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<tr>
<td>F</td>
<td>Force</td>
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<td>FOG</td>
<td>Freezing of Gait</td>
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<tr>
<td>FS</td>
<td>Fast Sway</td>
</tr>
<tr>
<td>GP</td>
<td>Globus Pallidus</td>
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<tr>
<td>GPi</td>
<td>Globus Pallidus Internus</td>
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<tr>
<td>H&amp;Y</td>
<td>Hoehn and Yahr</td>
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<tr>
<td>Hz</td>
<td>Hertz</td>
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<tr>
<td>IQR</td>
<td>Interquartile Range</td>
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<tr>
<td>J</td>
<td>Jacobian Matrix</td>
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<tr>
<td>LEDD</td>
<td>Levodopa Equivalent Daily Dose</td>
</tr>
<tr>
<td>LR</td>
<td>Load Release</td>
</tr>
<tr>
<td>M</td>
<td>Mean Vector of Muscle Modes Magnitude</td>
</tr>
<tr>
<td>ME</td>
<td>Motor Equivalent</td>
</tr>
<tr>
<td>ML</td>
<td>Medial-Lateral</td>
</tr>
<tr>
<td>ms</td>
<td>Millisecond</td>
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<tr>
<td>MS</td>
<td>Make Step</td>
</tr>
<tr>
<td>MVC</td>
<td>Maximal Voluntary Contraction</td>
</tr>
<tr>
<td>M-mode</td>
<td>Muscle Mode</td>
</tr>
<tr>
<td>N</td>
<td>Newton</td>
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<tr>
<td>NMF</td>
<td>Non-Negative Matrix Factorization</td>
</tr>
<tr>
<td>nME</td>
<td>Non-Motor Equivalent</td>
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<tr>
<td>ORT</td>
<td>Geometric subspace Orthogonal to UCM</td>
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<tr>
<td>PCA</td>
<td>Principal Component Analysis</td>
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<tr>
<td>PD</td>
<td>Parkinson’s Disease</td>
</tr>
<tr>
<td>PV</td>
<td>Performance Variable</td>
</tr>
<tr>
<td>QS</td>
<td>Quiet Standind</td>
</tr>
<tr>
<td>R</td>
<td>Pearson Product-Moment Correlation Coefficient</td>
</tr>
<tr>
<td>R²</td>
<td>Coefficient of Determination</td>
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<tr>
<td>RC</td>
<td>Referent Configuration</td>
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<tr>
<td>S</td>
<td>Second</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SE</td>
<td>Standard Error</td>
</tr>
<tr>
<td>SNPC</td>
<td>Substantia Nigra Pars Compacta</td>
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<tr>
<td>STN</td>
<td>Subthalamic Nucleus</td>
</tr>
<tr>
<td>t&lt;sub&gt;APA&lt;/sub&gt;</td>
<td>Time of APA initiation</td>
</tr>
<tr>
<td>t&lt;sub&gt;ASA&lt;/sub&gt;</td>
<td>Time of ASA initiation</td>
</tr>
<tr>
<td>TSR</td>
<td>Tonic Stretch Reflex</td>
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<tr>
<td>UCM</td>
<td>Uncontrolled Manifold</td>
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<tr>
<td>UPDRS</td>
<td>Unified Parkinson’s Disease Rating Scale</td>
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<tr>
<td>V&lt;sub&gt;ORT&lt;/sub&gt;</td>
<td>Variance within ORT</td>
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<tr>
<td>V&lt;sub&gt;UCM&lt;/sub&gt;</td>
<td>Variance within UCM</td>
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\( \Delta \text{COP} \) – Change in Center of Pressure
\( \Delta M \) – Change in Muscle Modes Magnitude
\( \Delta V \) – Index of Synergy
\( \Delta V_Z \) – Z-transformed Index of Synergy
\( \Delta \Delta V \) – Change in Index of Synergy

\( \alpha \text{-MN} \) – Alpha Motor Neuron
\( \lambda \) – Threshold of the Tonic Stretch Reflex
\( \mu \) – Mean of Data Distribution
\( \sigma \) – Standard Deviation of Data Distribution
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CHAPTER 1

Introduction

1.1 Problem statement

The ability to control the stability of natural actions involving multi-element (multi-muscle, multi-digit, and multi-joint) systems is one of the main features of the human motor control system. The neural mechanisms and substrates of this feature enable the central nervous system (CNS) to successfully interact with the environment and guide the intended actions despite the poorly predictable environmental conditions and imperfect knowledge of intrinsic body states. Various methods have been suggested to quantify the stability (ability to return to a state or trajectory following a small perturbation) and agility (ability to initiate or change an action quickly) of human movements, such as the inter-trial variance analyses based on the uncontrolled manifold (UCM; Scholz & Schöner, 1999) hypothesis, analysis of motor equivalence, response to the application of small transient perturbation, and drifts in movement performance over time. Both feedback and feed-forward mechanisms have been suggested for controlling the stability of actions (Belen'kiĭ et al., 1967; Massion, 1992, 1998; Santos et al., 2010a, 2010b; Todorov & Jordan, 2002). Impairment in controlling the stability of actions is one of the consequences of many neurological disorders such as Parkinson’s disease (PD). Falls, stuttering, illegible writing, and dropping objects are some consequences of loss of stability of motor performance, while inability to initiate a movement quickly is a consequence of lost agility. For example, a trivial everyday action such as keeping the vertical posture and preventing falls can become a challenge for patients with impaired control of stability. Indeed, a comprehensive coordination among all of the involved effectors such as muscles, joints, and digits is needed to maintain the stability of every day actions with varying body states and unpredictable environmental perturbations.
Studies have suggested two main impairments in the control of action stability as a result of neurological disorders: (1) maintaining movement stability during steady-state tasks; and (2) showing agility when a quick action or reaction is required, which are likely to have different underlying pathophysiological mechanisms (Falaki et al., 2017; Jo et al., 2016a). Altered patterns of coordination among involved effectors have been seen in patient populations as compared to the patterns observed in healthy individuals. Patients may adopt stereotypical patterns to perform motor actions which are less effective and less flexible in response to perturbations (Ambati et al., 2016; Brown & Almedia, 2011; Horak & Diener, 1994; Sainburg et al., 1995). Agility is reflected in feed-forward adjustments of the stability (anticipatory synergy adjustments, ASA) or controlled loss of stability in order to perform a desired quick action (Olafsdottir et al., 2005; Zhou et al., 2013).

Recently, an important concept to quantify task-specific stability has been introduced (Latash et al., 2007; Schöner, 1995). This concept, which is based on the idea of abundant degrees of freedom (Gelfand & Latash, 1998; Latash, 2012a), assumes that the CNS is able to organize the same set of effectors (digits, joints, muscles, etc.) to stabilize different task-specific salient performance variables. Within this concept, synergies are defined as hypothetical neural organizations of multiple elements that provide stability of task-specific performance variables. This definition implies that the CNS channels the variation in the multi-dimensional space of elements into directions that do not affect the task performance. If so, the inter-trial deviations of elemental variables are expected to be higher in directions that do not affect the salient performance variable. This concept has been applied to dissimilar tasks involving different effectors such as multi-digit object manipulation, multi-joint reaching, and multi-muscle whole body tasks. Although the concept of motor synergies has a solid theoretical background and its practical utility to quantify stability has been shown in a few cases of movement disorders (Latash & Huang, 2015; Latash et al., 2010), its application in clinics to quantify impairments in the control of stability has been limited.
This dissertation mainly aims to investigate changes in motor coordination that happen with Parkinson’s disease (PD) and explore effects of available treatments on stability and agility of whole-body actions. We investigated effects of PD and dopamine-replacement medication on the indices of synergic control (stability and agility) of whole-body postural tasks using electromyographic (EMG) data. We investigated effects of deep brain stimulation (DBS) on indices of synergic control across dissimilar tasks that span the spectrum of everyday actions, from multi-muscle whole-body to multi-finger force production tasks, to explore the existence of systemic neural mechanisms of synergic control. Finally, we tested effects of changes in visual scene just prior to the gait initiation on synergy indices to explore relations between stability and agility of actions in PD, and freezing of gait.

The application of the synergy analysis to clinical studies is important as it can provide us with indices of stability of motor actions (indices of synergies) that may be used as a theory-based, quantitative, and objective tool to assess the emergence of postural instability and quantify effects of treatments on balance. Results from assessing patients with this method may provide insights into the underlying neurological mechanisms of postural stability and effects of PD on these mechanisms. These insights can serve as a clinical tool to optimize treatment and rehabilitation of motor deficits and improve patients’ quality of life. Particularly, these indices may serve as early biomarkers of PD, a hypothesis which needs more investigations.

1.2 Goals of the dissertation

The main focus of this dissertation is to quantify changes in multi-muscle synergies that stabilize the vertical posture in PD patients, explore the relations between stability and agility of actions in PD, and try to link these effects to neural structures. The underlying neural mechanisms of synergy formation and effects of neurological disorders on these substrates are still unknown. Although there are several recent studies that have shown impaired motor synergies in disorders with impaired stability of action (Jo et al., 2015; Park et al., 2012, 2013a; Reisman & Scholz, 2003), yet
the synergic control of movements in patients with motor disorders is a major unexplored field of study, which can potentially provide a framework to quantify impairments in motor coordination. These studies underscore the importance of subcortical structures and basal ganglia in the proper control of movement stability. Identifying effects of these substrates on motor performance might lead to better understanding of the underlying mechanisms of controlling movements and developing novel treatments.

Importantly, the methodology for analysis of synergies might provide a theory-based and objective tool to quantify balance impairments and to predict the emergence of postural instability in PD patients. Postural instability and its associated symptoms usually emerge as the disease progresses, while the analysis of multi-muscle synergies may provide a sensitive biomarker for early diagnosis of balance problems. Early biomarkers of PD have potential utility for clinical research and practice, and would provide crucial information for making practical decisions on treatment and prevention plans for individual patients (Latash & Huang, 2015; Miller & O’Callaghan, 2015; Olanow & Obeso, 2012).

Studies that are included in this dissertation are outlined as follows. With the exception of the final study, which as of the time of writing (August 2018) is under the preparation to be submitted to a peer-reviewed journal, all other ones have been published in peer-reviewed journals.

1.2.1 Impaired multi-muscle synergies in Parkinson’s disease

In this study (Chapter 4), we explored whether multi-muscle synergy indices that stabilize the center of pressure (COP) coordinates in the anterior-posterior direction (COP_{AP}) are able to identify balance impairments in PD patients without clinically identifiable postural problems. For this purpose, we investigated effects of a self-initiated postural perturbation, which was generated by releasing a relatively light and brick-shaped load from fully extended arms, on multi-muscle synergy indices. Synergy indices were compared between a group of patients at Hoehn and Yahr (HY) stage $\leq$ 2 and healthy age-matched controls. In order to quantify synergy indices, we analyzed the structure of
inter-trial variance by identifying the mapping (Jacobian; Krishnamoorthy et al., 2013 b; Danna-Dos-Santos et al., 2007a) between changes in a low-dimensional set of elemental variables (M-modes, muscle groups with parallel changes in activation levels; Krishnamoorthy et al., 2013a) and resulted changes in COP$_{AP}$. We expected (1) lower synergy indices in PD patients during steady-state (quiet standing) and (2) significantly smaller ASAs in PD patients in preparation to the self-triggered perturbation as compared to controls. These differences were seen only in the synergy space and not in the kinematic variables obtained from the force platform or the variables computed from the muscle activation space such as anticipatory postural adjustments (APA; Belen'kiĭ et al., 1967; Massion, 1992).

1.2.2 Effects of dopamine-replacement medication on multi-muscle synergies

In this study (Chapter 5), we explored effects of dopamine-replacement medication on multi-muscle synergies stabilizing COP coordinates and their feed-forward adjustments in preparation to a self-initiated postural perturbation. Patients at H&Y stage II and III performed whole-body postural tasks both off- and on-medication while standing on a force platform. Based on an earlier study (Park et al., 2014), we expected that (1) dopamine-replacement drugs would result in a higher synergy index during steady-state and (2) significantly larger ASAs in preparation to the self-triggered perturbation. Larger ASAs can be interpreted as increased movement agility (Latash & Huang, 2015). Larger changes in the component of the inter-trial variance that does not affect the performance variable suggests that medication may lead to a more flexible behavior without adverse effects on precision of the performance with respect to COP$_{AP}$ coordinates. Medication also led to more consistent organization of M-modes.

1.2.3 Motor equivalence and structure of inter-trial variance

Inter-trial analysis of variance requires multiple trials at each task, which may not be feasible for some older participants and patients with neurological disorders. In this study (Chapter 6), we compared two types of analysis of motor synergies, the more common inter-trial (inter-cycle) analysis
of variance and the recently developed method exploring motion in different directions within the M-mode space (analysis of motor equivalence; Mattos et al., 2011, 2013, 2015). Analysis of motor equivalence quantifies the magnitude of the motion in the elemental variables space within the direction that does not affect the task (motor equivalent: ME) and does affect (non-motor equivalent: nME). Inter-cycle variances, and ME and nME components across consecutive body-sway cycles were quantified during whole-body sway task. Although both analysis of inter-trial variance and analysis of motor equivalence provide proxies of action stability (Latash, 2016, 2017), however they are not identical and differ in statistical properties of their corresponding set of metrics (Mattos et al., 2015). This study showed that both methods result in correlated metrics of stability that show similar effects of PD and medication. Results suggest that analysis of motor equivalence has the potential of developing into a method that requires only a few trials to produce indices of muscle synergies and becoming a broadly used clinical measure to analyze problems with action stability.

1.2.4 Effects of deep brain stimulation on synergic control of actions

In this study (Chapter 7), we explored effects of DBS in PD patients on indices of synergic control during dissimilar tasks involving different set of effectors (multi-finger force production and multi-muscle postural tasks) to explore generality of PD-related changes in synergies. Patients performed hand and postural tasks both off- and on-DBS in a counter-balanced design. Although we expected DBS to improve both stability during steady-state and agility in preparation to a quick action, but patients showed effects of DBS only on indices of agility. Our second aim was to investigate the generality of synergic control across different tasks, and we expected to observe systemic deficits in co-varying indices between two tasks. Results suggested that DBS is likely to result in a combination of chronic and acute effects.

1.2.5 The synergic control of gait initiation in PD

In this final study (Chapter 8, unpublished as of July 2018), we aimed to explore the utility of inter-trial analysis of synergies to quantify indices of COP stability and its modulation in preparation
to stepping. This study is potentially important for predicting the emergence of episodes of freezing, a major disabling sign of PD. A couple of recent studies of PD patients led to the hypothesis that reduced ASAs may reflect mechanisms that also contribute to freezing of gait (FOG) and other actions (Falaki et al., 2016; Park et al., 2012). Indeed, if a person is unable to destabilize a salient performance variable in preparation to an action, this variable may be too stable to show a desired change. Step or gait initiation is associated with a pattern of relatively quick COP shifts with the purpose to unload the stepping foot and generate moments of force contributing to the desired body motion (Breniere and Do, 1986; Crenna and Frigo, 1991; Halliday et al., 1998). In this study, PD patients and healthy age-matched controls started their gait in two different conditions: (1) looking straight forward and stepping (Step condition), (2) looking 45° to the left, turning the head to look straight forward, and stepping (Turn condition). Turning the head caused changes in the visual scene, which could contribute to freezing. We compared synergy indices of stability and agility in both anterior-posterior and medial-lateral direction to explore whether turning the head and the resultant changes in the head-centered frame of reference would affect movement agility in PD patients. We found lower indices of stability during steady-state and agility in preparation to gait initiation in the patient group compared to age-matched controls. The patient group showed higher sensitivity (a larger drop in the indices of both stability and agility) to the change in the visual scene during the Turn condition. Both ASAs and indices of stability during steady-state were larger in the medial-lateral direction. While results indicate that changes in the visual scene prior to the gait initiation can reduce stability and agility and potentially cause freezing, other factors, including effects of the vestibular system, could contribute to the findings. A more detailed experiment considering both changes in visual and vestibular information is needed to confirm result of this experiment. This information can shed light on the mechanisms of freezing that ultimately can reduce the number of falls in PD and elderly populations and prevent its devastating consequences.
1.3 Related publications

Results from the above mentioned studies, with the exception of the last one, are published as peer-reviewed articles. The investigation of effects of PD on synergic control of posture patients without clinically identifiable postural problems was published in 2016 in *Gait & Posture* (volume 44) as “Impaired synergic control of posture in Parkinson’s patients without postural instability”. The investigation of effects of dopamine-replacement medications on synergy indices was published in 2017 in *Journal of Electromyography and Kinesiology* (volume 33) as “Dopaminergic modulation of multi-muscle synergies in postural tasks performed by patients with Parkinson’s disease”. Comparing posture-stabilizing multi-muscle synergies obtained from analysis of inter-cycle variance vs. those that were obtained from analysis of motor equivalence was published in 2017 in *Experimental Brain Research* (volume 235(7)) as “Motor equivalence and structure of variance: multi-muscle postural synergies in Parkinson’s disease”. Investigation of effects of DBS on synergic control in a group of PD patients across dissimilar multi-digit accurate force control and multi-muscle whole-body tasks was published in 2018 in *Clinical Neurophysiology* (volume 129(6)) as “Systemic effects of deep brain stimulation on synergic control in Parkinson’s disease”. 
CHAPTER 2

Literature Review

2.1 Neural control of movement

The neuromusculoskeletal system, that forms the substrates of the human motor control, consists of a huge number of components, e.g., 86 billion neurons and 85 billion non-neuronal cells in the brain (Azevedo et al., 2009; reviewed in Herculano-Houzel, 2009), 1 billion neurons in the spinal cord (Kalat, 2011), about 200 bones, and more than 600 skeletal muscles. One of the main goals of the research on motor control is to understand how the CNS controls movements and particular functions of different brain regions. In the nineteenth and twentieth centuries, there were a significant advances in techniques used to study motor control system, for example brain imaging techniques augmented maps of the brain functional connectivity. However, the nature of the information that transfer between brain areas and parameters that are transmitted between the CNS and the peripheral structure are still unknown. Currently, there are two major approaches that are used to study and describe the neural control of movements.

One of these approaches, which is based on the control theory, assumes that the CNS performs computations to find optimal commands to generate a movement, while taking into account the interactions among body segments and between the body and the environment. During the process of computation, the controller has to solve a set of problems, for example consider a simple task of reaching an object. The first step is to find a configuration of body segments capable of touching the target, which is not unique considering the degrees of freedom in human body; inverse kinematic problem (Mussa Ivaldi et al., 1988). Second step consists of finding patterns of joint torques capable of moving body segments along the planned trajectories, which is known as inverse dynamic problem (Atkeson, 1989; Hollerbach & Atkenson, 1987). Third step is to find out patterns of muscle forces that produce the computed torques considering interaction torques (Zatsiorsky, 2002). Fourth and
fifth, each muscle activation level and the appropriate input into its alpha motor neuron (α-MN) should be computed considering the fact that reflexes would also contribute to the muscle activation. At each of aforementioned steps, CNS needs to deal with an ill-conditioned problem that has an infinite number of possible solutions. A recent version of model-based approaches assumes that CNS acquires neural models of internal body states and the environment (called ‘direct models’ or ‘forward internal models’, Bhushan & Shadmehr 1999; Kawato 1999) to predict the system behavior in response to the descending motor commands, such as forces and consequent torques in response to the activity of individual muscles (Shadmehr et al., 2010; Wolpert & Ghahramani, 2000). It has been suggested that sending descending commands simultaneously to both the motor system and the sensory one (cf. “reaffereence”; von Holst & Mittelstaedt 1950) enables the CNS to overcome long delays in feedback loops and make predictions of the resultant motor outputs. While it is a tempting idea to assume computations in the CNS similar to those in robotics, but the hierarchical structure and complexities of the neuromusculoskeletal system do not allow it to control actions based on the control theory. Instantaneous muscle force-velocity-length dependency, slowness of action potentials propagation, unclear relations between body states and related sensory inputs, and threshold based action potential generation in neurons, make the prospect of accurate predictions of internal body states and environment in a timely manner unlikely, and propose sever doubts about the fidelity of such an approach.

Considering the aforementioned complexities of the neuromusculoskeletal system, the second approach assumes that no computation is performed within the brain. This method uses laws of physics and neurophysiology (Kugler & Turvey, 1987; Latash, 2010, 2010a, 2014) to describe the interactions within the neuromuscular system and in contact with the environment. Equilibrium-point hypothesis (EPH; Feldman, 1986) is a particular example of this approach. EPH proposes a mechanism for smooth control of movements using subthreshold depolarization of α-MN pools. Within this approach, CNS controls the threshold of the tonic stretch reflex (TSR), known as λ.
Changes in $\lambda$ links changes in muscle force production to changes in muscle length and external conditions.

### 2.1.1 The equilibrium-point hypothesis

According to this theory (Feldman, 1986; Feldman & Levin, 2009), the CNS controls the threshold of the TSR ($\lambda$). The TSR is a reflex mechanism that relates the active force produced by a muscle to the muscle’s length. Lengthening of a muscle would result in an increase in the output from sensory receptors, which subsequently can excite $\alpha$-MNs innervating the muscle. The increased activity of the muscle through this feedback loop will subsequently increase the muscle’s resistance to the lengthening. Muscles are always subject to external forces and perturbations. By specifying a certain $\lambda$, the muscle-load system will move to an equilibrium state at a certain muscle length, which is specified by $\lambda$ and the external forces acting on the muscle. At equilibrium, the active force that is produced by the muscle is equal to the external forces acting on the muscle. According to this hypothesis, a change in $\lambda$ or a change in external forces will change the length of the muscle and move the system to a new equilibrium related to the external conditions and the force-length invariant characteristic of the muscle. *Figure 2.1* illustrates the muscle force-length relation as a function of TSR and its application to a joint crossed by one flexor and one extensor.

According to *Figure 2.1A*, at an initial equilibrium point, EP$_1$, the force produced by the muscle is equal to a certain load that acts on the muscle given $\lambda$ ($\lambda_1$), $F_{\text{muscle}}(L_1, \lambda_1) = F_1$. If the CNS changes the TSR threshold coordinate ($\lambda$) from $\lambda_1$ to $\lambda_2$, the muscle force at a given muscle length will change till a new equilibrium, EP$_3$, is established, where $F_{\text{muscle}}(L_3, \lambda_2) = F_2$. Note that whereas muscle length at EP$_1$ ($L_1$) and at EP$_3$ ($L_3$) are different, $F_{\text{muscle}}(L_1, \lambda_1)$ and $F_{\text{muscle}}(L_3, \lambda_2)$ are equal. Therefore, CNS can effectively change the desired muscle length by changing $\lambda$. Similarly, a change in external forces acting on the muscle will change the length of the muscle till a new equilibrium is established, where $F_{\text{muscle}}(L_2, \lambda_2) = F_2$. 
Figure 2.1 Control of a single muscle (Panel A) and a single joint (Panel B) using the equilibrium-point hypothesis. At equilibrium, muscle active force equals to the external forces that act on the muscle. FL represents a flexor muscle while EXT represents an extensor one. Figure is adapted from Latash, 2012b.

Figure 2.1B illustrates the application of the EP hypothesis to a single joint that is crossed by an agonist and an antagonist muscle. The net behavior of the force-length invariant characteristic of the muscle, specified by the threshold of the TSR for the flexor ($\lambda_{FL}$) and the extensor ($\lambda_{EX}$), defines the joint’s behavior. The angular equilibrium position of the joint (EP), at a specific combination of the joint angle and the external torque. Sometimes, this points is referred to as the reciprocal command (r-command), while the distance between $\lambda_{FL}$ and $\lambda_{EX}$ is referred to as the co-contraction (c-command). Reciprocal command determines the amount of force produced by each of the flexor and extensor muscle, i.e., if one muscle produces more force, the other one would produce less. Co-contraction command results in the activation of both the flexor and extensor muscles. Joint characteristics, the torque produced at an angle ($\alpha$) can be effectively shifted by the r-command while the c-command rotates it. Increasing co-contraction increases the joint resistance to angular perturbations.

2.1.2 Control with referent configuration hypothesis

The Referent Configuration (RC) Hypothesis (Feldman, 2009, 2015) generalizes the EP hypothesis to describe the intentional control of natural movements including multi-muscle, multi-joint whole-body actions. The RC defines a set of references for salient performance variables and the
configuration of body segments. Within this hypothesis, the neural variables controlled by the CNS are conceptualized as task specific referent configurations ($RC_{\text{TASK}}$) in a hierarchical system. In such a hierarchically controlled system, defining $RC_{\text{TASK}}$ defines other RCs at lower levels because of neural few-to-many mappings, which ultimately result in RCs at the level of single muscles and $\alpha$-MN pools. At this level, RCs are equivalent to specifying $\lambda$ (cf. Feldman’s 1986 lambda-model). Any discrepancy between RC and the actual configuration drives the corresponding motor neurons above their threshold; ultimately leads to non-zero activation of muscles that move the body towards RC till an equilibrium state emerges.

Similar to the EP hypothesis, a shift in the RC will result in either movement towards the new RC or force production in the direction of the new RC if the movement is blocked. As movement and force production are likely outcomes of the same neural mechanisms, RC hypothesis predicts equifinality. According to equifinality, a system will return back to its initial equilibrium as long as no change happens in the RC. Equifinality and its violations have been a topic of interest in the field of motor control (DiZio & Lackner, 1995; Hinder & Milner, 2003; Lackner & DiZio, 1994). Whereas, violations of equifinality have been discussed as an evidence against the control with spatial RCs, observations of equifinality (Bizzi et al., 1976; Kelso & Holt, 1980; Latash & Gottlieb, 1990; Schmidt & McGown, 1980) have been taken as evidence for RC hypothesis. Observation of systematic violations of equifinality suggests that the body’s referent configuration might drift towards its actual configuration (Ambike et al., 2014; Reschehtko et al., 2014, 2015; Wilhelm et al., 2013; Zhou et al., 2014).

### 2.1.3 Motor redundancy

Bernstein (1967) formulated the problem of motor redundancy by means of kinematic redundancy. Since then, motor redundancy has been a main issue in the field of neural control of movements. This apparent problem arises because, at any level of description of natural movement, the number of contributing elements is larger than the number of elements required to perform the
task in a particular way (or the number of constraints imposed upon the ongoing task). As a result, there is an infinite number of solutions satisfying a given motor task and the means by which movements are performed in a single particular way is unclear. A classical approach to solve this problem assumes that the CNS renders motor actions non-redundant by freezing redundant degrees of freedom (DoF). Although this approach seems to be feasible at a macroscopic level (for example, selecting the hand with which to reach a target), however the number of potentially involved elements increases dramatically as the level of description becomes microscopic. For example consider selecting a combination of ions required to generate an action potential which seems unfeasible. As a result elimination of redundant DoF has been criticized (Latash, 1996).

Another approach to the problem of motor redundancy is based on optimization principles (reviewed in Prilutsky & Zatsiorsky, 2002) and enables the motor control system to deal with redundant DoF without explicitly select a set of DoF. This scheme assumes that the neural controller administers some optimality criteria—such as minimizing movement time, torque, energy, or the noise in the CNS—to perform a motor task in an optimal (or sub-optimal) way among apparently redundant solutions (Harris & Wolpert, 1998; Nelson, 1983; Wolpert et al., 1995). This scheme has been of great interest in the field of motor control, despite the lack of agreement on the optimization principles and cost functions used by the CNS.

Whereas optimization techniques have modeled nicely certain movement behaviors and have given valuable insights, assuming a physiological motor system analogous to an optimal controller can has been criticized. Often, motor behaviors do not have an obvious and straightforward associated costs. So, as the task and associated cost become more sophisticated, it seems that the choice of the optimality criterion and associated cost function become more arbitrary, which makes it more questionable that the motor control system has access to the metrics of such cost functions. Moreover, in the current motor control methodology, any experimental result, commonly with respect to the energetic or performance cost, can be taken as evidence for a particular optimality criterion. As a
result, approaches based on the optimal control theory do not necessarily generate consistently falsifiable hypotheses, as observations that can serve as evidence for optimality are not clear (Diedrichsen et al., 2010). Recently optimal feedback control (Todorov & Jordan, 2002) and Analytical Inverse Optimization (ANIO, Niu et al., 2012; Terekhov et al., 2010) approaches have been proposed based on the optimal control theory. Optimal feedback control approach administers the theory of motor coordination to coordinates redundant biomechanical DoF to achieve a common goal reliably and repeatedly. ANIO has been proposed as a method to determine an optimality function based on experimental data, which reduces the number of assumptions made by the experimenter to model the optimality criterion. However, this approach lacks a physiological justification for the fitted criterion.

Recently, an alternative view of the apparently redundant DoF has been proposed that recontextualize it as the “bliss of motor abundance” (Gelfand & Latash, 1998; Latash, 2012a). Within this principle, CNS takes advantage of apparently redundant DoF to facilitate families of solutions and ensure the stability of movements. As all solutions are equally able to solve the ongoing action, the task solution can emerge through the interaction of the current status of the motor system and the environment (Latash, 2012a). Motor system can exhibit a stable level of performance as a result of this abundance and the consequent flexibility in selecting a particular solution. It has been hypothesized that, within the hierarchically structured motor control system, the CNS sets only a relatively small number of neutrally controlled variables corresponding to the constraints imposed upon the motor action to be produced (Latash, 2010b). It is envisioned that a hierarchical series of few-to-many mappings enable the motor control system to engage relevant DoF through the interaction between the internal body states and the external environment rather than explicitly specifying them through the neural controller. Engaging relevant DoF through this principle is in contrast with the classical approaches of DoF reduction.
2.2 Uncontrolled manifold hypothesis and task-specific stability

Experimentally, human motor behavior can be observed and analyzed at different levels of the motor system. Selecting the level of analysis would also specify how elemental variables contribute to the task performance variable(s). In a redundant system, this process can be considered as projecting elemental variables from a high-dimensional space onto the task (output) variables in a lower dimensional space. As a result of this mapping, changes in elemental variables may result to different amounts of change or even no change in the task variable(s), i.e., there can be a family of solutions with different combinations of elemental variables that result in the same output variable(s).

The Uncontrolled Manifold (UCM) Hypothesis (Sholz & Schöner, 1999) formalizes this concept. If elemental variables reside in an N-dimensional space and task constraints produce a P-dimensional space, there is a manifold with dimensionality of N – P (denoted as the UCM space) in which changes in elemental variables result in no change in the task space. Task performance is preserved as long as the values of the elemental variables fall into the UCM. A natural result of this hypothesis is that the motor system is free to vary along the UCM directions, i.e., the motor control system does not need to control the elemental variables while they lie along the UCM (Sholz & Schöner, 1999; Todorov & Jordan, 2002). Figure 2.2 demonstrates a task of producing a constant force with two effectors ($F_1$ and $F_2$) at two levels ($C_1$ and $C_2$), and different possible cloud of data points. UCM$_1$ is the solution manifold of $C_1$ while UCM$_2$ is the relevant solution manifold of $C_2$.

Considering the imperfect knowledge of the internal body states and unpredictable environment, providing the stability of actions is a constant challenge in implementing every day movements. Defining and quantifying stability of human actions is a topic of great importance that can help us to understand how the motor control system implement and control movements. It also can help to quantify motor deficits and impairments in the control of movements resulting from neurological disorders.
Figure 2.2 An illustration of the idea of the uncontrolled manifold (UCM). Ellipses at points 1, 2, and 3 show possible distributions of repetitive trials of a force-production task with two elements ($F_1$ and $F_2$). At point 1, inter-trial variance is mostly along the orthogonal to UCM (ORT) space, while at point 3 is mostly along the UCM space. Whereas the solid arrow between ellipse 1 and ellipse 2 demonstrates non-motor equivalent (nME) motion, the dashed arrow between ellipse 2 and ellipse 3 has both nME and motor equivalent (ME) displacements. Figure is adapted from Mattos et al., 2015.

2.2.1 Motor coordination and synergies

If a person performs a same task repeatedly, numerous trajectories would be observed. These variations are inevitable result of unpredictable processes (imperfect knowledge of internal body states and time-varying environment) that can affect the task. These variations were originally demonstrated by Bernstein in which he asked professional blacksmiths to hit a chisel by a hammer. In this classical Experiment, Bernstein observed smaller amount of variation in the end-point trajectory as compared to the trajectory of individual joint angles. The UCM hypothesis (Scholz & Schöner, 1999) has been introduced as a theoretical method to partition the observed inter-trial variance into directions that does not affect a salient important task-specific variable (UCM space) and directions that does affect the task output (Geometric subspace Orthogonal to UCM). The variance component within the UCM space is denoted as $V_{UCM}$ and within the ORT space is denoted as $V_{ORT}$. It is hypothesized that the motor control system limits the variations in directions that do affect the task performance (task-specific stability) as compared to the variation within the UCM space (Schöner, 1995).

Based on the principle of abundance and UCM hypothesis, the concept of motor synergy has evolved over the past 20 years (reviewed in Latash, 2012a; Latash et al., 2007). The term “synergy”
(“work together” in Greek) has been used in the literature with different ways. Clinically, synergy usually means a pathological, stereotypical pattern of muscle activations that interfere with purposeful movements (DeWald et al. 1995), which are seen in patients with neurological disorders, especially with cortical stroke (Bobath, 1978; Brunnstrom, 1970; DeWald et al., 1995). This definition has a strong negative connotation. Another meaning of synergy in motor control, refers to a group of variables with proportional scaling of changes over time or with changes in task parameters (d’Avella et al. 2003; Ivanenko et al. 2004; Ting and Macpherson 2005; Tresch & Jarc, 2009). It has been assumed that organizing these variables into groups controlled by the CNS can alleviate the problem of motor redundancy. In this dissertation, to avoid terminological confusion, we address such groups as modes and consider them as elemental variables for further analyses within the UCM hypothesis. Within this context, synergy is defined as neural organizations of elements (such as joints, digits, and muscle groups) that co-vary with each other to provide task-specific stability of important task variables (reviewed in Latash, 2007, 2016). Using this concept, the existence of a synergy implies that the inter-trial component of the variance within the ORT space is relatively smaller that the variance within the UCM (Latash et al., 2002a). This definition goes hand-in-hand with the inequality $V_{UCM} > V_{ORT}$. Figure 2.2 illustrates possible synergic (cloud of data points 1) and non-synergic (cloud of data points 3) distributions of inter-trial variance associated with the task of producing an accurate constant force with two effectors. Because of possible additional constraints, such as optimizing a particular cost associated with the motor system, only a range of solutions would be observed (Park et al., 2010).

Recently, another set of metrics (motor equivalence analysis) has been developed to quantify a potential consequence of task-specific stability within the framework of the UCM hypothesis (Mattos et al., 2011, 2013, 2015; Scholz et al., 2007), which theoretically can be quantified in single trials. Analysis of motor equivalence quantifies displacement of an abundant system in directions that affects and does not affect the task. The within UCM component (motor equivalent, ME) has no
effect on the output variables, while the ORT component (non-motor equivalent, nME) affects the task performance. This analysis can be performed between epochs across two consecutive trials (Falaki et al., 2017) or during a single trial (Mattos et al., 2015). According to the RC hypothesis, motor control system tends to minimize discrepancies between RC and actual body configuration. This process might underlie maintaining the pointing trajectory that was observed in standing subjects (Tomita et al., 2016). ME and nME components are displacements as they are defined as the motion of the system from one state to another state between two time points. While it seems that \( V_{UCM}/V_{ORT} \) and ME/nME are very similar metrics, but they are not directly related and might have statistically different distributions (Mattos et al., 2015). Whereas large ME motion can be potentially a direct outcome of task-specific stability and compatible with the synergic variance signature, ME > nME is not necessarily a consequence of a synergy stabilizing stability of salient task outputs (\( V_{UCM} > V_{ORT} \)). Figure 2.2 demonstrates this fact as there is no specific relation between the ME/nME motion from point 1 to point 2, between points 2 and 3, and the inter-trial variance at points 1, 2, and 3. Note that analysis of variance requires multiple trials to obtain an estimate the cloud of data points and the relative amount of \( V_{UCM} \) and \( V_{ORT} \), but ME and nME motions theoretically can be obtained in a single trial. However, at this point, it is not clear how many trials is needed for the motor equivalence analysis to reach asymptotic stability.

2.2.2 Anticipatory synergy adjustments

Although movement stability is crucial for everyday actions considering the unpredictable changes in the body states and the environment, however there are cases that high stability seems counter-productive. For example, having a very high stability seems to be undesirable when a person wants to perform a very quick movement. As a result, depending on the task context, high movement stability can be detrimental, e.g., during very fast movements, or beneficial, e.g., during steady-state tasks. Recently, it has been shown—within the concept of motor synergies—that the CNS is able to adjust synergies without changing the overall output of the motor system (reviewed in Latash, 2008;
This ability represents an important feature of feed-forward control in the motor control system that enables it to purposefully adjust the stability properties of a task variable prior to initiate a quick action, i.e., possess movement agility—initiate a quick action from steady state (reviewed in Latash & Huang, 2015). Otherwise, the system might need to act against the stability that it has produced (Hasan, 2005). Attenuation of synergies in preparation of a quick action, denoted as anticipatory synergy adjustments (ASAs), has been seen across hand (Olafsdottir et al., 2005; Shim et al., 2006) and postural tasks (Klous et al., 2011; Krishnan et al., 2011). In healthy humans, ASAs have been seen about 200-300 ms prior to the task initiation (Olafsdottir et al., 2005; Shim et al., 2006). In particular, ASAs have been reported to happen in advance of anticipatory postural adjustments (APAs; reviewed in Massion, 1992) and in case of postural perturbations with unpredictable directions when the classical anticipatory postural adjustments were absent (Piscitelli et al., 2017). Impaired ability to modulate synergies (delayed and reduced ASAs) has been reported in patients with even mildly impaired motor coordination (Olafsdottir et al., 2007a). It is hypothesized that inability to attenuate the stability properties, in patients with neurological disorders, may lead to reduced agility or even to such consequences as rigidity and episodes of freezing (reviewed in Latash & Huang, 2015).

2.3 Postural control in human

Except for the term body sway (sway), definitions that are given by Zatsiorsky (2002) will be used for the terms used in this dissertation, such as body posture, postural sway, center of pressure, quiet stance, and postural perturbation. The term “body posture” refers to the body configuration, that may or may not change, in the three dimensional space. The term “postural sway” denotes small variations in the configuration of the body when a person maintains a certain body posture. The term “Center of pressure” (COP) is the point where the total vector summation of the ground reaction force applies to the body. The term “postural perturbation” represents any force (with external or
internal origin) that applies to the body and causes perturbation that may change the body configuration. Forces with an external origin are generated by the environment, while internally originated forces are generated due to the movement of a body segment that exert mechanical forces/torques to other body segments. The term “quiet stance” is used when a person maintains an upright body posture without any other motor task or postural perturbations. The term “body sway” refers to the whole body continues sway in the anterior-posterior or medial-lateral direction when a person sways voluntarily about the ankle joints.

Controlling the postural actions is a complex and intricate system as many anatomical structures participate in postural control, such as cerebellum, spinal cord, vision, vestibular system, etc. Exploring this system and the underlying mechanisms has been a topic of great interest in the movement science literature. Sherrington (Sherrington, 1910) used decerebrated cat specimens to study the reflex mechanisms and means by which these reflexes are mediated through the midbrain and the spinal cord. Decerebration is a technique that allows to eliminate cerebral and higher CNS regions and isolate the midbrain and spinal cord. Sherrington performed this technique between superior and inferior colliculi and observed increased activity of extensor and other muscles that hold the posture, referred to as “rigidity”. Using deafferentation technique, which disrupting the afferent connection of nerves, resulted in opposite observations. These experiments suggested that the afferent signals have a crucial role in controlling the posture. Whereas Sherrington hypothesized the rigidity of extensor muscles as the substrate of postural control, later studies suggested that postural actions cannot be controlled by means of only reflexes (Aruin & Latash, 1996; Belen'kiĭ et al., 1967; Cordo & Nashner, 1982; Shiratori & Latash, 2000). Moreover, postural adjustments can occur prior to the application of an internal or external postural perturbation in a feed-forward fashion (Aruin & Latash, 1995; Bouisset & Zattara, 1987; Massion 1992).

Nicolai Bernstein suggested formation of synergies for partially controlling human actions including the complex system of postural actions (postural Synergies, Bernstein, 1967). He
considered synergies as building blocks that form motor actions and denoted them as neutrally coordinated structures of muscles and joints to stabilize the body equilibrium in response to an internal or external body perturbation (Alexandrov et al., 1998; Bernstein, 1967) and hypothesized that “movements react to changes in one single detail with a whole series of others which are sometimes very far removed from the former, both in space and in time”. Synergies have been proposed to provide a means by which the CNS might control redundant set of effectors and were explored through proportional changes (over time or space) in large sets of kinematic, kinetic, and EMG variables during movement execution (d’Avella and Bizzi, 2005; d’Avella et al., 2003; Ivanenko et al., 2004; Krishnamoorthy et al., 2003a; Tresch et al., 2006). Whereas many studies considered synergies mainly as co-varied groups of variables, it has been suggested that motor synergies should have a strict definition that links them with the stability and flexibility observed in natural movements (Gelfand & Latash, 1998; Latash, 2008; Latash et al., 2005, 2007; Scholz et al., 2000).

2.3.1 Postural perturbations and falls prevention

Because of the intrinsic instability of the postural system resulted from the organization of body segments along the longitudinal axis, maintaining vertical posture is a very complex and challenging task in the gravitational field. As joints that connect body segments have different axes of rotation, moving one segment produces forces and torques that propagates to other body segments leading to postural perturbations. In addition to the complex interactions among body segments, muscles often cross more than one joint that requires counteraction forces to keep the postural stability (Bolhouis et al., 1998; Jacobs & Macpherson, 1996). However, healthy humans can easily maintain the body posture while performing skilled limb movements and postural actions despite all the challenges that this system faces in terms of postural control.

Several underlying mechanisms have been proposed to counteract perturbations that threat the postural stability. These corrective actions are listed as follows with respect to their latency.

2. Peripheral elasticity of the soft tissue around the joints (also referred to as “preflexes”, Prochazka et al., 2000).

3. Muscles stretch reflexes with the latency about 30-50 ms.

4. Pre-programmed reactions (also referred to as “triggered reactions or long-latency reflexes”) with the latency about 50-100 ms (Cheney & Fetz, 1984; McKinley et al., 1983; Nashner & Cordo, 1981; Phillips, 1969; Tatton et al., 1978).

5. Voluntary actions.

Voluntary movements can pose substantial postural perturbations in particular when performed with large body segments and larger accelerations. These perturbations might cause threats to the stability of the posture because 1) complex interactions among body segments result in propagation of produced forces/torques to other body segments; and 2) changes in the body geometry changes the total mass distribution of the body segments and the coordination of the center of mass (COM; Bouisset & Zattara, 1987; Massion, 1992). It is hypothesized that actions such as rapid arm movements can produce forces and moment of forces that might cause falling by shifting the COM out of the base of support if not compensated by postural muscles (Ramos & Stark, 1990).

However, it seems that the CNS is able to anticipate upcoming postural perturbations and produce anticipatory modulations in the activity of postural muscles. Feed-forward adjustments of the background activity of postural muscles are referred to as anticipatory postural adjustments (APAs, Belen'kiï et al., 1967; Massion, 1992). They were first observed experimentally in standing persons as an increase in the activity of leg muscles 50-100 ms prior to raising the arm (Belen'kiï et al., 1967). Using EMG data, body kinematics, and displacements of the COP, APAs have been documented in different actions, including moving arm, leg, trunk, and head (Breniere & Do, 1986; Cordo & Nashner 1982; Danna-Dos-Santos et al., 2007b; Mouchino et al., 1991), loading and unloading of the
forearm (Aruin & Latash 1995a; Dufossé et al., 1985; Hugon et al., 1982; Laquantini & Maioli, 1989), and loading and unloading of the upper extremities (Aruin & Latash, 1995b; Aruin & Latash, 1996; Piscitelli et al., 2017; Shiratori & Latash, 2000).

APAs can partially compensate effects of an upcoming perturbation by producing mechanical outcomes, e.g., COM shifts, in directions counteracting effects of the perturbation (Bouisset & Zattara, 1987). Although APAs are associated with a postural perturbations, their magnitude seems to be modified with respect to the generated motor action (Aruin 2016; Aruin and Latash, 1995). APAs characteristics depend on several factors: 1) the magnitude of an anticipated postural perturbation; 2) properties of the motor task associated with the perturbation; 3) stability properties of the body posture; and 4) task associated time constraints (Slijper, 2001). While larger APAs are expected in preparation of a larger perturbation (Aruin & Latash, 1996), APAs magnitude depends on the stability of the posture (Aruin et al., 1998; Nouillot et al., 1992) and scales with the amplitude of the action generating a postural perturbation with an internal origin (Aruin & Latash, 1995b). When the posture is highly stable, APAs magnitude reduces or even becomes absent. Moreover, in case of postural perturbations during whole-body cyclical tasks, APAs seem to be associated with the phase of the movement at the time of the perturbation (Hirschfeld & Forssberg, 1991; Krishnamoorthy & Latash, 2005).

2.3.2 Muscle modes and multi-muscle synergies

It has been proposed that the CNS unites muscles into groups and controls these muscles as elemental variables rather than controlling individual muscles independently from each other (Bernstein, 1967; d’Avella et al., 2003; reviewed in Latash 2012a; Tresh et al., 1999). Initially proposed by Bernstein (1967), it has been a long-standing idea that combining individual elements into groups might simplify the problem of motor redundancy in the motor control system, e.g., spinal force fields (Giszter et al., 1993) or muscle synergies (Saltiel et al., 2001; Tresch et al., 1999). However, the number of groups, that are hypothetically controlled by the CNS and observed
experimentally, is more than the number constraints associated with natural motor actions. In another definition, muscle synergies were assumed as a particular example of structural units (Gelfand & Tsetlin, 1966), i.e., ensembles of elements associated with a motor tasks. The term muscle synergies has been used intensively, but with different definitions, in basic and clinical literature, e.g., to study postural control (Allum & Honegger, 1993; Bouisset et al., 1977; Chvatal & Ting, 2013; Crenna et al., 1987; d’Avella & Lacquaniti, 2013; Massion et al., 1992; Nazifi et al., 2017; Robert et al., 2008; Sabatini, 2002; Wang et al., 2015).

One of the commonly used definition of muscle synergies implies a number of muscles that show co-varied changes with task parameters or over the task time duration (d’Avella et al., 2003; Ivanenko et al., 2004; Ting and Macpherson, 2005). Non-negative matrix factorization (NMF) algorithm is a methods that has been widely used in these studies to define groups of muscles with co- vary scaling of their activation among large sets of EMG data. Researchers in favor of this method argue that muscles’ activation is a non-negative quantity and NMF assumes non-negative coefficients to identify muscle groups from independent EMG vectors.

Another definition, which is used along this dissertation, uses groups of muscles with close to parallel scaling of their activation levels as elemental variables that are controlled by the CNS to ensure stability of salient performance variable(s), e.g., COP coordinate. Note that, synergies are defined as hypothetical neural organizations of elements (such as joints, limbs, digits, muscle groups, etc.) that ensures task-specific stability of important performance variable(s) in the hierarchically structured motor control system (reviewed in Latash, 2008, 2016, 2017). Within this definition, the notion of muscle modes (M-modes, Krishnamoorthy et al., 2003a) is used to refer to group of muscles with co-varied scaling of activation levels. M-modes can be considered as hypothetical neural commands to control large muscle groups. As a result, changes in a value (gain) of one M-mode leads to proportional modulations in the activation of all muscles united in that group. This approach uses the context of UCM hypothesis to quantify muscle synergies and describe a system with co-varied M-
modes to preserve task variables. As a result synergies are quantified using the relative amount of the inter-trial variance in the M-mode space that does not affect \( V_{UM} \) and does affect \( V_{ORT} \) the task performance, i.e., existence of a synergy goes hand-in-hand with \( V_{UM} > V_{ORT} \) signature. Because of the inter-trial variance analysis, principal component analysis (PCA) with Varimax rotation and factor extraction is used to identify orthogonal M-modes (Danna-Dos-Santos et al., 2007a; Klous et al., 2011; Krishnamoorthy et al., 2003a; Wang et al., 2006). Note that orthogonal eigenvectors are more convenient for the variance analysis.

Whereas both PCA and NMF based methods are able to identify coherent patterns in large datasets of muscle activity, in case of simultaneous recruitment of several muscle groups, pairwise correlations based methods are unable to accurately identify these patterns. An earlier study, comparing different matrix factorization methods, has shown comparable muscle groups and reconstruction accuracy from NMF and from PCA based analysis with rotation (Tresch et al., 2006).

### 2.4 Human hand and multi-digit synergies

The human hand has an anatomically complex structure, it provides a convenient model to explore redundant motor tasks. Whereas it is capable of performing many complex actions, in isometric force production tasks it can be considered as a parallel chain with four effectors (the index, middle, ring, and little fingers) which provides a redundant system with only a few DoF. It is a very simplified model that does not consider major sources of the complexity of the hand. Indeed, each finger is itself organized by three segments and is articulated by means of several intrinsic and extrinsic muscles. Intrinsic muscles are those that reside inside the hand, while extrinsic ones are located outside of the hand. However, measuring outputs of this simplified model, such as forces and moment of forces, is easy and well-stabilized that provides a particularly attractive multi-elements system for studying motor coordination. Due to these advantages, multi-finger accurate force production or prehensile tasks have been of great interest to explore multi-digit synergies, especially
synergies that stabilize the total force produced by all fingers (Latash et al., 2001; Scholz et al., 2002; Shim et al., 2005).

However, there is limited individuation in movement and forces produced by each finger, e.g., by flexing an individual finger, most often other fingers would accompany the intended finger and flex to some extent. Similar phenomenon happens in an isometric force production task by exclusively one finger at a time, i.e., involuntary forces are produced by non-intended fingers. The interdependence among fingers or lack of individuation is denoted as enslaving (Li et al., 1998; Zatsiorsky et al., 2000) reflecting involuntary contraction of non-intended fingers that can cause co-varied actions among fingers. Considering the separate skeletal structure of each individual finger, limited independent finger motions are due to peripheral and neural factors associated with multi-tendoned and multi-articulated muscles. Whereas enslaving is assumed to happen across a wide range of tasks with different amount of forces (Danion et al., 2003a; Li et al., 1998), it affects mostly the ring finger while the index finger shows the least interdependence. Also, it varies across persons, mainly as a result of age, practice, or disorders (Shinohara et al., 2004; Wu et al., 2013).

Due to the fact that analysis of synergies depends on co-varied modulation of elements, the notion of finger modes was introduced to eliminate the potential effects of enslaving on synergy indices (Latash et al., 2001). Finger modes can be considered as hypothetical motor command that can be independently controlled by the CNS and sent to each of fingers, i.e., they reflect the desired contribution of each finger in multi-digit tasks (Danion et al. 2003b; Latash et al., 2001). Similar to muscle modes, a change in a finger mode produces co-varied motion or force production by all fingers of a hand that depends on the respective contribution of each of fingers. Relations between finger forces can be quantified experimentally and used to link finger forces and finger modes according to \( F = E m \), where \( m \) and \( F \) are vectors of modes and forces, respectively. Enslaving matrix \( (E) \) represents the mapping between modes and forces that can be estimated using single finger pressing tasks. Each mode produces forces in all fingers and, similar to finger forces, is expressed in
newton (N). At any given point in time, the total amount of force produced by modes is equal to the total amount of force produced by all fingers.

Indices of multi-digit synergies have shown sensitivity to aging (Olafsdottir et al., 2007a, 2007b; Shinohara et al., 2003, 2004), practice (Latash & Anson, 2006; Olafsdottir et al., 2008; Wu et al., 2013), and neurological disorders (Latash & Anson, 2006; reviewed in Latash & Huang, 2015). In healthy elderly, synergy indices quantified during multi-digit force production and prehensile tasks and their feed-forward adjustments in preparation of the task have been reduced as compared to the young individuals. These observations have suggested the role of aging in impaired synergic control of action stability (Olafsdottir et al., 2007a, 2007b; Shinohara et al., 2004). Moreover, strength training exercise and practice with specific adjustment of task difficulty may improve the synergic control in elderly population (Olafsdottir et al., 2008; Wu et al., 2013).

2.5 Parkinson’s disease

Parkinson’s disease (PD) is a chronic, progressive neurodegenerative disorder with motor and non-motor symptoms that is caused by progressive death of dopamine-producing neurons in the substantia nigra. This disease, after Alzheimer’s disease, is the second most common age related disorder. More than one million Americans suffer from major motor impairments and other consequences caused by PD, which costs society nearly $27 billion annually. The social, health, and economic cost of PD is expected to rise substantially in the coming decades as the population get older (Obeso et al., 2000; Reeve et al., 2014). Whereas significant progress has been made to control PD related symptoms, patients suffer from a significant degradation of quality of life (Marras et al., 2005) in later stages of the disease as there is no cure for it. Postural instability and freezing of gait (FOG) are the most disabling motor symptoms of PD that emerge with disease progression affecting patients’ independence and quality of life (Marras et al., 2005; Obeso et al., 2000). Many of the most visible symptoms of PD are motor-related. PD is initially diagnosed in clinic based on the presence of
bradykinesia (slowness in executing or problem in initiating movements), akinesia (poverty of movement), and rigidity with or without observing tremor. PD derives its name from James Parkinson’s, whose description of this disorder contains prominent motor symptoms including tremor, entitled An Essay on the Shaking Palsy, originally published in 1817 as a monograph (Parkinson, 2002).

2.5.1 Etiology

The cause of PD is unknown, but it might involve both genetic and environmental components. A pathological hallmark of PD is the death of dopamine-producing cells in the substantia nigra pars compacta (SNPC) of the basal ganglia (Watts et al., 2012). This neurological hallmark is essential for pathologic diagnosis of PD. Even in a mildly affected patient, at the time of clinically identifiable signs of the disease, about 60% of dopaminergic neurons is lost, when the drop in the dopamine availability cannot be rapidly compensated resulting in the emergence of deficits. This significant loss, in addition to possible dysfunction in the remaining cells, accounts for approximately 80% of dopamine degradation in the corpus striatum (Zigmond & Burke, 2002).

Nigrostriatal dopaminergic deficits leads to abnormal patterns of activity of the nuclei within the basal ganglia that subsequently results disrupted basal ganglia-thalamic-cortical circuitry (DeLong & Wichmann, 2007). Loss of dopamine content has been assumed to disinhibit globus pallidus internus (GPi), which ultimately results in the inhibition of the motor output via the Direct Pathway (inhibiting the excitatory thalamic output to the motor cortex). It was the Nobel Prize-winning (2000) work of Arvid Carlsson that pointed to dopamine loss as the principal deficit in PD and led to the treatment for PD using levodopa, a dopamine precursor which can cross the blood-brain barrier. Given the dopaminergic cause of the disease, common pharmacological drugs include a combination of levodopa and dopamine agonists. Recently, deep brain stimulation (DBS) has been used as a treatment of PD, most often in combination with dopamine-replacement drugs, in patients who fail to respond or have developed resistance to pharmacological interventions (DeLong & Wichmann, 2015;
reviewed in Kalia et al., 2013). DBS involves implanting electrodes deep within the brain, generally targeting globus pallidus or subthalamic nucleus in PD, to deliver high frequency electrical pulses to specific targets aiming to disrupt the abnormal patterns of neural activity through the stimulation site. Although current available therapies treat PD symptoms well at early stages, but they are not able to address the disabling motor and non-motor symptoms at late stages. The phenomenological description of PD is useful clinically, however, it has limited contribution in knowing the substrates of different aspects of abnormalities associated with PD.

2.5.2 General Symptomology

PD patients not only suffer from neurological signs and symptoms with both motor and non-motor manifestation, but also suffer from disturbing sensory symptoms such as feeling pain in affected limbs. They also might represent signs of constipation, orthostatic hypertension, and urinary hesitancy (Koike & Takahashi, 1997; Mathias, 1998; Quigley, 1996). Because of the remarkable plasticity within the CNS that seems to substantially compensate for low dopamine levels, either within the dopaminergic system or through the circuits modulated by dopamine, PD symptoms become clinically identifiable after substantial loss of nigrostriatal neurons (about 70%; Bernheimer et al., 1973).

While patients with PD present both motor and non-motor symptoms, we will discuss here only motor symptoms, although motor and non-motor symptoms are likely related. Motor symptoms mainly include movement poverty (akinesia), rigidity, slow movement execution (bradykinesia), and tremor. Akinesia is associated with decreased postural sway, and lack of facial expression and arm-swing. In addition to exhibiting bradykinesia, patients, particularly in later stages, have problems to start a movement, e.g., episodes of freezing during which patients are unable to initiate a task. Rigidity usually manifests in resistance to passively move a limb or in posture associated signs such as decreased postural sway. Resting tremor has a frequency content of 4-6 Hz that might also manifest itself during actions. PD symptoms most often appear unilaterally at initial stages, but will affect both
side of the body as the disease progresses. There two different main forms of PD: patients showing predominant tremor symptoms and patients with gait disorder and postural instability. Although different clinical subtypes might have different pathophysiological substrates, it is believed that changes of the basal ganglia circuitry are responsible for associated symptoms across all clinical subtypes. Most often, postural instability and FOG are the most disabling motor features of PD that emerge in later stages with disease progression (Obeso et al., 2000; Marras et al., 2005; Jankovic, 2008).

In clinic, Hoehn and Yahr (H&Y, Hoehn & Yahr, 1967) scale and the unified Parkinson’s disease rating scale (UPDRS) are generally used to quantify PD symptoms. H&Y scores range from I to V, where stage I represents minimal disability (clinical signs limited to one side of the body and no axial symptoms) and stage V denotes when patients cannot stand or walk by themselves. The emergence of postural problems demonstrates a major transition from stage II to III. UPDRS is the most commonly used rating scale in clinical assessment of PD (Ramaker et al., 2002), which includes H&Y scale as one of its six sections. However, UPDRS is mainly a qualitative and subjective assessment of the disease, it offers limited insight into motor coordination and the neurophysiological substrates of PD, and might not always accurately predict clinical outcomes (e.g., Weaver et al., 2009). Due to the variability in the assessment of PD and its associated symptoms using current clinical tests, and the variable nature of this disease, developing theory-based quantitative methods to diagnose PD and assess its progression has been a topic of great interest.

2.6 Motor synergies in patients with Parkinson’s disease

The neurophysiological substrates of impairments in postural control in PD is still unknown. In clinical settings, balance problems are mainly assessed using shoulder pull test (Fahn & Jankovic, 2007; Goetz et al., 2008), where a clinical profession quickly and unexpectedly pulls the patient’s shoulder and observes postural responses to report fall incidence. Deficits in postural control has been
assessed by exposing patients with PD to postural perturbations, e.g., backward and forward motion of the standing platform (Horak et al., 1992). In response to the perturbation, patients have shown excessive activation of the antagonist muscles that points to decreased movement flexibility in patient population. Similar results as altered coordination among body segments (intersegment reorientation) and lack of anticipatory movements have been reported using kinematic data collected during walking and/or making turns (Ambati et al., 2016; Crenna et al. 2007; Hong et al., 2009; Huxham et al., 2008). Decreased flexibility suggests inability of patients to effectively respond to postural perturbations with internal or external origin.

Impaired motor coordination in hand function and manual dexterity is one of the most representing signs of PD. Patients with PD may show excessive grip force and bradykinesia (Fellows et al., 1998; Neely et al., 2013; Nowak et al., 2005), unstable output forces (Vaillancourt et al., 2002), and impaired mechanisms of anticipatory control, e.g., feed-forward adjustments of forces produced by individual fingers (Muratori et al., 2008; Santello et al., 2004) during grasping and manipulating objects. Considering the unpredictable and dynamical nature of everyday actions, coordination among fingers (and also all other body parts) is necessary for dexterous object manipulation (Lawrence et al., 2014).

A number of studies have been used UCM-based methodologies (reviewed in Latash, 2016; Latash et al., 2007) in PD population to quantify stability and agility of multi-effector movements (reviewed in Latash and Huang, 2015). Using the concept of motor synergies, PD patients have shown lower stabilizing synergies during steady-state tasks as compared to healthy, age-matched elderly population (Park et al., 2012, 2013a, 2014). These observations, in agreement with PD associated symptoms such as decreased manual dexterity and postural instability, suggest potential impairments in the ability of the CNS to stabilize multi-effector actions. Moreover, PD patients have shown impaired ability to modulate these stabilizing synergies (ASAs; Olafsdottir et al., 2005) in preparation to perform a quick action such as producing a quick force pulse with four fingers: the
magnitude of the drop in the synergy index is smaller and delayed (start with a shorter time interval from the onset of task initiation) in patients. In particular, similar impairments were observed in both hands of patients even at H&Y stage I. Note that patients at this stage are assumed to show unilateral PD associated symptoms with no axial involvement. Impaired ASAs suggests potential problems with task initiation as patients might not be able to destabilize their motor output to start an action, i.e., ASAs may be related to the emergence of disabling episodes of freezing. Similar changes in the structure of the inter-trial variance have been observed in patients performing whole-body postural (Falaki et al., 2016, 2017a) and prehensile tasks (Jo et al., 2015). Testing same patients on- and off-medication, partial restoration of synergic control of actions (larger synergy indices during steady-state and improved ASAs) has been observed after taking pharmacological medication (Falaki et al 2016; Park et al. 2014).

In addition to the impaired synergic control observed in PD, patients have shown greater deficits in their performance after removing visual feedback as compared to healthy controls (Jo et al., 2016b). Such drifts in performance, e.g., during isometric force production tasks, have been attributed to the limits in working memory. However, some experimental observations question this explanation. For example, participants often are able to recall the amount of force that they produced after resting for a similar amount of time (Solnik et al., 2017) or the participants’ tendency to drift only towards lower amount of force (Jo et al., 2016b). With respect to such drifts, it has been hypothesized that physical systems tend to reach states with lower amount of potential energy. Based on the RC hypothesis, the referent configuration of the system might migrate towards the actual configuration as the participants’ finger tips are bound to the surface of force sensors (Latash et al., 2005). In this view, task performance drifts toward a more stable configuration. If so, patients with neurological disorders might represent increased force drifts due to compromised neurophysiological substrates ensuring action stability that allows possible compensatory mechanisms to push the whole system toward a more stable configuration.
2.7 Neurophysiology of motor synergies in relation to Parkinson’s disease

Neurophysiological substrates of motor synergies is all but unknown. Several studies have been reported the importance role of subcortical structures, in particular basal ganglia and cerebellum (Jo et al., 2015, 2016a; reviewed in Latash & Huang, 2015; Wu & Hallett, 2013) and the brain stem (Hacker et al., 2012) in the synergetic control of voluntary movements. These substrates are more likely to involve different brain structures that are shared across dissimilar tasks and effectors, which is similar to what Bernstein (1935) denoted as operators and Houk (2005) called as distributed processing modules (DPMs). Using brain-imaging techniques, PD related pathological changes has been identified in the cerebellum (Giompres & Delis, 2005; Heman et al., 2012; reviewed in Wu & Hallett, 2013) and cerebellum has been suggested to play an important role in the pathophysiology of PD (reviewed in Wu & Hallett, 2013; Wu et al., 2011; Yu et al., 2007). Reciprocal connections between cerebellum and the basal ganglia have been discovered (Bostan et al., 2010). It has been suggested that weakened striatum-cerebellar connections in PD (Wu et al., 2011) might be related to problems with movement initiation. Moreover, compensatory role of cerebellum in response to primary dysfunctions in basal ganglia has been suggested (Lewis et al., 2007; Sen et al., 2010).

In line with the view of the importance of cerebellum in synergetic control of actions, significant reduced synergies have been documented in patients with multiple system atrophy (also known as olivio-ponto-cerebellar atrophy) with parkinsonism predominant motor symptoms (Park et al., 2013b). Improved synergy indices in PD patients after taking pharmacological medication (Falaki et al., 2017a ; Park et al., 2014) points to the importance cortico-striato-thalamo-cortical pathways in synergetic control of actions. In general, observations of impaired motor synergies in patients with PD, support the general idea that points to PD related pathological changes in the functioning of loops through multiple brain structures especially subcortical regions. Within this viewpoint, impaired
synergic control of actions and loss of stability might be direct consequences of disrupted functioning of subcortical loops passing through the basal ganglia and cerebellum.
CHAPTER 3
Common Methods

3.1 Experimental apparatus

All of the experiments in this dissertation were performed at Penn State Milton S. Hershey Medical Center. Experiments involved hand and postural tasks. Hand tasks required measurement of forces that participants produced by their fingertips, while postural tasks required measurement of the COP coordinates and EMG data. In this section, equipment and apparatus that were used for each of hand and postural tasks are briefly introduced.

3.1.1 Hand setup

Participants sat comfortably behind a table facing a 19” monitor placed about 0.8 m away at their eye level. They rested the instructed forearm on a wooden wrist-forearm brace fixed to the table. Four PCB 208A03 single-axis piezoelectric force transducers (PCB Piezotronics, Depew, NY) were used to record vertical forces produced by the index (I), middle (M), ring (R), and little (L) fingers. Using an aluminum panel with four slots, 7.5 cm long and separated by 3 cm from each other in the medio-lateral direction, enabled adjustments of the sensor location in the anterior-posterior direction to provide comfortable positioning of the fingers for each subject and each hand. One of the two custom-made wooden pieces, designed for the left hand and the right hand, was placed underneath the palm to help maintain the inter-phalangeal joint configuration slightly flexed and constant during the course of the experiment. The top surface of each force sensor was covered with a round piece of sandpaper (300-grit) to increase friction. A Velcro strap was used to hold the forearm on the wrist-forearm brace. PCB 484B06 signal conditioners (PCB Piezotronics, Depew, NY) were used to amplify force signals before sending them to a 16-bit analog-to-digital board (PCI-6225, National Instrument Corp., Austin, TX). A customized LabVIEW-based program (National Instruments Corp.,
Austin, TX) was used to collect data at 200 Hz, and to provide real-time visual feedback for participants and the experimenter. *Figure 3.1* represents an illustration of the hand setup.

![Figure 3.1 A schematic of the hand setup. The wooden piece was customized separately for the left hand (L) and the right hand (R) to keep the inter-phalangeal joints slightly flexed during the course of the experiment.](image)

3.1.2 Postural setup

Participants stood barefoot on a force plate (OPTIMA AMTI, Watertown, MA) with their feet parallel and shoulder width apart. The foot position on the plate surface was marked and reproduced across tasks. PD patients and elderly adults wore a safety harness affixed to the ceiling while standing on the force platform, and an experimenter stood nearby. Horizontal ($F_X$ and $F_Y$) and vertical ($F_Z$) components of the ground reaction force and the three moments of force about the $X$, $Y$, and $Z$ axes were recorded to compute the $X$- and $Y$-coordinates of the center of pressure (COP; Winters et al., 1996) using the force plate coordinate system (*Figure 3.2*). Visual feedback on the COP coordinates in the anterior–posterior ($COP_{AP}$) and medial–lateral ($COP_{ML}$) direction was provided as a 0.5-cm white cursor presented on a 23" monitor mounted 1 m away from the participants at eye level. $COP_{AP}$ motion was shown as the up-down motion of the cursor and $COP_{ML}$ motion was shown as the left-right motion of the cursor.
A 16-channel Trigno wireless system (Delsys Inc., MA) was used to record EMG signal of 13 leg and trunk muscles on the right side of the body: tibialis anterior (TA), soleus (SOL), gastrocnemius medialis (GM), gastrocnemius lateralis (GL), biceps femoris (BF), semitendinosus (ST), rectus femoris (RF), vastus lateralis (VL), vastus medialis (VM), tensor fasciae latae (TFL), lumbar erector spinae (ESL), thoracic erector spinae (EST), and rectus abdominis (RA). Rectangular shaped EMG sensors (37×26×15 mm, 14 g) with pre-amplifiers on the electrode heads (by a factor of 909) were placed according to the published guidelines (Criswell & Cram 2011). Electrode placement was confirmed by asking participants to perform a set of isometric and isotonic contractions and observing the resulting EMG patterns. Trigno EMG parallel-bar sensors utilize four bar contacts (99.9% silver, 5×1 mm, fixed contacts distance: 10 mm parallel to muscle fibers) to ensure effective detection of the signal from the muscle below the skin with minimal crosstalk. Prior to affixing EMG sensors, the skin at the sensor site was properly wiped with isopropyl alcohol swabs to remove oils and dry dermis. Trigno EMG sensors provide the following specifications: common mode rejection noise >80 db; EMG baseline noise <750 nV RMS; and ±5 V analog output range.
During the task in which participants made a step, EMGs from the following muscles on both side of the body were recorded: tibialis anterior (TA), soleus (SOL), gastrocnemius medialis (GM), biceps femoris (BF), rectus femoris (RF), vastus lateralis (VL), tensor fasciae latae (TFL), and lumbar erector spinae (ESL). Two foot switches were placed under each of the left and right feet (four in total); one under the medial process of calcaneal tuberosity (to identify the heel off onset) and one under the head of the first metatarsal near the big toe (to detect the onset of toe off). A square-shaped wooden plate with the exact height as of the force platform was placed in front of the force platform to make the stepping as natural as possible. Each side of the wooden plate was 75 cm long and its surface was padded with carpet to make stepping with barefoot comfortable.

Analog EMG, force platform, and foot switches data were digitized at a 1 KHz sampling frequency using a PCI-6225 board and recorded by means of a customized LabVIEW-based program.

3.2 Procedures

For all PD patients participated in each of experiments, a trained rater assessed Unified Parkinson’s Disease Rating Scale motor scores (UPDRS-III) and H&Y stage. The levodopa equivalent daily dose (LEDD) was calculated according to published guidelines (Tomlinson et al., 2010) and handedness was decided upon the participants’ preferential hand use during eating and writing. To avoid fatigue, participants were given rest-intervals and were encouraged to ask for additional rest intervals, drinks, and snacks as needed. Information regarding the hand and postural tasks used in this dissertation are provided in this section.

3.2.1 Hand tasks

For each participant both the left hand and the right hand were tested in a random order. Prior to each trial, participants relaxed their fingertips on the sensors. During this period, sensor readings were set to zero to remove the weight of fingers from force measurements. There were three main
tasks in the following order: maximal voluntary contraction (MVC), single-finger ramp force production, and quick force pulse production tasks.

**MVC task:** Participants were asked to press as strongly as possible with all four fingers on the force sensors and given 8 s to reach peak force. Each participant performed this task twice with visual feedback on the total force ($F_{TOT}$). There was a 30-s rest between the two trials. The trial with the higher peak force ($MVC_{TOT}$) was selected to define the maximal forces of individual fingers ($MVC_i; i = I, M, R, L$). These values were used to adjust the force levels in subsequent tasks.

**Single-finger ramp task:** Participants pressed with one finger at a time to trace a ramp template shown on the screen while keeping all other fingertips on the sensors. This task was performed to quantify the finger force interdependence (enslaving, Zatsiorsky et al., 2000; Danion et al., 2003). The total template was 20 s long and consisted of three segments: (1) a horizontal segment for 4 s corresponded to zero force, (2) a slanted line that increased smoothly from 0% to 40% of $MVC_i$ over 12 s, and (3) a horizontal segment for 4 s corresponding to 40% of $MVC_i$.

**Quick force pulse production task:** Each trial started by pressing and maintaining an initial force level, set at 8% of $MVC_{TOT}$, as steady as possible for 5 s. A vertical line at 5 s showed the point in time after which participants were allowed to produce the quick force pulse into the target set at 25 ± 5% of $MVC_{TOT}$ in a self-paced manner with Visual feedback on $F_{TOT}$. The initial and target force levels were shown on the screen by two horizontal lines. Each trial lasted for 10 s with 10-s rest between trials. Participants were asked to pay attention to the quickness of the action rather than the accuracy of the force pulse level. In case of major errors such as pressing multiple times in one trial, obvious drift in force level prior to the pulse, or a very slow pulse production, the trial was repeated.

### 3.2.2 Postural tasks

The postural part involved different tasks that participants performed a set of them in each of experiments: quiet standing (QS), continuous voluntary sway (VS), fast-sway (FS), load release (LR),
and make step (MS). Making step trials were administered only during Stepping-Turning experiment, in which these trials substituted the load release part. Also only in Stepping-Turning experiment, participants performed voluntary body sway task in medial-lateral direction in addition to the anterior-posterior direction. Prior to each trial, participants were asked to stand on the force platform and maintain a standard initial foot position. Except for the QS task, participants performed a set of familiarization trials prior to each task: on average, 2-3 trials for the VS task and 4-6 trials for the LR task.

**QS task:** This task was performed to measure the background EMG activity of the recorded muscles during natural quiet standing. Each participant maintained the initial posture for 60 s with the arms crossed over the chest while looking at the screen without any visual feedback and trying to avoid body movements.

**VS task:** Each participant performed this task twice with visual feedback on both $COP_{AP}$ and $COP_{ML}$. Each trial began with crossing the arms over the chest and maintaining the natural initial position, after which participants swayed at 0.5 Hz for 30 s mainly about the ankle joints in the anterior-posterior direction. A sound metronome was used to pace the sways. Sway amplitude (6 cm peak-to-peak of $COP_{AP}$, centered about the initial position) was shown with two horizontal lines on the screen. There was a 30-s rest interval between trials. During the course of the trial, participants were asked to keep their feet in full contact with the platform, avoid excessive hip and knee joints motion, and attempt to minimize deviations of the $COP_{ML}$. Data from the VS trials were used to estimate a set of a muscle groups with co-varied EMG signals (M-modes; Krishnamoorthy et al., 2003a) and to relate changes in M-modes to $COP_{AP}$ shifts (the Jacobian matrix; discussed in more details in data processing).

Swaying in the medial-lateral direction were similar to the VS task in the anterior-posterior direction. Participants swayed at 0.5 Hz for 30 s mainly about the ankle joints in the medial-lateral direction while trying to minimize deviations in the anterior-posterior direction. Sway amplitude was
set to 8 cm peak-to-peak of $COP_{ML}$, centered about the initial position, and was shown with two vertical lines on the screen.

*FS task:* The purpose of this task was to compare the ability to make fast whole-body actions off- and on-drug. Each trial began with standing quietly in the initial position. Subjects then were asked to reach the posterior target shown on the screen (3 cm away from the natural $COP_{AP}$ position), keep this position for about 2 s, and perform, in a self-paced manner, a discrete body motion forward to a target located 6 cm anterior as fast as they could. Participants were asked to perform movements about ankle joints, while keeping full contact of their feet with the platform, and pay attention mainly to the speed of the forward motion rather than to its accuracy. Seven trials were performed for this task.

*LR task:* Participants held a brick-shaped load with fully extended arms (20 cm long; 1.5 kg for women and 2 kg for men) and leaned forward about the ankle joints to reach a target corresponding to a 3-cm shift of the $COP_{AP}$ anterior to the neutral standing position. Subjects were asked to keep their posture at the target as stable as they could for about 2-3 s and then release the load in a self-paced manner by a quick, low-amplitude bilateral abduction of the arms (Aruin and Latash, 1995). Subjects repeated this task for 24 trials with 10- sec rest between trials and a 2-3 min break after each set of 12 trials.

*MS task:* Participants crossed the arms over the chest and leaned forward about the ankle joint to reach a target corresponding to a 3-cm shift of the $COP_{AP}$ anterior to the neutral standing position. They kept their posture at this target as stable as they could for 2-3 s and then make two steps under two conditions in a block randomized design: (1) Participants were looking at a screen mounted in front of them to stabilize their posture at the target shown on the screen; (2) participants rotated their head for 45˚counter-clockwise to look at the screen and stabilized their posture. In this condition they were asked to turn their head to look straight forward, after which they stepped as soon as possible. They were explicitly reminded to minimize the time between turning the head and
stepping forward, and to try to step at their natural walking speed. Subjects performed this task for 24 times per each condition with 10-sec rest between trials and a 2-3 min break after each set of 12 trials.

3.3 Data processing

Data from the hand and postural tasks were processed separately using customized Matlab (Mathworks Corp., Natick, MA) codes. In this part, first, a general scheme of computing synergy indices is explained, after which a more detailed description of the analysis for each of the experiments is provided.

The method is based on the uncontrolled manifold (UCM) hypothesis (Scholz and Schöner, 1999); it includes computation of two components of inter-trial variance ($V_{UCM}$ and $V_{ORT}$) that do and do not affect a specific performance variable (PV) produced by a set of elemental variables (EVs). Studies of multi-finger pressing tasks use finger modes as EVs and resultant force as a PV. Finger mode is a hypothetical variable reflecting a person’s intent to change force by using only one digit. Because of the phenomenon of digit non-independence, such a command leads to force production by all the digits of the hand. Using modes allows removing effects of this interdependence of digit forces (Latash et al., 2001). Finger modes were defined using regression analysis across trials with accurate ramp force production while using one instructed finger at a time.

Studies of whole-body postural tasks used muscle modes (M-modes) as EVs and coordinate of the center of pressure as PV (Krishnamoorthy et al., 2003a,b). M-modes are hypothetical neural variables used for control of large muscle groups; changing a value (gain) of each M-mode leads to proportional changes in the activation levels of the involved muscles. M-modes were defined as eigenvectors in the space of muscle activations using principal component analysis with Varimax rotation and factor extraction.

The general logic of the inter-trial analysis of variance is as follows: Individual trials are aligned; variance in the space of the EVs is computed across trials for each time sample. The UCM is
approximated as the null-space of the Jacobian ($\mathbf{J}$) that links small changes in EVs to changes in the selected PV. For multi-finger tasks, $\mathbf{J}$ was computed taking into account the enslaving matrix ($\mathbf{E}$, see below). For multi-muscle tasks, $\mathbf{J}$ was found with a multiple linear regression technique. Variance in the space of EVs was computed within the UCM and within its orthogonal complement, $V_{\text{UCM}}$ and $V_{\text{ORT}}$, respectively. Further, a metric ($\Delta V$) reflecting the difference between the two was computed:

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

where $V_{\text{TOT}}$ means the total variance; each value was quantified per degree-of-freedom in its corresponding spaces. Note that $\Delta V > 0$ implies presence of a synergy stabilizing the PV by co-variation of EVs. A larger $\Delta V$ implies stronger synergies. $\Delta V \leq 0$ implies no synergy. For parametric statistical analysis, however, $\Delta V$ must be transformed using a Fisher’s z-transformation (Solnik et al., 2013) to normalize the $\Delta V$ distribution given the limits of this index imposed by its computation; with a 3-dimensional UCM and 1-dimensional ORT, $-4 \leq \Delta V \leq 1.33$.

Anticipatory synergy adjustments (ASAs) were quantified using two indices, namely the magnitude of ASA ($\Delta V_{\text{ASA}}$) and the time of ASA initiation ($t_{\text{ASA}}$). For each study, a time interval prior to the task initiation ($t_0$), during which the participants were at an stable position, was considered as steady state (SS) and used to compute the mean and standard deviation (SD) of $\Delta V_Z$. In hand experiment, $t_{\text{ASA}}$ was defined as the point in time prior to $t_0$ when $\Delta V_Z$ dropped below its mean value during SS ($\Delta V_{\text{SS}}$) by two SDs, and $\Delta V_{\text{ASA}}$ was defined as the difference between $\Delta V_{\text{SS}}$ and the value of $\Delta V_Z$ at $t_0$: $\Delta V_{\text{ASA}} = \Delta V_{\text{SS}} - \Delta V_0$ for both experiments. Because of $\Delta V_Z$ variations, $t_{\text{ASA}}$ was defined in postural experiment as the point in time prior to $t_0$ when $\Delta V_Z$ dropped below its mean and remained less than the mean until $t_0$.

Similar to the analysis of the inter-trial variance in the space of EVs, motor equivalence analysis (Mattos et al., 2011, 2013, 2015) is based on the UCM hypothesis (Sholz & Schöner, 1999) and the principle of motor abundance (Gelfand & Latash, 1998; Latash, 2012a). However, instead of projecting the inter-trial variance, motor equivalence analysis projects the displacement in the space of EVs onto the UCM and ORT spaces. Computationally, analysis of motor equivalence is similar to
the analysis of inter-trial variance except for: 1) projecting changes in the space of EVs between two epochs of interest (when the motor system is in a same configuration with respect to the PV) within a single trial or between consecutive trials; and 2) as ME and nME components are displacements, they are normalized by the square root of the dimensionality of their respective sub-spaces.

If CNS stabilizes a salient performance variable, it is expected to observe larger deviations in directions that does not affect the performance (motor equivalent, ME; displacements within UCM) as compared to the motion in directions that does affect the task performance (non-motor equivalent, nME; displacements within ORT). Note that large values of $V_{UCM}$ or $V_{ORT}$ does not necessarily lead to respective large values of ME or nME component. Although several studies have reported correlated variance indices with motor equivalent components (Falaki et al., 2017b; Furmanek et al., 2017) or similar changes in the structure of inter-trial variance and output variables of motor equivalence analysis (Yamagata et al., 2018), currently, our understanding of relations between these methods is very weak. Another recent study has reported relations between $V_{UCM}$ and ME, but not between $V_{ORT}$ and nME (Cuadra et al., 2018). Whereas self-produced motions lead to more ME motion ($ME > nME$; Mattos et al., 2015), externally introduced perturbations seems to generate similar levels of ME and nME displacements (Reschechtko et al., 2014, Zhou et al., 2014b). These observations suggest potential influences of the experimental circumstances on ME and nME motions.

3.3.1 Hand tasks

To avoid effects of tremor, especially in the DBS-off state, a fourth-order, zero-lag Butterworth filter was used to digitally low-pass filter the data at 4 Hz. Filtered data from the single-finger ramp task were used to define finger modes and data from the quick force pulse production task were used for variance analysis.

*Defining the enslaving matrix and finger modes:* Enslaving reflects the involuntary contraction of non-intended fingers when producing force with an instructed finger (Zatsiorsky et al., 2000). To quantify enslaving for each participant, a $4 \times 4$ matrix was constructed using data from
the single-finger ramp force production trials. In each trial, the force produced by non-intended fingers increased approximately in parallel with the force produced by the instructed finger. As a result, linear regression analysis was used to evaluate the contribution of each finger towards $F_{TOT}$:

$$F_{i,j} = F_{i}^{0} + k_{i,j} \times F_{TOT,j}$$

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

where $i, j = \{I, M, R, L\}$, $F_{i,j}$ is the $i$-th finger force and $F_{TOT,j}$ is the total force when $j$ represents the task finger. The first and last seconds of each trial were excluded from regression analysis to avoid potential edge effects. Finger modes can be subsequently computed as: $m = [E]^{-1} F$, where $m$ and $F$ are vectors of modes and forces, respectively.

**Analysis of variance using finger modes:** For each trial of force pulse production, the onset of pulse initiation ($t_0$) was defined as the time point when the first derivative of force ($dF/dt$) reached 5% of its maximum value in that trial. The time to peak force ($T_{Peak}$) was defined as the time, with respect to $t_0$, when $F_{TOT}$ reached its maximum value during that trial. Trials with any of the following major errors were excluded from analysis: $T_{Peak}$ was greater than 1 s, there were multiple peaks in the force pulse, and the total force was not stabilized prior to the pulse initiation. After converting force data into modes, $V_{UCM,F}$ and $V_{ORT,F}$ were quantified and used to compute $\Delta V_F$ and ASA indices. In order to compare the variance in each subspace, it is necessary to normalize by the dimensionality of that subspace. In the analyses presented in this dissertation, the dimensionality of the UCM is 3, whereas the dimensionality of the orthogonal subspace (ORT) is 1. An index of multi-finger synergy ($\Delta V$) has been developed which incorporates both $V_{ORT}$ and $V_{UCM}$ into a single quantity.

### 3.3.2 Postural tasks

Data from the force platform were digitally filtered at 10 Hz using a low-pass, fourth-order, zero-lag Butterworth filter to compute $COP_{AP}$ coordinates according to standard methods (Winter et
al., 1996). The cut-off frequency was set to 4 Hz only for one participant in the study that explored effects of DBS because of significant tremor during the DBS-off state, which caused fluctuations in the $F_Z$ component of the ground reaction force and erroneous trial alignment.

EMG signals were filtered between 20-350 Hz (fourth-order, zero-lag Butterworth filter), rectified, and low-pass filtered using a 100-ms moving average window to detect EMG envelopes. To account for the electromechanical delay (Corcos et al., 1992), EMG signals were shifted backward by 50 ms. EMG signals were normalized ($EMG_{\text{NORM}}$) by subtracting the background EMG activity— from the QS tasks—and then dividing by the maximal EMG levels:

\[
EMG_{\text{NORM}} = \frac{EMG - EMG_{\text{QS}}}{EMG_{\text{MAX}}} \tag{3.2}
\]

where $EMG_{\text{QS}}$ is the averaged EMG level within {5 s; 15 s} time period of the QS task and $EMG_{\text{MAX}}$ is the maximal activity of individual muscles across VS trials. EMG data averaged over each 50-ms time-window were used for $EMG_{\text{PEAK}}$ computation.

**Defining muscle modes and the Jacobian matrix:** For each participant, EMG data from the VS trials were used to identify M-modes and subsequently to find the mapping between M-mode changes and $COP_{\text{AP}}$ shifts (Danna-Dos-Santos et al., 2007a; Klous et al., 2010). The first 3-s and the last 2-s were removed from each trial to avoid effects of action initiation and termination. The period between two successive anterior-most $COP_{\text{AP}}$ coordinates was defined as a sway cycle. COP and EMG data from the beginning of the first cycle until the end of the last cycle were averaged over each 50-ms time window and were used for the analyses.

Based on the Kaiser criterion (Kaiser, 1960), the first four PCs with the greatest eigenvalues were selected as M-modes after applying PCA with Varimax rotation and factor extraction on the correlation matrix of the averaged EMGs. The first two M-modes involved significantly loaded muscles on the ventral or dorsal side of the body, respectively, and will be addressed as “ventral M-mode” and “dorsal M-mode”. The composition of these M-modes was similar in all participants.
regardless of the disease, medication, or DBS status. A fixed number of M-modes were selected across groups and states, because having variable mode numbers would change the dimension of UCM space without affecting the ORT space and affect the outcome variables. Considering loadings beyond ±0.5 as significant, all M-modes had at least one significantly loaded muscle. We computed a matrix including muscle loadings by multiplying the matrix that had eigenvectors in its columns by the diagonal matrix that had the square root of eigenvalues as its diagonal elements (Johnson and Wichern 1982). EMG data were multiplied by M-modes, transforming the EMG signals into the four-dimensional mode space.

For each participant, the $J_M$ was reduced to a vector formed by coefficients of the regression analysis between small deviations of M-mode magnitudes ($\Delta M$) and changes in COP$_{AP}$ coordinates ($\Delta COP_{AP}$). To remove high frequency components of $\Delta M$ and $\Delta COP_{AP}$ unrelated to voluntary sway of the whole body, a fourth-order, zero-lag Butterworth filter with 2 Hz cut-off frequency was used prior to the analysis.

\[
\Delta COP_{AP} = k_1 \Delta M_1 + k_2 \Delta M_2 + k_3 \Delta M_3 + k_4 \Delta M_4
\]
\[
J = [k_1 \ k_2 \ k_3 \ k_4]
\]

(3.3)

where the $J$ matrix determines how small deviations of M-mode magnitudes affect the selected performance variable (COP$_{AP}$ coordinate).

**Analysis of APA:** Anticipatory postural adjustments (APAs; Belen'kii et al., 1967; Massion, 1992) were seen prior to the self-initiated LR task. APA initiation was defined based on two methods: (1) changes in the EMG envelopes ($t_{APA,m}$) and (2) changes in the magnitude of M-modes ($t_{APA,mode}$). For each participant, the mean value and SD of EMG and the first two M-modes ventral and dorsal M-modes) were computed during the SS period. APA initiation was defined as the time point when the averaged across trial M-mode values or muscles activation levels deviated more than ±2 SD from their respective mean values and this deviation remained until $t_0$. The time when the earliest change
happened across M-modes and across muscles were selected as $t_{\text{APA,mode}}$ and $t_{\text{APA,m}}$, respectively. These values were further confirmed visually.

**Analysis of UCM-based variance using muscle modes:** LR trials were aligned by the time when the $dFZ/dt$ reached 5% of its minimum value. Trials in which $COP_{\text{AP}}$ trajectory was not stabilized prior to $t_0$ ($COP_{\text{AP}}$ coordinate within 200 ms interval prior to $t_0$ deviated from the initial target value by more than ±2 SD; SD was computed during SS interval), and trials with faulty EMG signals were removed from the analysis. In order to perform variance analysis, normalized EMGs were transformed into M-mode space. Residual mean-free vectors of M-mode changes ($\Delta \hat{M} = \Delta M - \bar{M}$) were projected onto the UCM ($f_{\text{UCM}}$) and the ORT ($f_{\text{ORT}}$) spaces to compute $V_{\text{UCM}}$, $V_{\text{ORT}}$, $\Delta V_Z$, and ASA indices. The null-space of the $J$ matrix served as a linear approximation of the UCM space. Inter-trial variance of M-modes were partitioned into the UCM and ORT and normalized by dimension as (Klous et al., 2011; Singh et al., 2011):

$$V_{\text{UCM}} = \sigma_{\text{UCM}}^2 = \frac{\sum_{i=1}^{N} |f_{\text{UCM}}|_2^2}{(n-d) N_{\text{trials}}}$$

$$V_{\text{ORT}} = \sigma_{\text{ORT}}^2 = \frac{\sum_{i=1}^{N} |f_{\text{ORT}}|_2^2}{d N_{\text{trials}}}$$

(3.4)

where ($n = 4$) is the dimensionality of the M-mode space and ($d = 1$) is the number of constraints associated with the task (ORT space dimension). $N_{\text{trials}}$ represent the number of repetitions of the task. To quantify the synergy index at $t_0$, we used the average of $\Delta V_Z$ within the 51-ms time window centered about $t_0$ ($\approx t_0 = \{t_0-25 \text{ ms}; t_0+25 \text{ ms}\}$).

**Analysis of motor equivalence:** The motor equivalence analysis (Mattos et al., 2013; Mattos et al, 2015) quantifies ME component as deviations in the space of EVs (M-modes) within the UCM space (preserving the performance variable, $COP_{\text{AP}}$) and nME component as displacements within the ORT space (results in $COP_{\text{AP}}$ changes). For the experiment explained in Chapter 6, deviations of M-modes from each phase of one sway cycle to the corresponding phase of the next cycle were projected onto the null-space of $J$ ($f_{\text{ME}}$) and its orthogonal complement ($f_{\text{nME}}$):
\[ \Delta M = M_i - M_{i+1} \]
\[ f_{ME} = \sum_{i=1}^{n-d}(e_i^T \cdot \Delta M)^T \cdot e_i^T \]
\[ f_{nME} = \Delta M - (f_{ME})^T \]

where \( e_i \) stands for basis vectors spanning the null-space of \( J \). The length of \( f_{ME} \) was the ME component, whereas the length of \( f_{nME} \) reflected the nME component. ME and nME components were normalized by the square root of the dimension of their respective sub-spaces (cf. Mattos et al. 2011):

\[
ME = \frac{\|f_{ME}\|}{\sqrt{n-d}} \\
nME = \frac{\|f_{nME}\|}{\sqrt{d}}
\]

For statistical comparisons, the ME and nME components were averaged across time-normalized cycles. Note that we used average indices over all cycles for statistical analyses. We viewed this as appropriate for the first step in using the ME analysis to identify postural stability problems in PD. For further studies, quantifying ME and nME indices as averages over 3–4 trials only, particularly for non-cyclical tasks, should be explored.

### 3.4 Statistical methods

Data are mainly presented as means ± standard errors (SE), unless stated otherwise. For studies presented in chapters 4, 5, and 6 (Falaki et al., 2016, 2017a, 2017b), statistical tests were performed in SPSS (IBM Corp., Armonk, NY). For the rest of studies, SAS (The SAS Institute, Cary, NC) and Minitab (Minitab Inc, State College, PA) were used to perform statistical tests. The most common analyses run at Wilcoxon’s signed-rank test and repeated measures ANOVA, for which we used mixed model methodology that treats experimental contrasts as fixed effects and subjects as random effects. Quantile-quartile plots of residuals were used to check the normality and homoscedasticity of data distributions and appropriate data transformations were used as needed. We performed z-transformations (Solnik et al., 2013) before analysis to normalize the data in cases where
observed responses were bounded within a certain range due to the computations that were used. In case of observing a significant main effect of a treatment with more than two levels, post-hoc pairwise comparisons with Bonferroni corrections were employed to ascertain levels of statistically significance. Correlation analyses were performed using Pearson correlation coefficient. For all statistical tests, \( p < 0.05 \) was assumed for statistical significance.
CHAPTER 4
Impaired Multi-Muscle Synergies in Parkinson’s Disease

Parkinson’s disease (PD) is diagnosed clinically by the presence of rest tremor, rigidity, and bradykinesia. Postural instability and associated symptoms, such as episodes of freezing, emerge as the disease progresses and represent the most disabling symptoms of PD (Marras et al., 2005). The presence of postural instability is a clinically important landmark in PD, signifying the transition from Hoehn-Yahr (H&Y; Hoehn & Yahr, 1967) stage-II to stage-III. During typical clinical evaluations, postural instability is assessed using qualitative tests such as the pull test (Goetz et al., 2008; Fahn & Jankovic, 2007). Whereas limitations of posturography in clinical studies have been emphasized recently (Visser et al., 2008), consistent changes in postural sway, postural adjustments prior to stepping, and responses to perturbations have been reported in stage-III PD (Boonstra et al., 2014; King et al., 2010; Nardone & Schieppati, 2010; Rogers et al., 2011).

The concept of motor synergy has evolved over the past 20 years (Latash, 2012a; reviewed in Latash et al., 2007). Synergy is defined as a neural organization of a large set of effectors providing the stability of important performance variables (Latash et al., 2007). For example, during multi-digit prehension, individual digit forces and moments co-vary to stabilize the resultant force/moment acting on the grasped object (Zatsiorsky & Latash, 2008). A synergy index has been introduced reflecting the relative amount of across-trials variance that does not affect a salient performance variable (Latash et al., 2007). During steady-state actions, the synergy index typically is high. When a person is preparing for a quick action from a steady state, the synergy index drops 200-300 ms prior to action initiation. These anticipatory synergy adjustments (ASAs; Olafsdottir et al., 2005; Shim et al., 2005) represent an important reflection of controlled stability that allows combining stability during steady state and agility in transition to a quick action (Latash & Huang, 2015).
Recent studies in PD patients have suggested that indices of motor synergies may be used as sensitive biomarkers of PD even in extremities that show no clinically identifiable motor symptoms (Park et al., 2012, 2013a, 2014). In particular, patients at H&Y stage-I (with clinical signs limited to one side of the body) showed comparably impaired indices of multi-finger synergies and impaired ASAs in both the symptomatic and asymptomatic hands (Park et al., 2012).

In the current study, we explored whether indices of multi-muscle synergies stabilizing the coordinate of the center of pressure (COP) are able to detect postural stability changes in PD patients at H&Y stage-II without clinically identifiable postural instability. Our main hypothesis had two parts. First, during steady state (quiet standing) we expected lower synergy indices in PD patients compared to age-matched controls. Second, we expected significantly smaller ASAs in PD patients during preparation to a self-triggered postural perturbation.

4.1 Methods

Many of the procedures detailed in this section recapitulate information in Chapter 3 Common Methods. However, certain quantitative specifics are only presented here.

4.1.1 Subjects

A group of 11 right-handed (6 females) PD patients without clinical postural instability (H&Y stage II, aged 69 ± 6 years, mean ± standard deviation, SD) and 11 (5 females) healthy controls (aged 65 ± 8 years) participated in this study. Clinical postural stability was defined as lack of falls and negative on pull back test as part of Unified PD rating scale-part III. Detailed demographic and clinical information is presented in Table 4.1. All PD participants were tested on their prescribed medications. Written informed consent was obtained from all participants according to the protocol approved by the Penn State Hershey Institutional Review Board.
Table 4.1 Description of the participants

<table>
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<th>PD group</th>
<th>Patient</th>
<th>Gender, M/F</th>
<th>Age (years)</th>
<th>Symptom Onset, R/L</th>
<th>Years since diagnosis</th>
<th>UPDRS motor score</th>
<th>Total LEDD (mg)</th>
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<td>R</td>
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<td></td>
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<td>71.6 ± 4.6</td>
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</table>

CO group

<table>
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<th>Age (years)</th>
</tr>
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<tbody>
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</tr>
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</tr>
<tr>
<td>Mean</td>
<td>M (6)</td>
<td>68.0 ± 8.4</td>
</tr>
</tbody>
</table>

M/F, male/females; R/L, right/left; LEDD, levodopa equivalent daily dose; UPDRS, Unified Parkinson’s Disease Rating Scale

4.1.2 Procedures

Subjects were tested while standing on a force platform (AMTI, OPTIMA). A 16-channel Trigno Wireless System (Delsys) was used to record EMG signals. To ensure participant safety, all subjects used a safety harness. Initially, subjects were asked to stand on the force plate while keeping their feet parallel at shoulder width; the foot position was marked and reproduced across trials. The experiment started with a 30-s quiet standing trial used to record baseline EMG signals. The main
experiment consisted of three tasks: voluntary sway (VS), fast-sway (FS), and load release (LR). Prior to each task, subjects performed a few familiarization trials.

4.1.3 Data processing

Recorded signals were processed offline using a customized MATLAB program. Force platform signals were low-pass filtered at 10 Hz with a fourth-order, zero-lag Butterworth filter. The filtered data were used to compute time-varying \( \text{COP}_{AP} \) (Winter et al., 1996). For the VS task, signals in the interval \( \{3 \text{s}; 28 \text{s}\} \) were considered for data analysis in order to avoid edge effects. On average, each participant performed ten full cycles within this period. During the FS and LR tasks, trials without major errors were accepted, \( 17 \pm 1 \) for both groups.

Initiation of APAs (Belen'kiï et al., 1967; Massion, 1992) in the LR task was defined using the time when the averaged across trials muscle activation level within a series performed by a subject exceeded \( \pm 2 \text{SD} \) from its respective mean activity (computed over the time interval \( \{T_0-1000 \text{ms}; T_0-300 \text{ms}\} \)). GM, BF, ST, EST, and ESL muscles showed clear APAs in all participants (see Results); hence, the time when the earliest APA happened across these muscles was selected as \( t_{APA} \) (confirmed visually).

To quantify anticipatory synergy adjustments (ASAs), the synergy index was averaged within two time intervals during the LR task. The first was a 200-ms steady state (SS1, Figure 4.2A) from \( (T_0-1000) \) ms to \( (T_0-800) \) ms, whereas the second was a 50-ms time interval about \( T_0 \) (\( T_0 \), Figure 4.2A). ASA was quantified as the amount of \( \Delta V_Z \) drop in preparation to the movement, \( \Delta \Delta V_Z \).

4.1.4 Statistics

Data are presented as means and standard errors (SE) in the text and figures. Two-way repeated measures ANOVA with factors Phase (two levels: SS0 and \( T_0 \)) and Group (two levels: PD and controls) was performed to investigate possible differences in the synergy index (\( \Delta V_Z \)) and its changes during ASAs. We also used t-tests and linear regression in the analysis of the Jacobian. For
all analyses, the data were checked for violations of normality and sphericity. Geenhouse-Geisser correction was used to adjust the degrees-of-freedom when necessary. Pair-wise contrasts with Bonferroni corrections were used to explore significant ANOVA effects.

4.2 Results

4.2.1 Fast sway movement kinematics

All subjects initiated the forward sway (FS) action with a brief shift backwards in the COP<sub>AP</sub>. The magnitude of this shift did not differ between the groups, 1.5 ± 0.28 cm in PD and 1.4 ± 0.23 cm in controls. The overall magnitude of the forward COP shift also was similar between the groups (10.3 ± 0.35 cm and 10.3 ± 0.53 cm, respectively). There were no statistically significant differences between the peak rates of COP<sub>AP</sub> shift, (dCOP/dt)<sub>MAX</sub> being 38.3 ± 3.11 cm/s and 42.0 ± 5.91 cm/s for the PD and controls, respectively.

4.2.2 EMG patterns and anticipatory postural adjustments

Averaged time profiles of normalized EMGs for a few selected leg and trunk muscles across LR trials performed by a representative PD subject are presented in Figure 4.1. Most subjects showed consistent EMG profiles across trials, although muscle activation patterns were highly variable across subjects making across-subject data averaging meaningless. Significant EMG modulation was observed 140 ms before releasing the load (T₀), signifying anticipatory postural adjustments (APAs). APAs were observed in all subjects with GM, BF, ST, EST, and ESL muscles showing the most clear and reproducible APAs across participants. Arrows in Figure 4.1 show t<sub>APA</sub> for the PD subject. There was no statistically significant group difference in t<sub>APA</sub> (138.3 ± 11.63 ms and 140.4 ± 8.86 ms for PD and controls, respectively).
4.2.3 Defining M-modes and Jacobian

On average, the first four M-modes accounted for less of the total variance in PD subjects compared to controls (71.5 ± 1.74% vs. 78.3 ± 1.74%; F(1,20) = 7.969; p < 0.05). Multiple regression analysis of shifts in COP\textsubscript{AP} (ΔCOP\textsubscript{AP}) as functions of changes in M-modes (ΔM-modes) showed that all M-modes were significant predictors of ΔCOP\textsubscript{AP} for each subject (p < 0.001). The linear regression, on average, showed similar adjusted R\textsuperscript{2} values of 0.66 ± 0.03 and 0.70 ± 0.04 for PDs and controls, respectively (no group difference).
4.2.4 Analysis of the synergy index

During quiet standing (SS₁), the synergy index (ΔV₂) was significantly lower in PD subjects compared to controls (0.014 ± 0.07 vs. 0.22 ± 0.06; p < 0.05; see Figure 4.2A). There was a larger drop in the synergy index in controls from steady state to the moment of load release (Phase × Group interaction; F₁,₂₀ = 9.84, p < 0.01). The magnitudes of the synergy index at the two time intervals studied are presented in Fig. 2B. Note that the synergy index drops in controls in preparation to action initiation (ASAs) and this is absent in the PD group.

4.3 Discussion

To our knowledge, the current study demonstrates for the first time that studies of multi-muscle synergies during postural tasks are able to identify sub-clinical postural stability changes in
PD patients. This finding suggests the potential of using multi-muscle synergy analysis to develop a quantitative biomarker able to identify issues with postural stability in patients with PD who show no postural instability during clinical examination.

4.3.1 Synergies in PD

The word ‘‘synergy’’ is used in the movement science literature in at least three different ways (reviewed in Latash, 2008). In the clinical literature, this word has a negative connotation and means stereotypical patterns of muscle activation that interfere with intentional movements (Bobath, 1978; DeWald et al., 1995). In the motor control literature, ‘‘synergy’’ frequently means a number of performance variables that show parallel changes in task parameters or over time (d’Avella et al., 2003; Ivanenko et al., 2004; Ting & Mcpherson, 2005; Tresch et al., 2006). In particular, muscle activation analysis allows identifying muscle groups (M-modes) within which muscles show parallel activation changes. We define synergies as a neural organization of a set of M-modes that ensures stability of a task-specific performance variable (COP<sub>AP</sub> coordinate) by covariation of the M-mode involvement across repetitive trials (Latash, 2008).

A number of earlier studies documented synergic control changes in PD. Until now, those studies focused on finger coordination (Jo et al., 2015; Park et al., 2012, 2013a, 2014). The current study extended these previous experiments to the synergic control of posture. Two aspects of changed synergic control were observed across systems (digits and muscles) and tasks (pressing, prehension, and vertical posture). All studies reported reduced ∆V indices at steady states and lower ASAs in preparation to a quick action. The similarity of the findings across systems and tasks suggests a general impairment in the neural mechanisms involved in the control of stability of motor performance in PD. This makes the individual results specific reflections of a basic problem reviewed recently as impaired control of stability, ICS (Latash & Huang, 2015).

To our knowledge this is first study to test multi-muscle synergies in PD during a postural task. As hypothesized, PD patients showed a significantly smaller amount of variance in muscle
activation that was accounted for by the first four M-modes. This observation suggests a less consistent organization of muscles into M-modes, possibly related to the sway task being perceived as more challenging by the PD group (cf. Danna-Dos-Santos et al., 2008). In addition, PD subjects showed significantly reduced indices of M-mode synergies stabilizing COP$_{AP}$. Note that we tested PD patients without clinically identifiable signs of postural instability. Early-stage PD is associated with measurable changes in gait and balance indices, which can even be observed in persons at high risk of PD (Baltajieva et al., 2006; Maetzler & Hausdorff, 2012). These indices include, in particular, trunk sway measures (Maetzler et al., 2012). Our study provides a complementary approach to early problems with postural control in PD based on the theory of synergic control. Future studies are warranted to follow the progression of postural synergic indices to investigate whether these measures may be able to predict future clinical postural instability.

### 4.3.2 Impaired feed-forward control of synergies in PD

We explored two aspects of feed-forward postural control, anticipatory postural adjustments, APAs (Belen'kiï et al., 1967; Massion, 1992) and anticipatory synergy adjustments, ASAs (Klous et al., 2011; Olafsdottir et al., 2005). APAs typically are observed about 100 ms prior to the action/perturbation initiation. The purpose of APAs has been assumed to generate net forces and moments of force acting against those expected from the anticipated action/perturbation. PD patients with clinical postural instability (H&Y stage-III) show reduced and delayed APAs (Bazalgette et al., 1986; Dick et al., 1986; Diener et al., 1989). In our study, no significant difference in the APAs was observed between PDs and controls, a finding that is consistent with the lack of clinical postural instability in our PD patients.

Another aspect of feed-forward control is anticipatory synergy adjustments (ASAs; Olafsdottir et al., 2005), which are seen as changes in the synergy index stabilizing a salient performance variable prior to a quick change in that variable. ASAs are seen as early as 250–350 ms prior to action initiation. Their purpose has been assumed to induce gradual destabilization in order to
facilitate a planned quick change. We observed significantly reduced ASAs in PD subjects, suggesting that this aspect of feed-forward postural control may be more sensitive than APA to measure PD-related impairment. The documented reduction in ASAs in the PD group in the current study (as well as in earlier studies of hand function (Jo et al., 2015; Park et al., 2012, 2014) is a key finding and should be emphasized. Without ASAs, the nervous system would have to fight its own synergies stabilizing a variable in a preceding steady state. Indeed, it is possible that some actions may be nearly impossible to initiate without ASAs, in particular those starting from a steady state where stability is essential. Vertical posture is an example of a steady-state task that serves as the background for many whole-body actions. Although speculative, an impaired ability to generate ASAs could be related causally to episodes of disabling freezing, which are common in later stages of PD.

4.3.3 Concluding comments

The most obvious limitation of our study is the relatively small size of the PD and control groups. Nevertheless, the current study provides the first evidence of impaired synergic control during postural tasks in PD and follow-up studies are warranted. It would be highly desirable to conduct a longitudinal follow-up study of these subjects and/or compare synergy indices across H&Y stages to evaluate the predictive value of synergy indices. In addition, it also would be important to compare indices of synergies with a broader range of clinical indices reflecting postural stability and freezing of gait such as postural sway and step/turn initiation in PD.
CHAPTER 5

Effects of Dopamine-Replacement Medication on Multi-Muscle Synergies

Postural instability represents one of the important features of Parkinson’s disease (PD), which is also a major source of disability in PD as the disease advances. The emergence of postural instability signifies a major landmark of progression from stage-II to stage-III according to the Hoehn and Yahr (1967) staging for PD. Clinical assessment of postural instability in PD typically is subjective (Ozinga et al., 2015), e.g. based on observations of patient’s reaction during the shoulder pull-test and reports of the incidence of falls. Recently, we have shown that the measurement of impaired stability control may be used as an early biomarker of PD, sensitive in detecting the problems with postural stability even in H&Y stage-II patients (reviewed in Latash & Huang, 2015).

In earlier studies, we analyzed synergies defined as neural organizations of large sets of effectors, e.g., digits, joint, or muscles, providing the stability of important performance variables (Latash, 2012a; Latash et al., 2007). These studies used an index of multi-muscle synergies computed within the framework of the uncontrolled manifold (UCM) hypothesis (Scholz & Schöner, 1999) and representing the relative amount of inter-trial variance that had no effect on shifts of the center of pressure (COP) in the total amount of this variance (Krishnamoorthy et al., 2003a, 2003b). Quantitative analysis of such task-specific synergies has shown that during steady-state action synergies are typically strong while they show a drop in the synergy index when a person prepares to perform a quick action. These anticipatory synergy adjustments (ASAs; Olafsdottir et al., 2005; Shim et al., 2005) are seen 200-300 ms prior to the action initiation; ASAs represent an important reflection of controlled stability that allows combining stability during steady state and agility in transition to a quick action (Latash & Huang, 2015). Recent studies have shown that the synergy index during steady-state performance is lower and ASAs are reduced and delayed in PD subjects (Jo et al., 2015; Park et al., 2012), in particular in postural tasks (Falaki et al., 2016).
In this study, we explored whether indices of synergies in PD patients performing a postural task are sensitive to dopamine-replacement medication. Based on an earlier study (Park et al., 2014), we expected that dopamine-replacement therapy would lead to higher synergy indices (increased stability) during quiet standing (Hypothesis 1) and larger ASAs (increased agility) in preparation to the self-imposed perturbation (Hypothesis 2). The confirmation of these hypotheses would underscore the importance of the basal ganglia in synergic control, and the potential utility of synergy indices for clinical research and practice.

5.1 Methods

Many of the procedures detailed in this section recapitulate information in Chapter 3 Common Methods. However, certain quantitative specifics are only presented here.

5.1.1 Subjects

A group of 6 H&Y stage-II and 4 stage-III (4 females) PD patients (aged 69 ± 6 years, mean ± standard deviation, SD) participated in this study. No healthy controls were tested because this comparison had been performed in an earlier study (Falaki et al., 2016). Table 5.1 presents general information about the subjects. All subjects were diagnosed by an experienced clinician. All subjects gave written informed consent approved by the Hershey Medical Center Institutional Review Board.

5.1.2 Procedures

Subjects stood on a force platform (OPTIMA, Advanced Mechanical Technology Inc., MA, USA) while EMG signals were recorded using a 16-channel Trigno wireless system (Delsys Inc., MA, USA). PD patients were tested twice: early in the morning prior to taking their first medication following an overnight withdrawal (off-drug condition) and one hour after taking their medication (on-drug condition). Participants stood barefoot on the force platform with their feet parallel and shoulder width apart. The foot position was marked on the surface of the platform and reproduced across all trials. There were four tasks: (1) quiet standing (QS), (2) voluntary sway (VS), (3) load...
release (LR), and (4) fast-body motion (FS). Tasks always were performed in this order: QS, VS, and block randomized LR and FS.

Table 5.1 Description of PD participants

<table>
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<th>Gender, M/F</th>
<th>Age, years</th>
<th>Symptom Onset, R/L</th>
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<th>UPDRS Off-drug</th>
<th>UPDRS On-drug</th>
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<th>Axial motor sub-score On-drug</th>
<th>LEDD mg</th>
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<td>M</td>
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</table>

H&Y: Hoehn and Yahr stage, M/F: male/females, R/L: right/left, LEDD: levodopa equivalent daily dose, UPDRS: Unified Parkinson’s Disease Rating Scale part III – motor scores (UPDRS-III), levodopa equivalent daily dose (LEDD) was estimated based on (Tomlinson et al., 2010).

Prior to data collection, participants went through a familiarization session during which the following number of practice trials were performed for each task: two trials prior to the VS task; four trials prior to the LR task; and four trials prior to the FS task. During the on-drug testing, participants performed only one practice trial prior to the LR and FS tasks.

5.1.3 Data processing

Recorded signals were processed offline using a customized MATLAB program (MathWorks Inc., MA, USA). Force platform signals were low-pass filtered at 10 Hz with a fourth-order, zero-lag Butterworth filter. The filtered data were used to compute time-varying COPAP (Winter et al., 1996). To avoid edge effects for VS trials (the action during its initiation and close to its termination), only the data within the interval \( \{3 \text{ s} \; ; \; 28 \text{ s} \} \) were used. On average, each subject performed 10 full cycles within this interval. Trials without major errors were accepted; the number of those trials was \( 16 \pm 2 \) and \( 16 \pm 1 \) for LR, \( 6 \pm 2 \) and \( 6 \pm 1 \) for FS, for the off-drug and on-drug conditions, respectively.
Initiation of anticipatory postural adjustments (APAs; Belen'kiĭ et al., 1967; Massion, 1992) in the LR task was defined using the time when the averaged across trials muscle activation level within a series performed by a subject exceeded ±2 SD from its respective mean activity (computed over the time interval \{T_0-1000 \text{ ms}; T_0-300 \text{ ms}\}). Dorsal muscles showed clear APAs in all participants; hence, the time when the earliest APA happened across those muscles was selected as \( t_{\text{APA}} \). The identified \( t_{\text{APA}} \) values were further confirmed visually to avoid false starts due to spontaneous transient EMG changes, including possible episodes of co-contraction.

To quantify anticipatory synergy adjustments (ASAs), the synergy index was averaged within two time intervals during the LR task. The first was a 200-ms steady state (SS, Figure 5.1A) from \((T_0-1000) \text{ ms to } (T_0-800) \text{ ms, whereas the second was a 50-ms time interval about } T_0 (T_0, Figure 5.1A). ASA was quantified as the amount of \( \Delta V_Z \) drop in preparation to the movement, \( \Delta \Delta V_Z \).

5.1.4 Statistics

Data are presented as means ± standard errors (SE) with median and inter-quartiles (IQR) values. We used Wilcoxon signed-rank test and two-way and three-way ANOVAs with repeated measures, factors Variance (\( V_{\text{UCM}} \) and \( V_{\text{ORT}} \)), Phase (SS and T_0), and Condition (off-drug and on-drug) to analyze effects of medication on the main outcome variables across phases. In case sphericity and normality violations; Geenhouse-Geisser correction was applied. Pair-wise comparisons with Bonferroni corrections were used to explore significant effects at \( p < 0.05 \).

5.2 Results

5.2.1 Characteristics of COP displacements and EMG pattern

Both the average rate of \( \text{COP}_{\text{AP}} \) shift, \((d\text{COP}/dt)_{\text{AV}} \) and the maximum rate of \( \text{COP}_{\text{AP}} \) shift, \((d\text{COP}/dt)_{\text{MAX}} \) during the fast body motion task were significantly smaller in the off-drug condition than in the on-drug condition: 15.0 ± 1.05 (median: 14.6; IQR: 13.1, 17.1) cm/s vs. 18.0 ± 1.22
(median: 17.2; IQR: 15.7, 19.1) cm/s, p < 0.005; and 34.8 ± 2.68 (median: 31.1; IQR: 28.9, 38.5) cm/s vs. 40.0 ± 2.89 (median: 37.9; IQR: 33.5, 45.1) cm/s, p < 0.01, respectively.

In the load release (LR) task, consistent changes in the EMG signals prior to the load release time (T₀) were seen in all subjects, starting as early as 150 ms prior to T₀. This early modulation, anticipatory postural adjustment (APA), was observed most commonly in GM, BF, ST, EST, and ESL. On average, there was only a small, non-significant difference in tAPA between the two medication conditions (off-drug: –135.5 ± 15.15 (median: -132.5; IQR: -178.5, -107.5) ms vs. on-drug: –156.1 ± 14.18 (median: -179.5; IQR: -193.5, -110.5) ms).

5.2.2 Defining M-modes and Jacobian

The PCA with rotation and factor extraction on IEMG₅:NORM in the VS task allowed identifying the first four M-modes, which accounted for 68.6 ± 2.2% (median: 68.7; IQR: 65.5, 72.9) of the total variance in the off-drug condition, and 74.7 ± 2.4% (median: 74.8; IQR: 68.2, 80.7) in the on-drug condition (p < 0.01; Wilcoxon signed-rank test).

For each participant and medication condition, multiple linear regression analysis was used to correlate shifts of COP₅:AP (∆COP₅:AP) with small M-mode magnitude changes (∆M, see ‘Common methods’). In both medication conditions, all ∆M values were significant predictors of ∆COP₅:AP (p < 0.001). Adjusted R² values were 0.62 ± 0.04 (median: 0.61; IQR: 0.53, 0.69) and 0.66 ± 0.04 (median: 0.67; IQR: 0.6, 0.73) in the off-drug and on-drug conditions, respectively (p < 0.05; Wilcoxon signed-rank test).

5.2.3 Analysis of M-mode variance

EMG data from the LR trials were used to quantify across-trial variance in two M-mode subspaces, VUCM (variance leading to unchanged COP₅:AP) and VORT (variance leading to COP₅:AP shifts). When subjects were standing quietly (steady state), VUCM was nearly two-fold higher in the on-drug condition.
condition compared to the off-drug condition (Figure 5.1A), whereas there were no major differences between the $V_{\text{ORT}}$ magnitudes (Figure 5.1A).

By the time of load release ($T_0$), there was a small drop in $V_{\text{UCM}}$ and a small increase in $V_{\text{ORT}}$ in the on-drug condition, without consistent difference in either index in the off-drug condition.

ANOVA on $V_{\text{UCM}}$ and $V_{\text{ORT}}$ showed a significant $\text{Condition} \times \text{Phase} \times \text{Variance}$ interaction [$F_{(1,18)} = 5.74, p < 0.05$] with no other significant effects. The interaction reflected counter-directional changes in the two variance components between the two phases confirmed by a two-way ANOVA showing a significant $\Delta \text{Variance} \times \text{Condition}$ interaction [$F_{(1,18)} = 5.74, p < 0.05$]. Wilcoxon’s signed-rank test confirmed that $V_{\text{UCM}}$ was significantly greater ($p < 0.05$) in the on-drug condition compared to the off-drug condition during both SS (median: 0.02; IQR: 0.0145, 0.037) vs. median: 0.0107; IQR: 0.0096,
Time profiles of the synergy index, $\Delta V_Z$ with standard error shades are presented in Figure 5.2C; $\Delta V_Z$ during steady state was significantly lower in the off-drug condition compared to the on-drug condition (median: -0.124; IQR: -0.264, 0.069 vs. median: 0.104; IQR: 0.038, 0.239; p < 0.01, Wilcoxon’s signed-rank test). Nine out of 10 subjects showed a > 40% increase in the magnitude of the synergy index from the off-drug condition to the on-drug condition. Two-way repeated measures ANOVA showed a significant Condition $\times$ Phase interaction [$F_{(1,18)} = 5.47, p < 0.05$] reflecting a significant drop in $\Delta V_Z$ from SS to $\approx T_0$ (median: 0.04; IQR: -0.076, 0.168; $F_{(1,9)} = 7.63, p < 0.05$), i.e.
5.3 Discussion

In this study, we hypothesized that dopamine-replacement medication would result in: (1) higher synergy indices during the quiet standing (higher stability); and 2) larger anticipatory synergy adjustments (ASAs) in preparation to a self-triggered perturbation (higher agility). Both hypotheses have been confirmed in the experiment. The latter effect may be related to the improved performance in the fast-sway task. We observed larger changes in the component of variance ($V_{UCM}$) that had no effect on the center of pressure coordinate. This result is important, as it suggests that medication led to more flexible behavior in the patients and increased variability at the level of M-modes without negative impact on precision of performance with respect to COP$_{AP}$. In addition, we observed significant medication effects on the ability of patients to unite muscles into stable groups (muscle modes, M-modes). Our results, together with the results of an earlier study, which documented synergy index and ASA differences between PD patients and healthy controls (Falaki et al. 2016), point at several critical actions of dopamine replacement medications related to synergic control of muscles in postural tasks.

5.3.1 Drug effects on synergies in PD

The term ‘synergy’ has at least three different meanings in movement science. In the clinical literature, this word commonly implies stereotypical patterns of muscle activation that interfere with purposeful actions after stroke (Bobath, 1978; DeWald et al., 1995). Another commonly used meaning is a number of performance variables, kinetic, kinematic, or electromyographic, that show parallel changes with task parameters or over time (d’Avella et al., 2003; Ivanenko et al., 2004; Krishnamoorthy et al., 2003a; Ting & Macpherson, 2005); e.g., M-modes in our study. We define
synergies as neurophysiological mechanisms providing for stability of salient performance variables (reviewed in Latash et al., 2007).

In our study, we used PCA with rotation and factor extraction to identify a set of orthogonal M-modes, which is a major advantage for inter-trial variance analysis of multi-M-mode synergies stabilizing the COP\textsubscript{AP} coordinate (cf. Tresch et al., 2006). If subjects use a consistent set of M-modes over the performance of the cyclical sway task, the amount of variance accounted for by a set of M-modes is expected to be relatively high. If the subjects switch the way muscles are organized into M-modes during the cyclical sway task, the index is expected to drop. The amount of variance in the muscle activation space accounted for by four M-modes was significantly higher in the on-drug condition. This observation suggests that the drug helped the participants to be more consistent in using the same M-modes throughout the cycle.

Recently, we have documented a drop in the index of M-mode synergies in PD, which was seen even in H\&Y stage-II patients (Falaki et al., 2016). In the current study, these synergy index values, on average, were negative or close to zero in patients off-drug. PD patients, however, showed positive synergy index values while on-drug. This may be interpreted as a complete loss in the ability to organize M-modes into COP\textsubscript{AP} stabilizing synergies in our patient group, which is partly recovered with the help of medications.

We would like to emphasize that the medication did not lead to significant changes in V\textsubscript{ORT}, a component of variance affecting COP\textsubscript{AP}. The other component of variance, V\textsubscript{UCM}, which did not affect COP\textsubscript{AP}, increased nearly two-fold in the on-drug condition. In more intuitive terms, the subjects became more variable (less stereotypical) without becoming less accurate.

5.3.2 Feed-forward control of postural tasks in PD

PD is known to affect feed-forward adjustments across motor tasks. In particular, PD has been reported to lead to delayed and reduced anticipatory postural adjustments (APAs) during
postural tasks (Bazalgette et al., 1986; Dick et al., 1986; Latash et al., 1995). In our experiment, we quantified only the timing of APAs and found no significant medication effects on this index. These results are consistent with earlier observations of minor or lacking effects of dopamine-replacement drugs on APAs (e.g., de Kam et al. 2014).

Another aspect of feed-forward control, anticipatory synergy adjustments (ASAs; Olafsdottir et al., 2005; Shim et al., 2005) represent gradual attenuation of a synergy stabilizing a salient performance variable in preparation to an action involving a quick change of that variable. ASAs are functionally important and their impairment potentially can lead to difficulties with movement initiation (Latash & Huang 2015). In contrast to the unchanged APAs, ASAs were significantly smaller in the off-drug condition compared to on-drug. This could be related to the improved performance of participants in the fast-sway task on-drug. Our observations suggest that feed-forward control of the stability of multi-muscle actions may be improved by medications without necessarily affecting the net mechanical effects of APAs.

One of the drawbacks of the current study is the relatively small sample of PD patients. Whereas we obtained statistically significant effects, it is possible that testing a larger group would also reveal differences between H&Y stage-II and stage-III patients. Future studies with larger sample sizes and with levodopa-challenge (suboptimal dosages of medication) are warranted to provide a better understanding of the clinical and neurobiological implications of synergy measurements.

5.3.3 Concluding comments

To conclude, our study has shown that dopamine-replacement drugs lead to higher indices of multi-muscle synergies and higher ASA indices in PD. These results underscore the importance of the basal ganglia circuitry for both stability of multi-muscle action and agility of behavior.
CHAPTER 6

Motor Equivalence and Structure of Inter-Trial Variance

The term “synergy” has been used in the literature in different ways. In clinical literature, synergy usually means a pathological, stereotypical pattern of muscle activations interfering with purposeful actions (DeWald et al., 1995). Another meaning of synergy is a group of variables with proportional scaling of changes over time or with changes in task parameters (d’Avella et al., 2003; Ivanenko et al., 2004; Ting & Macpherson, 2005). To avoid terminological confusion, we prefer to address such groups as modes (Krishnamoorthy et al., 2003a) and use them as elemental variables in the analysis of synergies defined as neural organizations of elements (such as joints, limbs, digits, muscle groups, etc.) ensuring task-specific stability of salient performance variables (reviewed in Latash 2008, 2016). A number of recent studies quantified multi-element motor synergies in different populations, including patients with Parkinson’s disease (PD; reviewed in Latash 2012a, 2016). These studies defined synergies as neural organizations of abundant sets of elements whose purpose is to provide stability of salient performance variables (reviewed in Latash 2012a, 2016). In particular, synergies in the space of activations of muscle groups (M-modes) stabilizing coordinates of the center of pressure (COP) were studied (Falaki et al., 2016). This analysis was performed using the framework of the uncontrolled manifold (UCM) hypothesis (Latash et al., 2007; Scholz and Schöner, 1999) to quantify two components of inter-trial (or inter-cycle, for cyclical tasks) variance within the space of M-modes. The variance component within the UCM space ($V_{UCM}$) had no effect on the COP coordinate, whereas the variance component within the space orthogonal to the UCM ($V_{ORT}$) did. The normalized difference between $V_{UCM}$ and $V_{ORT}$, quantified per dimension in each space, has been used as an index of stability (a synergy index). In this context, stability means an ability to return to a state or trajectory following a small transient perturbation or a change in initial state. Analysis of inter-cycle variance may be viewed as a method producing a proxy of stability.
(reviewed in Latash, 2008, 2016). In particular, repeating a task from slightly different initial states is expected to lead to trajectories converging in more stable directions and diverging in unstable directions resulting in different variance indices within the UCM and ORT.

Two aspects of impaired control of stability in PD patients have been identified, namely, impaired stability and impaired agility (reviewed in Latash & Huang, 2015). In particular, PD patients typically show weaker synergies stabilizing COP coordinates during steady-state tasks interpreted as signs of impaired stability. Weaker synergies in postural tasks have been documented in early-stage PD patients with no identifiable clinical signs of postural instability (Falaki et al., 2016). These changes in the synergy index show sensitivity to dopamine-replacement drugs (Falaki et al., 2017; Park et al., 2014).

Figure 6.1 An illustration of the main notions for a simple task of producing a constant sum with two effectors: $E_1 + E_2 = C$. For a given $C$, the solution space is shown with the slanted dashed line (UCM$_1$). The cloud of data points measured in consecutive trials is elongated along the UCM ($V_{UCM} > V_{ORT}$). If the subject of this experiment is asked to produce a transient quick change in $C$ and then come back to the initial value, motion to a new UCM (UCM$_2$) will be followed by a return motion ending up in a new point (2) that deviates from the original point (1) along the UCM more than along the orthogonal to the UCM direction (ME > nME).

One of the problems with using analysis of inter-trial variance in patient populations is the necessity to collect multiple trials to obtain clouds of data points (illustrated in Figure 6.1) to estimate $V_{UCM}$ and $V_{ORT}$. Recently, another set of metrics has been developed within the framework of the UCM hypothesis, which can be measured in single trials. This analysis quantifies the magnitudes of motion of an abundant system within the UCM and ORT spaces (Mattos et al., 2011, 2013, 2015;
Scholz et al., 2007). The within UCM component, by definition, has no effect on the salient performance variable; it has been addressed as motor equivalent (ME). The ORT component, non-motor equivalent (nME), changes the performance variable.

*Figure 6.1* illustrates the notions of $V_{\text{UCM}}$, $V_{\text{ORT}}$, ME and nME using a task of producing a particular magnitude of the sum of two variables: $E_1 + E_2 = C$. For a given $C$, the solution space is shown with the slanted dashed line (UCM$_1$). A synergy stabilizing ($E1 + E2$) is reflected in the cloud of data points measured in consecutive trials elongated along the UCM ($V_{\text{UCM}} > V_{\text{ORT}}$). If the subject of this experiment is asked to produce a transient quick change in $C$ and then return to the initial value, motion to a new UCM (UCM$_2$) will be followed by a return motion ending up at a new point (2) that deviates from the original point (1) along the UCM more than along the orthogonal to the UCM direction (ME > nME).

Both the inter-trial variance analysis and the ME analysis provide proxies of stability of the performance variable (reviewed in Latash, 2016, 2017). They are not identical, however, and a few recent studies have documented different statistical effects on the corresponding sets of metrics (Mattos et al., 2011, 2015). Note that ME analysis has never been performed in the space of muscle activations (or M-modes) during whole-body tasks. This analysis also has never been applied to data in neurological patients. In this study, we explore the links between the ME and variance analyses, and the potential usefulness of the ME analysis for clinical studies by re-analyzing data from two earlier experiments (Falaki et al., 2016, 2017). Specifically, we addressed the following hypotheses.

**Hypothesis-1** PD patients will show smaller ME components during voluntary cyclical sway compared to control subjects (cf. smaller $V_{\text{UCM}}$ in PD, Falaki et al., 2016). **Hypothesis-2** PD patients will show smaller ME components off-drugs compared to the on-drug state (cf. smaller $V_{\text{UCM}}$ off-drugs, Falaki et al., 2017a). **Hypothesis-3** the ME component will correlate with $V_{\text{UCM}}$, whereas the nME component will correlate with $V_{\text{ORT}}$. The last hypothesis is based on statistical considerations described in more detail in the “Discussion”. 
We also explored the time profiles in the outcome indices within the sway cycle using a factor *Phase*. This exploration was based on earlier studies showing correlations of $V_{ORT}$ with the rate of change of the salient performance variable and correlation of $V_{UCM}$ with the magnitude of that variable (Latash et al., 2002b; Scholz et al., 2002). These findings were interpreted later within a model of synergic control (Goodman et al., 2005), which assigned $V_{ORT}$ to variance in setting timing parameters during a cyclical action and $V_{UCM}$ to variance in setting spatial parameters. We expected similar relations between the rate of change of COP and nME, and between its magnitude and ME.

### 6.1 Methods

Many of the procedures detailed in this section recapitulate information in Chapter 3 *Common Methods*. However, certain quantitative specifics are only presented here.

This section reports results of additional analysis of the data collected in *Chapters 4 and 5*, and published earlier (Falaki et al., 2016, 2017). Here we briefly describe the materials and methods of the two studies.

#### 6.1.1 Subjects

In the first experiment, 11 patients (6 females) diagnosed with PD at stage-II according to Hoehn and Yahr (H&Y; Hoehn and Yahr, 1967), age 69 ± 6 years (mean ± standard deviation), and 11 healthy adults (age 65 ± 8 years, 5 females) volunteered to participate. In the second experiment, 10 PD patients (6 H&Y stage-II and 4 H&Y stage-III; age 69 ± 6; 5 females) participated. Three patients took part in both experiments. All of the participants were right-hand dominant according to their preferential hand use during writing and eating, except for one ambidextrous control subject (Sub #C07, experiment 1) and one ambidextrous patient (Sub #P17, experiment 2). *Table 6.1* presents the general characteristics of the participants, as well as the Unified Parkinson’s Disease Rating Scale (UPDRS-III) motor scores, disease duration since diagnosis, and the Levodopa equivalent dose (LED; Tomlinson et al., 2010).
### Table 6.1 Description of the participants

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M/F: male/females, R/L: right/left, LED: levodopa equivalent dose

Parkinson’s disease participants who were common in both experiments are shown in bold.

Control subjects were free from any diagnosed neurological or musculoskeletal disorder, and patients had no other known neurological or motor disorder except PD. None of the H&Y stage-II patients showed signs of clinically identifiable postural instability (falls or positive responses to the shoulder pull test described in UPDRS) and no patient showed drug-induced dyskinesia on their...
prescribed medications. Participants were recruited from a large subject pool of an ongoing clinical study at the Penn State Milton S. Hershey Medical Center and were referred by their neurologist. All participants gave written informed consent according to the protocol approved by the Institutional Review Board of the Hershey Medical Center.

6.1.2 Procedures

Subjects stood on a force platform (AMTI, OPTIMA) and EMG data were collected using rectangular-shaped active electrodes that housed built-in pre-amplifiers on the recording heads (Delsys, Trigno Wireless EMG). We recorded EMGs on one side of the body based on earlier studies documenting bilateral changes in indices of synergies with no side differences in PD patients, even in those at H&Y stage-I that is defined clinically as the stage at which PD symptoms are limited to one side of the body (Park et al., 2012, 2014). Initially, participants were asked to stand barefoot on the platform while keeping their feet parallel at shoulder width. We enforced the same initial posture throughout different trials by marking the position of each foot on the platform surface and asking subjects to reproduce this initial position at the beginning of each trial.

In Experiment 1, patients were tested on their normal schedule of medication. The experiment started with measuring UPDRS-III motor scores by a trained clinician, after which all participants (PD patients and controls) performed the QS task followed by the VS task. Experiment 2 involved two sessions in which only PD patients participated. The first session started early in the morning following an overnight withdrawal of the prescribed PD medication (off-drug condition). When participants finished the first session, they took their prescribed medication. The second session started 1 h after taking the medication (on-drug condition). Each session started with measuring UPDRS-III motor scores followed by performing the QS and VS tasks.

6.1.3 Data processing

EMG and force platform signals were processed offline using a customized Matlab program. For VS trials, to avoid edge effects and incomplete cycles at the beginning and end of each trial, only
the data within \{3 \text{s}; 28 \text{s}\} time interval were accepted. The time interval between two consecutive anterior-most COP_{AP} coordinates was defined as a sway cycle. On average, each participant performed 10 cycles within each VS trial. There was no statistically significant difference between the average number of cycles performed by PD and CO groups (Experiment 1), or between on-drug and off-drug conditions (Experiment 2). For the analysis of variance and motor equivalence, cycles that had an extra local COP_{AP} peak and those with the most anterior (posterior) COP_{AP} coordinates that differed from the corresponding means by more than ±2 SD were removed from further analysis. Such aberrant cycles likely reflected distracted attention by the subject; they had to be removed to satisfy one of the main assumptions of the analysis, namely that the subjects were trying “to do the same” across cycles. The total number of rejected cycles varied between 0 and 3 per subject.

As in the aforementioned earlier studies, we decided to accept a fixed number of M-modes across groups and conditions rather than aim for a similar amount of total variance accounted for by the selected modes. Note that adding an M-mode to a set increases the UCM dimensionality without affecting ORT dimensionality (see later). Since variance magnitudes are normalized per dimension (whereas ME and nME indices are normalized per square root of dimensionality), this would result in unfair comparisons. Indeed, adding an M-mode that accounts for little variance would reduce variance within the UCM (and ME) after normalization without affecting variance within ORT (and nME). Moreover, adding a fifth M-mode would create more modes with only one muscle significantly loaded, which goes against the basic idea of identifying muscle groups with parallel scaling of activation.

**Analysis of variance:** According to the uncontrolled manifold (UCM) hypothesis (Scholz & Schöner 1999), elemental variables (in this study M-modes) are organized to provide stability of a potentially important performance variable (in this study, COP_{AP}). Within this approach, two inter-trial (inter-cycle) variance components are quantified in the M-mode space. The first component is within the UCM (\(V_{UCM}\), variance preserving the COP_{AP} coordinate), whereas the second component is
in the orthogonal to the UCM sub-space ($V_{ORT}$, variance affecting the COP$_{AP}$ coordinate). The M-mode space had the dimensionality of $n = 4$. Since the hypothesis of COP$_{AP}$ stabilization accounted for one degree of freedom ($d = 1$), the UCM sub-space had the dimensionality of three. For each participant, the duration of all of the accepted sway cycles during the VS task was normalized to 100%. For each time-normalized step (1% of the sway cycle), the mean vector of M-mode magnitudes across cycles ($\bar{M}$) was subtracted from vectors of individual M-mode magnitudes from each cycle resulting in mean-free values of M-modes changes, $\Delta M_{demeaned}$ ($\Delta M_{demeaned} = M - \bar{M}$). $V_{UCM}$ and $V_{ORT}$ were calculated by projecting $\Delta M_{demeaned}$ onto the UCM and ORT spaces, respectively.

**Analysis of motor equivalence:** The motor equivalence analysis quantifies the amount of deviations in the space of elemental variables (M-modes) that occurs in directions preserving (motor equivalent, ME), and changing (non-motor equivalent, nME) the performance variable, COP$_{AP}$. For each subject and each time-normalized step, deviations of M-modes from one sway cycle to the next were projected onto the null-space of $J$ and its orthogonal complement (see Common methods chapter). For quantitative comparisons, ME and nME components were normalized by the square root of the dimension in the respective spaces (cf. Mattos et al. 2011). For each subject, the average of the ME and nME components across time-normalized cycles was computed for statistical analyses.

### 6.1.4 Statistics

Statistical analysis was performed with SPSS (IBM Corp.). In the text and figures, data are shown as means ± standard errors (SE). To explore the dependence of outcome variables (kinematics of sway, $V_{UCM}$, $V_{ORT}$, ME and nME) on the phase of swaying, the factor *Phase* with four levels was used to represent four windows with a length equal to 11% of the sway cycle and centered about the maximum, minimum, and in-between phases of the cycle: ‘95–5%’ (representing 95–100% of cycle $n-1$ and 1-5% of cycle $n$), ‘20–30%’, ‘45–55%’, and ‘70–80%’. In Experiment 1, two-way repeated measures ANOVAs were used to explore the effects of factor *Phase* (four levels) and *Group* (two levels: PD and CO) on the outcome variables. Repeated measures ANOVAs with factors *Group*,
Variance (two levels: \(V_{UCM}\) and \(V_{ORT}\)), and/or Motor equivalence (two levels: ME and nME) were used to investigate effects of PD on the averaged across cycle variances and motor equivalence components. In Experiment 2, factor Medication (two levels: off-drug and on-drug) replaced factor Group in order to explore effects of the dopamine-replacement drug on the outcome variables. Data were checked for normality and sphericity. In case of violation of the assumption of sphericity, Greenhouse-Geisser correction was used for degrees-of-freedom adjustments. To explore significant effects at the level of \(p < 0.05\), pair-wise comparisons with Bonferroni corrections were performed. Correlations between variance components (\(V_{UCM}\) and \(V_{ORT}\)) and motor equivalence components (ME and nME) were explored using Pearson correlation coefficients. We present median values and inter-quartile ranges (IQR) for coefficients of determination (\(R^2\)).

6.2 Results

6.2.1 Voluntary sway kinematics

All participants, including patients in the off-drug condition, were able to perform qualitatively similar ‘sine-like’ time-profile of COP\(_{AP}\) during the voluntary body sway task. Figure 6.2 shows the mean (top panels) and SD (bottom panels) of the \(COP_{AP}\) averaged over VS cycles and across participants separately for Experiment 1 and Experiment 2. Participants were at the anterior-most position at 0 and 100% of the time-normalized sway cycle, whereas they were at the posterior-most position approximately at 50% of the sway time. There was no statistically significant difference in the \(COP_{AP}\) coordinate at different sway phases between PD and control participants (Experiment 1), and between the off-drug and on-drug conditions (Experiment 2) in the two-way ANOVAs with factors Phase and Group (Medication). The ANOVA showed only the trivial main effect of Phase. The average peak rate of \(COP_{AP}\) shifts, averaged across forward and backward phases, \((dCOP/dt)_{MAX}\), however, was significantly smaller in PD subjects (19.4 ± 1.65 cm/s) than controls (25.9 ± 1.61 cm/s), confirmed by a one-way ANOVA with factor Group (\(F_{(1,20)} = 7.98; p < 0.05\)). Although the SD of the
$COP_{AP}$ was larger in controls, the group difference was non-significant ($F(1,20) = 3.83; p > 0.05$). In Experiment 2, there was no statistically significant differences between ($dCOP/dt$)$_{MAX}$ in the off-drug (19.1 ± 1.80 cm/s) and on-drug (20.9 ± 1.49 cm/s) conditions, and no difference between the SD of the $COP_{AP}$ (off-drug: 0.82 ± 0.05; on-drug: 0.92 ± 0.07).

![Figure 6.2](image)

**Figure 6.2** Time-normalized profiles of the COP coordinate in the anterior–posterior direction ($COP_{AP}$; A and B) and the standard deviation of $COP_{AP}$ (SD-COP; C and D) with standard error shades. Participants were at the anterior-most position at 0 and 100%, of the sway cycle. At about 50% of the sway cycle, participants were at the posterior-most position. A and C Experiment 1. The dashed line represents the mean data for PD patients and the solid line represents the mean data for the controls. B and D Experiment 2. The dashed line represents the mean data for the off-drug condition and the solid line represents the mean data for the on-drug condition.

### 6.2.2 Defining M-modes and Jacobians

Based on the criteria described in the Methods, four M-modes were identified in all subjects. *Table 6.2* represents a typical set of muscle loadings for a PD participant in the on-drug and off-drug conditions. M1-mode and M2-mode typically involved significantly loaded dorsal or ventral muscles and are called either dorsal or ventral M-mode. The composition of those modes was similar in all
subjects and did not differ in PD patients based on the side of symptom onset. The other two M-modes compositions were more variable across subjects. Loadings over 0.5 are shown in bold.

**Table 6.2** Muscle loadings for the first four M-modes in a typical PD patient

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Off-drug</th>
<th>On-drug</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M1</td>
<td>M2</td>
</tr>
<tr>
<td>TA</td>
<td>0.75</td>
<td>-0.38</td>
</tr>
<tr>
<td>SOL</td>
<td>-0.45</td>
<td>0.72</td>
</tr>
<tr>
<td>GM</td>
<td>-0.46</td>
<td>0.77</td>
</tr>
<tr>
<td>GL</td>
<td>-0.42</td>
<td>0.74</td>
</tr>
<tr>
<td>BF</td>
<td>-0.01</td>
<td>0.90</td>
</tr>
<tr>
<td>ST</td>
<td>0.81</td>
<td>-0.09</td>
</tr>
<tr>
<td>RF</td>
<td>0.86</td>
<td>-0.31</td>
</tr>
<tr>
<td>VL</td>
<td>0.78</td>
<td>-0.17</td>
</tr>
<tr>
<td>VM</td>
<td>0.88</td>
<td>-0.34</td>
</tr>
<tr>
<td>TFL</td>
<td>0.87</td>
<td>-0.08</td>
</tr>
<tr>
<td>ESL</td>
<td>-0.16</td>
<td>0.16</td>
</tr>
<tr>
<td>EST</td>
<td>-0.17</td>
<td>0.20</td>
</tr>
<tr>
<td>RA</td>
<td>0.02</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Loading factors after Varimax rotation for a typical Parkinson’s disease patient in off-drug and on-drug conditions.

TA tibialis anterior, SOL soleus, GM gastrocnemius medialis, GL gastrocnemius lateralis, BF biceps femoris, ST semitendinosus, RF rectus femoris, VL vastus lateralis, VM vastus medialis, TFL tensor fasciae latae, ESL lumbar erector spinae, EST thoracic erector spinae, RA rectus abdominis

Significant loadings (greater than 0.5) are shown in bold.

In Experiment 1, the four M-modes accounted for, on average, significantly less variance in the muscle activation space in the PD group compared to controls (71.5 ± 1.74% vs. 78.3 ± 1.74%; $F_{(1,20)} = 7.969; p < 0.05$). In Experiment 2, the M-modes accounted for significantly less variance in the muscle activation space in the off-drug condition compared to its respective value in the on-drug condition (68.6 ± 2.2% vs. 74.7 ± 2.4%; $t(9) = -4.51, p < 0.01$). In both Experiments, all M-modes were significant predictors of $COP_{AP}$ shifts for each subject ($p < 0.001$).

6.2.3 Analysis of variance and motor equivalence

For each subject and/or medication condition, we used the framework of the UCM hypothesis to quantify two components of the inter-cycle variance in the M-mode space: the component affecting
(V\textsubscript{ORT}) and not affecting (V\textsubscript{UCM}) the COP\textsubscript{AP} coordinate during the VS task. The same data also were used to quantify the deviations in the M-mode space across consecutive cycles that preserved (ME) or changed (nME) the COP\textsubscript{AP} coordinate. The time profiles of V\textsubscript{UCM} and ME were similar to each other, whereas the time profiles of V\textsubscript{ORT} and nME were aligned closely.

![Graphs showing time profiles](image)

**Figure 6.3** Results of the motor equivalence and variance analyses in Experiment 1. Time-normalized profiles of the motor equivalent (ME, panel A) and non-motor equivalent (nME, panel B) components, variance within the UCM (V\textsubscript{UCM}, panel C), and within ORT (V\textsubscript{ORT}, panel D) for PD patients (dashed line) and controls (CO, solid line). Note the higher magnitudes of all indices in the controls and the typical double-peaked patterns of nME and VORT.

Figure 6.3 and Figure 6.4 present averaged time profiles over cycles of ME and nME (top panels) and V\textsubscript{UCM} and V\textsubscript{ORT} (bottom panels) for the two Experiments. Note the qualitative similarity of the top and bottom graphs. In particular, the nME and V\textsubscript{ORT} plots show a two-peak profile resembling that expected for the absolute value of \(dCOP(t)/dt\) if COP\((t)\) were a perfect sine wave (compare to the bottom panels in Figure 6.2).
To explore possible links of the outcome variables to parameters of the task, such as \( COP(t) \) and \( dCOP(t)/dt \), we used linear regression analysis. To explore the similarity between the pairs of outcome variables, \( V_{UCM} \) vs. ME and \( V_{ORT} \) vs. nME, we performed statistical analyses on the effects of the main factors (Phase, Group, and Medication) and correlation analyses within these pairs of variables.

**Experiment 1:** A two-way ANOVA, Group × Variance, showed that control subjects had significantly larger amounts of total inter-cycle variance in the M-mode space compared to PD patients (0.023 ± 0.002 vs. 0.016 ± 0.002; effect of Group \( F_{(1,20)} = 10.32; \ p < 0.01 \)). Both \( V_{UCM} \) and
$V_{\text{ORT}}$ in the PD group ($V_{\text{UCM}}$: 0.012 ± 0.001; $V_{\text{ORT}}$: 0.020 ± 0.003) were smaller compared to the control group ($V_{\text{UCM}}$: 0.018 ± 0.001; $V_{\text{ORT}}$: 0.029 ± 0.003). $V_{\text{ORT}}$ was, on average, larger than $V_{\text{UCM}}$ (effect of Variance; $F_{(1,20)} = 23.15; p < 0.001$). A two-way ANOVA, Phase × Group, performed separately on $V_{\text{UCM}}$ and $V_{\text{ORT}}$ showed no significant modulation of $V_{\text{UCM}}$ across the four phases of the sway cycle, whereas $V_{\text{ORT}}$ showed a significant Phase effect ($F_{(3,60)} = 12.80; p < 0.001$), and a significant Group × Phase interaction ($F_{(3,60)} = 3.39; p < 0.05$). Pair-wise comparisons revealed that $V_{\text{ORT}}$ in phases 1 and 3 was smaller than its respective values in phases 2 and 4 ($p < 0.05$). The interaction reflected the fact that the effect of phase on $V_{\text{ORT}}$ was significant in the control group only.

**Hypothesis 1** Similar results were obtained in the analysis of motor equivalence. In particular, both ME and nME in PD (ME: 0.121 ± 0.005; nME: 0.139 ± 0.10) were significantly smaller than their respective values in controls (ME: 0.138 ± 0.005; nME: 0.171 ± 0.010). This was confirmed by a significant effect of Group ($F_{(1,20)} = 8.24; p < 0.01$) in a two-way ANOVA Group × Motor equivalence. The nME component was larger than the ME component in both groups ($F_{(1,20)} = 14.64; p < 0.001$) without an interaction. A two-way ANOVA, Group × Phase, on nME showed significant effects of Group ($F_{(1,20)} = 5.50; p < 0.05$), Phase($F_{(3,60)} = 14.54; p < 0.001$), and a Group × Phase interaction ($F_{(3,60)} = 2.97; p < 0.05$). Similar to $V_{\text{ORT}}$, pair-wise comparisons revealed smaller magnitudes of nME in phases 1 and 3 compared with phases 2 and 4 ($p < 0.05$). In PD patients, only the amount of nME in phase 2 was larger than in phase 3 ($p < 0.05$). Further, we explored correlations between the nME (and $V_{\text{ORT}}$) indices and the derivative of the $COP_{\text{AP}}(t)$ for each subject using a liner regression analysis: $V_{\text{ORT}}$ (nME) = $a + b |dCOP/dt|$. The values of $V_{\text{ORT}}$ (nME) and $|COP_{\text{AP}}(t)/dt|$ were taken at each 1% from the time-normalized cycles. Table 6.3 summarizes the median, the first quartile, and the third quartile values. In 10 out of 11 controls, $V_{\text{ORT}}$ was correlated linearly with $|dCOP/dt|$. A similar relationship existed between nME and $|dCOP/dt|$. For the PD group, these correlations were significant in seven out of 11 patients.
The correlation between $V_{UCM}$ and $COP_{AP}(t)$ was also investigated using linear regression:

$$V_{UCM} \text{ (ME)} = a + b \ COP(t).$$

The values of $V_{UCM}$ and $COP(t)$ were taken at each 1% of the sway cycle. $V_{UCM}$ was correlated linearly with $COP_{AP}(t)$ in nine controls and 10 PD patients. Comparing ME and $COP_{AP}(t)$, a linear relation was observed in nine controls and nine PD patients.

**Table 6.3 Results of the correlation analysis**

| Study Group | $V_{ORT}$ vs. $|dCOP/dt|$ | nME vs. $|dCOP/dt|$ | $V_{UCM}$ vs. COP(t) | ME vs. COP(t) |
|-------------|--------------------------|------------------|------------------|----------------|
|             | Median Q₁, Q₃           | Median Q₁, Q₃   | Median Q₁, Q₃    | Median Q₁, Q₃  |
| PD patients | 0.11 0.04; 0.26         | 0.07 0.03; 0.20 | 0.17 0.13; 0.21  | 0.11 0.05; 0.19 |
| Controls    | 0.37 0.24; 0.42         | 0.31 0.24; 0.47 | 0.26 0.05; 0.39  | 0.10 0.08; 0.18 |
| Off-drug    | 0.08 0.02; 0.16         | 0.07 0.04; 0.29 | 0.27 0.10; 0.38  | 0.09 0.02; 0.36 |
| On-drug     | 0.06 0.02; 0.09         | 0.07 0.05; 0.11 | 0.18 0.04; 0.26  | 0.14 0.07; 0.24 |

The mean and inter-quartile values of the correlation between $V_{ORT}$ (nME) indices and $dCOP_{AP}(t)$, and between $V_{UCM}$ (ME) indices and $COP_{AP}(t)$

Q₁: the first quartile, Q₃: the third quartile

**Experiment 2:** Dopaminergic medications led to an increase in the amount of VUCM (0.017 ± 0.002 vs. 0.012 ± 0.002 on and off-drug, respectively; $F(1,9) = 6.08; p < 0.05$) without a change in VORT (0.021 ± 0.004 vs. 0.021 ± 0.003; on- and off-drug, respectively). There was also an effect of Phase ($F_{(3,54)} = 3.96; p < 0.05$) on $V_{UCM}$: On average, $V_{UCM}$ in phase 2 (0.012 ± 0.001) was smaller than in phase 3 (0.017 ± 0.002), as confirmed by pair-wise comparisons. There were no significant effects of Phase on $V_{ORT}$.

**Hypothesis 2** Similar results were obtained in the analysis of the ME and nME components. In particular, ME on-drug was larger compared to the off-drug condition (0.134 ± 0.005 vs. 0.118 ± 0.006; $F_{(1,9)} = 17.60; p < 0.01$). In contrast, there were no effects of Medication on the nME component (on-drug: 0.143 ± 0.008; off-drug 0.141 ± 0.010). There were no significant Phase effects on either ME or nME.

Overall, correlations between $ME(t)$ and $COP_{AP}(t)$ and between $nME(t)$ and $dCOP_{AP}(t)/dt$ were weak, although statistically significant in some of the patients. On-drug, the absolute value of
\[ \frac{dCOP(t)}{dt} \] was related linearly to \( V_{ORT} \) indices in seven patients and to the nME in eight patients. Off-drug, these relationships were significant for \( V_{ORT} \) in six patients and for nME in seven patients. In addition, there was a significant relationship between \( V_{UCM} \) and \( COP_{AP}(t) \) in seven patients and between ME and \( COP_{AP}(t) \) in nine patients in the on-drug condition. Off-drug, \( COP_{AP}(t) \) was correlated with \( V_{UCM} \) indices in nine patients and with ME in seven patients. A summary of the median and inter-quartile values is presented in Table 6.3.

**Hypothesis 3** Correlations between ME and \( V_{UCM} \), and between nME and \( V_{ORT} \) were explored using Pearson correlation coefficients. For each subject, time-normalized data points of variance components (\( V_{UCM} \) and \( V_{ORT} \)) were averaged over the cycle and plotted against the respective motor equivalence components (ME and nME), also averaged over the cycle. Figure 6.5 represents scatter plots of \( V_{UCM} \) and ME, as well as \( V_{ORT} \) and nME for Experiment 1 (panels A and B) and Experiment 2 (panels C and D) with the least squares line of best fit. In this Figure, data points refer to individual subjects. There was a significant correlation between \( V_{UCM} \) and ME (PD: \( R^2 = 0.49; \) CO: \( R^2 = 0.4; \) \( p < 0.05 \)), and between \( V_{ORT} \) and nME component (PD: \( R^2 = 0.87; \) CO: \( R^2 = 0.84; \) \( p < 0.05 \)) in Experiment 1. In Experiment 2, there also was a significant correlation between \( V_{UCM} \) and ME (off-drug: \( R^2 = 0.76; \) on-drug: \( R^2 = 0.42; \) \( p < 0.05 \)), and between \( V_{ORT} \) and nME (off-drug: \( R^2 = 0.48; \) on-drug: \( R^2 = 0.91; \) \( p < 0.05 \)).

We also quantified correlations between the same pairs of variables within each participant using cross-correlation analysis of time-normalized data points. Peak correlation coefficients were large for both Experiment 1 and Experiment 2. In Experiment 1, peak correlation coefficients between \( V_{UCM} \) and ME ranged from 0.35 to 0.87 for PD subjects (median: 0.77; IQR: 0.67, 0.84) and from 0.39 to 0.91 for controls (median: 0.73; IQR: 0.65, 0.79). For the analysis of \( V_{ORT} \) vs. nME, peak correlation coefficients ranged from 0.56 to 0.93 for PD subjects (median: 0.75; IQR: 0.70, 0.86) and from 0.55 to 0.96 for controls (median: 0.87; IQR: 0.76, 0.92). The time-lag of the peak correlation coefficient was close to zero in all comparisons (note that we used cycle percentage as a unit of time):
The mean ± SE of the time-lag for the controls was -3.6 ± 3.35 in % cycle for the ME-V_{UCM} analysis and 0 ± 0 for the nME-V_{ORT} analysis. For PD patients, the time-lag of cross-correlation analysis was -1.9 ± 1.91 for the ME-V_{UCM} analysis and -1.3 ± 1.27 for the nME-V_{ORT} analysis. There was no statistically significant difference between the groups.

Figure 6.5 Scatter plots of the variance and motor equivalence indices across subjects. Correlations between V_{UCM} and the ME component for Experiment 1 (panel A) and Experiment 2 (panel C) and between V_{ORT} and the nME component for Experiment 1 (panel B) and Experiment 2 (panel D) are presented with regression lines and coefficients of determination.

In Experiment 2, the time-lag was zero for all participants. For the off-drug condition, correlation coefficients between V_{UCM} and ME ranged from 0.68 to 0.90 (median: 0.84; IQR: 0.78, 0.88) and between V_{ORT} and nME ranged from 0.54 to 0.91 (median: 0.83; IQR: 0.77, 0.87). For the on-drug condition, correlation coefficients between V_{UCM} and ME ranged between 0.62 and 0.94.
(median: 0.77; IQR: 0.70, 0.87) and between \( V_{\text{ORT}} \) and nME from 0.54 to 0.88 (median: 0.80; IQR: 0.76, 0.86). There was no statistically significant difference between correlation coefficients due to the medication that was confirmed by a one-way ANOVA.

6.3 Discussion

The three main hypotheses formulated in the Introduction have been supported by the data. Indeed, in Experiment-1, PD patients showed smaller motor equivalent (ME) components within the space of muscle modes during voluntary cyclical sway compared to control subjects in support of our Hypothesis-1. In Experiment-2, PD patients showed smaller ME components off-drugs compared to the on-drug state in support of Hypothesis-2. Both qualitative comparisons (Figs. 3, 4) and correlation analyses confirmed similar patterns between the ME component and the variance within the UCM \( (V_{\text{UCM}}) \) and between the nME component and the variance within the ORT space \( (V_{\text{ORT}}) \). Effects of the main factors on the metrics computed in the analysis of variance and in the analysis of motor equivalence were similar in both experiments. These observations support Hypothesis-3.

Our comparisons of the two types of indices, those reflecting inter-cycle variance structure \( (V_{\text{UCM}} \) and \( V_{\text{ORT}}) \) and those reflecting motor equivalence estimated across consecutive cycles (ME and nME), have shown that they both are sensitive to PD and dopamine-replacement medications. Note that our Experiment 1 involved PD patients at stage-II according to Hoehn and Yahr (1967), which is defined as a stage without clinically identifiable postural instability. Nevertheless, both ME and variance indices showed significant differences between the PD and control groups. Both pairs of indices are proxies for the stability of a functionally important variable \( (\text{COP}_{\text{AP}}) \) estimated within the muscle mode space. The results suggest that indices of motor equivalence may be sensitive to emerging problems with postural stability even at stages when clinical examination fails to detect those problems. Experiment 2 confirmed that these indices also are sensitive to effects of dopamine-replacement medication. The fact that these two indices are correlated closely suggests that ME
indices may become a practical measurement for clinical research to gauge synergic control of postural stability. Although we used averages over numerous cycles to produce ME indices in the current study, theoretically a few trials may be sufficient. This is something to explore in the future.

6.3.1 Synergistic mechanisms of task-specific stability

Our study is based on the concept of multi-element synergies stabilizing important, task-specific variables in a hierarchical system (reviewed in Latash, 2010b, 2016, 2017). This general theoretical framework is based on the idea of parametric control, i.e., the neural control of movements based on specifying time patterns of parameters of natural laws. It suggests that neural variables at a hierarchically high, task-specific level encode referent coordinates (RCs) for salient performance variables. Further, as a result of several few-to-many transformations, these task-specific RCs are transformed into RCs for individual effectors, joints, and muscles. At the muscle level, RC is equivalent to threshold of the tonic stretch reflex, as in the classical equilibrium-point hypothesis (Feldman, 1966, 1986). The transformations are organized in such a way that spontaneous deviations of performance at the level of elements (due to changing intrinsic neural states and external forces) co-vary to keep variability of the salient variable relatively low. Such organizations have been addressed as synergies stabilizing those performance variables (Latash et al., 2007).

Note that proper stability, as ensured by synergies, is a crucial feature of all functional actions. For example, during steady-state performance, low stability may lead to failure and/or necessity to monitor performance and make corrections at all times. Another important aspect of synergies is their task-specificity: different performance variables can be stabilized by the same set of elemental variables (e.g., M-modes) depending on the task. This allows several tasks to be performed with a single set of effectors and to avoid interference among salient performance variables when a few tasks are conducted simultaneously.

The story about synergies and their changes in neurological disorders would be incomplete without mentioning the phenomenon of anticipatory synergy adjustments (ASAs, Olafsdottir et al.,
2005), which represents attenuation of a synergy in preparation for a quick action. This important functional mechanism allows a person to avoid fighting one’s own synergies during quick actions. ASAs have been documented across systems and tasks (Klous et al., 2011; Krishnan et al., 2011, 2012; Shim et al., 2005). This mechanism is impaired in a variety of patients with both subcortical and cortical disorders (Jo et al., 2016a; reviewed in Latash and Huang, 2015; Park et al., 2012), which may lead to difficulty with movement initiation and even episodes of freezing.

Whereas mechanisms of synergies (those responsible for organizing muscles into M-modes and those responsible for M-mode synergies stabilizing salient performance variables) remain largely unknown, recent studies in neurological patients provide insights into possible neurophysiological mechanisms of synergic control of different sets of effectors, from multi-finger actions, to multi-joint reaching, and to multi-muscle whole-body actions (reviewed in Latash and Huang, 2015). In particular, those studies have documented significantly impaired synergy indices during steady-state tasks in patients with subcortical disorders, but not following cortical stroke (Jo et al., 2016a; Reisman and Scholz, 2003). These findings are compatible with the idea of distributed processing modules (Houk, 2005) involving loops through the basal ganglia and the cerebellum. In contrast, ASAs are reduced and decreased in magnitude in patients with both cortical and subcortical disorders (Jo et al., 2016a; Park et al., 2012). Indices of synergic control are sensitive to very early stages of PD; they can be seen in the apparently non-involved hands of patients at H&Y stage-I (Park et al., 2012, 2014) and even in asymptomatic persons at elevated risk for parkinsonism, such as professional welders (Lewis et al., 2016).

So far, all the clinical studies of synergies have used analysis of the structure of inter-trial variance in two subspaces, the UCM where the salient performance variable does not change, and the ORT where it changes (see Figure 6.1). These methods have provided a wealth of useful information. Their broad application, however, has been slowed by the necessity to analyze clouds of data points that requires collecting numerous trials in patients. This is not always feasible given that many patient
populations are characterized by quick fatigue. One of the goals of our study has been to define whether a method that is capable of producing indices of stability based on a few trials, i.e. analysis of motor equivalence, is comparably sensitive to changes in synergies resulting from PD and/or dopaminergic medication. Whereas our experiment used indices of motor equivalence averaged over all of the cycles, such indices can be computed using individual cycles/trials and then averaged over only a few cycles or trials.

6.3.2 Indices of variance and motor equivalence

During cyclical tasks, analyses of inter-cycle variance and inter-cycle mean distances are linked if one assumes a perfectly normal distribution of the data. Indeed, if we assume that each measurement at a particular phase of the cycle represents a sample from a normal distribution, the difference between two random samples will be another normal distribution with the mean $\mu_D = 0$ and standard deviation $\sigma_D$ linearly related to standard deviation of the original distribution, $\sigma_D = \sigma \sqrt{2}$. In the analysis of motor equivalence, we computed absolute distances between data points in consecutive cycles (see "Methods"). This makes the distribution of those distances non-negative (folded) with a new mean ($\mu_X$) and new standard deviation ($\sigma_X$). From classical statistics (Leone et al., 1961):

$$\mu_X = \sigma \sqrt{\frac{2}{\pi}}$$

$$\sigma_X^2 = \sigma^2 - \mu_X^2$$

(6.1)

These equations can be applied separately to data in different sub-spaces of the original space. They suggest, in particular, that ME is expected to be proportional to the standard deviation within the UCM ($\sigma_{UCM}$), whereas nME is expected to be proportional to the standard deviation within the ORT space ($\sigma_{ORT}$). Correlations with squared magnitudes of standard deviations, $V_{UCM}$ and $V_{ORT}$, also are expected, although they may be weaker.
Indeed, our analysis has shown that ME correlated with $V_{UCM}$, whereas nME correlated with $V_{ORT}$ (see also the similar shapes of $V_{UCM}$ and ME and of $V_{ORT}$ and nME in Figures 6.3 and 6.4). Although the current data set is limited and does not allow distinguishing between correlations with standard deviation and with variance (we explored both and found no significant differences), they allow drawing an important conclusion: at least in some tasks, indices of motor equivalence (ME and nME) can be used as synergy indices instead of metrics of inter-cycle variance. This conclusion is corroborated by the observations of similar significant differences in both variance indices and motor equivalence indices between the PD and control groups in Experiment 1 and between the PD patients on- and off-drug in Experiment 2. This result allows collecting only a handful of cycles/trials ($<$ 5 trials) to obtain quantitative estimates of synergies stabilizing salient variables based on the ME and nME indices. As a result, analysis of motor equivalence may be applicable more easily to studies of populations with movement disorders who may be able to perform only a few cycles/trials of a given motor task.

The aforementioned statistical analysis potentially also can be applied to non-cyclical data. In discrete actions, however, it is more likely that individual trials differ from each other more than cycles within a continuous cyclical task due to the larger variance in setting central parameters that define the neural control process (cf., Friedman et al. 2009). As a result, a relatively small set of data points may deviate more from what is expected regarding a perfectly normal distribution. This may be the reason why, in some earlier studies, statistical effects on variance and motor equivalence indices were different (Mattos et al., 2011, 2015).

The time profiles of the ME and variance indices showed characteristic shapes, consistent across all subjects (Figures 6.3 and 6.4). In particular, ME and $V_{UCM}$ showed a relatively fat time profile with a small peak in the middle, whereas nME and $V_{ORT}$ showed double-peaked profiles with the peaks approximating the times of maximal COP$_{AP}$ rate shifts. Such time profiles of $V_{ORT}$ were reported earlier in studies of multi-finger force production (Latash et al., 2001, 2002b; Scholz et al., 2002a).
Our correlation analyses confirmed associations between the COP\textsubscript{AP} coordinate and both $V_{UCM}$ and ME, and between the absolute magnitude of $COP(t)$ rate and both $V_{ORT}$ and nME in support of the model introduced earlier (Goodman et al., 2005).

The double-peaked profile of $V_{ORT}$ and nME was more pronounced in the control subjects possibly reflecting two factors. First, the controls showed larger peak rates of COP\textsubscript{AP} shift, which are expected to lead to higher $V_{ORT}$ even if variance in setting the timing parameter is unchanged between the groups (see equations in Friedman et al., 2009). Second, variance in setting timing parameters across cycles also may be higher in PD as suggested by observations of higher temporal variability in motor performance in PD subjects (Almeida et al., 2002; Pastor et al., 1992; Wing et al., 1984).

### 6.3.3 Analysis of synergies as a sensitive clinical tool

Studies of action stability during whole-body movements have used a variety of methods applied to different patient populations and functional tasks including vertical posture (Cavanaugh et al., 2005; Hausdorff et al., 1985; Riva et al., 2013; van Emmerik et al., 2014). Studies of patients with postural disorders explored analysis of postural sway during quiet standing (Visser et al., 2008), postural preparation to self-initiated action (King et al., 2010; Rogers et al., 2011), and responses to unexpected postural perturbations (Boonstra et al., 2014). Some of these studies produced indices sensitive to early stages of postural problems and effects of treatment.

We would like to emphasize the following advantages of our approach based on quantifying multi-muscle synergies during postural tasks. First, this approach is theory-based and rooted deeply in both physics and physiology. It is linked intimately to the theory of control of movements with time-varying spatial referent coordinates organized in a hierarchical way, to the principle of abundance, to the uncontrolled manifold hypothesis, and to the idea of control with spatial RCs (reviewed in Latash, 2010b, 2016; Feldman 2015). Second, the approach has proven its specificity to subcortical neurological disorders (reviewed in Latash & Huang, 2015) in support of the idea of distributed processing modules involving loops through the cerebellum and the basal ganglia (Houk, 2005).
Third, the approach is highly sensitive to very early stages of disorders (such as PD subjects in H&Y stage-I, Park et al., 2012, 2013a, 2014) and even to subclinical changes in persons at elevated risk for parkinsonism (Lewis et al., 2016). Other mentioned approaches are typically computational, use behavioral indices with no clear links to physics and physiology, and/or are not as sensitive to disease-related changes.

Given the obvious importance of proper control of action stability for motor function, we believe that analysis of synergies should be incorporated broadly into clinical research. So far, applications of this analysis have been limited, partly due to the necessity to collect numerous trials for analysis of inter-trial variance. We hope that the current study will pave the way toward broader use of this method by showing that, at least for some tasks, analysis of only a few trials may be able to provide data sensitive to early-stage PD and the effects of medication. We would like to emphasize that our methods were able to detect significant changes in indices of postural stability in PD patients at H&Y stage-II, i.e., those who show no detectable problems with postural stability during neurological examination.

6.3.4 Concluding comments

This study has lessons for both basic and clinical research. It shows that indices of inter-cycle (potentially also inter-trial) variance and those of motor equivalence are strongly correlated with each other and show similar statistical effects. Within the idea of movement control with changes in referent body configurations (RC, Feldman, 2015; Latash, 2010b), muscle modes may be viewed as reflections of elemental changes in the body RC, which are used as the basis for a variety of whole-body actions (Latash, 2016). The elemental RC changes are used as elemental variables to produce synergies stabilizing task-specific salient variables. Both inter-trial variance structure and ME deviations are natural consequences of this scheme: An input from hierarchically higher levels leads to deviations in less stable directions, i.e., within the UCM, rather than in directions leading to shifts of the salient variable (i.e., within ORT). This is true for spontaneous, natural variations in the task-
specific input as well as for its purposeful changes. Within this scheme, loss of stability produced by synergies is expected to be reflected in both variance and ME indices, as demonstrated in our study. This makes both indices potentially sensitive to neurological disorders characterized by reduced action stability such as PD. The fact that ME indices can be measured in individual trials makes this index very attractive for clinical studies, particularly when examination time may be a limiting factor.

We would like to acknowledge limitations of our study. In particular, we recorded and analyzed EMG signals from one side of the body only. This approach was chosen based on earlier studies showing bilateral changes in synergy indices that demonstrated no side differences in PD patients, even in those with major bilateral differences in clinical symptoms (Park et al., 2012, 2014). As a result, we opted to analyze more muscles on one side of the body only given the limited number of EMG channels.
CHAPTER 7
Effects of Deep Brain Stimulation on Synergic Control of Actions

Deep brain stimulation (DBS) of nuclei within the basal ganglia, typically the subthalamic nucleus and globus pallidus, has been used as an effective treatment of Parkinson’s disease (PD), commonly in combination with dopamine-replacement medications (DeLong & Wichmann, 2015; reviewed in Kalia et al., 2013). Many studies have reported significant positive effects of DBS on clinical indices such as Unified Parkinson’s Disease Rating Scale (UPDRS) scores and general characteristics of movements such as maximal force, peak velocity, and movement time (Alberts et al., 2008; Brown et al., 1999; Daneault et al., 2016). In contrast, effects of DBS on motor coordination have been ambiguous, with some reporting positive effects, whereas others reporting negative or no effects (Alberts et al., 2008; Collomb-Clerc & Welter, 2015; Daneault et al., 2016; Israeli-Korn et al., 2013; Schettino et al., 2009; ). This controversy likely reflects a different understanding of coordination and methods of its assessment across studies.

Recently, a theory of synergic control of motor function has been developed (reviewed in Latash, 2016) that allows objective quantitative analysis of stability and agility of multi-effector movements, which both are impaired in PD (reviewed in Latash & Huang, 2015). Synergies are defined as neural organizations of multiple elements (e.g., muscles, joints, or digits) into task-specific groups stabilizing the production of salient performance variables (e.g., center of pressure coordinate during standing, hand trajectory during reaching, and resultant force during pressing and prehensile tasks). The theory is based on a physical (physiological) approach to motor control; it accepts the principle of abundance (Gelfand & Latash, 1998; Latash, 2012a), which views the apparently redundant sets of elements at any level of analysis of human movements not as a source of computational problems, but as a powerful design that allows ensuring task-specific stability of various salient performance variables.
Several recent studies have documented impaired synergies in early-stage PD even when the clinical examination failed to detect motor impairment (Falaki et al., 2016; Park et al., 2012). For example, impaired synergic control of both hands has been shown in patients with PD signs on only one half of the body (H&Y stage-I, Hoehn and Yahr, 1967), whereas impaired control of vertical posture has been documented in patients without clinically identifiable postural instability (H&Y stage-II). Problems in synergic control of the hand also have been documented in healthy persons at elevated risk for parkinsonism (professional welders, Lewis et al., 2016).

Deficits in the synergic control in PD are two-faceted (reviewed in Latash & Huang, 2015). During steady-state tasks, PD patients typically show reduced synergy indices interpreted as decreased stability of the salient performance variables. During preparation to a quick action from steady state, PD patients show reduced adjustments in synergy indices (anticipatory synergy adjustments, ASAs, Olafsdottir et al., 2005) interpreted as reduced agility. Both types of impairment are sensitive to dopaminergic replacement drugs (Falaki et al., 2017; Park et al., 2013a). The current study had two main aims.

First, we explored effects of DBS on indices of synergic control. We expected DBS to improve both stability of steady-state actions and agility in preparation to a quick action as reflected in the synergy index and ASAs (first hypothesis). To explore generality of the effects of DBS, we used two contrasting tasks, accurate force production by the hand and multi-muscle control of whole-body actions, performed in the DBS-on and DBS-off states.

The second aim was to explore indices of synergic control in a group of PD patients across dissimilar tasks that span the spectrum of everyday actions: multi-finger accurate force control and multi-muscle whole-body tasks involving vertical posture. We expected the deficits to be systemic based on the idea of distributed processing modules involving the basal ganglia (Houk, 2005) that likely are shared across effector systems and tasks. This prediction also is corroborated by earlier studies showing generality of the phenomena of freezing in PD (v; Nieuwoer et al., 2009;
Vercruysse et al., 2014); note that ASA deficits have been discussed as possible contributors to freezing (Latash & Huang, 2015). As such, our second hypothesis was that synergic indices of stability and agility would co-vary between the two tasks with and without DBS.

7.1 Methods

Many of the procedures detailed in this section recapitulate information in Chapter 3 Common Methods. However, certain quantitative specifics are only presented here.

7.1.1 Subjects

A group of 10 male PD patients (aged 61 ± 10 years, mean ± standard deviation), without any other known neurological disorders, volunteered to participate in this study. Seven patients had bilateral DBS leads in the subthalamic nucleus and three had bilateral leads in the globus pallidus internus. Patients were on their routine schedule of oral medication. The levodopa equivalent daily dose (LEDD) was calculated according to a published article (Tomlinson et al., 2010) and handedness was decided upon the participants’ preferential hand use during eating and writing. Only five patients were able to perform both hand and postural tasks satisfactorily because of excessive tremor preventing hand task performance and spinal deformity preventing postural task performance in some patients. Data on healthy controls who performed the same tasks in previous studies (Falaki et al., 2016; Jo et al., 2015; Lewis et al., 2016) were used; the selected healthy controls were matched by age to the patients. Table 7.1 presents the general description of patients and controls. All participants gave written informed consent according to the study protocol approved by the Pennsylvania State University-Hershey Medical Center Institutional Review Board.

7.1.2 Procedures

Participants performed multi-finger hand tasks and multi-muscle whole body postural tasks twice; both DBS-on and DBS-off states (counter-balanced across patients). The order of performing hand tasks (Experiment 1) and postural tasks (Experiment 2) was counter-balanced across patients.
After completing tasks in the initial DBS condition, participants were either provided with a 10-min break during which DBS state was changed or given a lunch break. A trained rater recorded Unified Parkinson’s Disease Rating Scale motor scores (UPDRS-III) in both DBS conditions. The total experiment took approximately 5 hours including a lunch break in-between task conditions.

Participants were encouraged to ask for additional rest intervals, drinks, and snacks as needed.

**Table 7.1** Description of participants

<table>
<thead>
<tr>
<th>SID</th>
<th>Sex</th>
<th>Age (y)</th>
<th>Onset side</th>
<th>Disease duration</th>
<th>DBS side</th>
<th>DBS duration</th>
<th>UPDRS III (Off)</th>
<th>UPDRS III (On)</th>
<th>H&amp;Y (Off)</th>
<th>H&amp;Y (On)</th>
<th>LEDD (mg)</th>
<th>Hand task</th>
<th>Postural task</th>
</tr>
</thead>
<tbody>
<tr>
<td>P01</td>
<td>M</td>
<td>74</td>
<td>L</td>
<td>9 y</td>
<td>GPi</td>
<td>30 Mo</td>
<td>26</td>
<td>17</td>
<td>2</td>
<td>2</td>
<td>650</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>P02</td>
<td>M</td>
<td>48</td>
<td>B</td>
<td>12 y</td>
<td>STN</td>
<td>4 Mo</td>
<td>16</td>
<td>15</td>
<td>2</td>
<td>2</td>
<td>767.5</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>P03</td>
<td>M</td>
<td>58</td>
<td>R</td>
<td>6 y</td>
<td>STN</td>
<td>30 Mo</td>
<td>79</td>
<td>27</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P04</td>
<td>M</td>
<td>55</td>
<td>L</td>
<td>16 y</td>
<td>STN</td>
<td>21 Mo</td>
<td>59</td>
<td>19</td>
<td>3</td>
<td>3</td>
<td>200</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>P05</td>
<td>M</td>
<td>58</td>
<td>R</td>
<td>8 y</td>
<td>GPi</td>
<td>4 Mo</td>
<td>49</td>
<td>38</td>
<td>2</td>
<td>2</td>
<td>1200</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>P06</td>
<td>M</td>
<td>73</td>
<td>R</td>
<td>22 y</td>
<td>GPi</td>
<td>10 Mo</td>
<td>12</td>
<td>13</td>
<td>2</td>
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<td>780</td>
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<tr>
<td>P07</td>
<td>M</td>
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<td>L</td>
<td>3 y</td>
<td>STN</td>
<td>7 Mo</td>
<td>44</td>
<td>42</td>
<td>2</td>
<td>2</td>
<td>1250</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>P08</td>
<td>M</td>
<td>64</td>
<td>R</td>
<td>9 y</td>
<td>STN</td>
<td>48 Mo</td>
<td>17</td>
<td>28</td>
<td>3</td>
<td>4</td>
<td>292.5</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>P09</td>
<td>M</td>
<td>55</td>
<td>R</td>
<td>11 y</td>
<td>STN</td>
<td>8 Mo</td>
<td>21</td>
<td>23</td>
<td>2</td>
<td>2</td>
<td>1250</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>P10</td>
<td>M</td>
<td>75</td>
<td>R</td>
<td>14 y</td>
<td>STN</td>
<td>5 Mo</td>
<td>47</td>
<td>49</td>
<td>2</td>
<td>3</td>
<td>755</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

**Controls**

<table>
<thead>
<tr>
<th>Hand Task</th>
<th>Postural Task</th>
</tr>
</thead>
<tbody>
<tr>
<td>SID</td>
<td>Sex</td>
</tr>
<tr>
<td>-----------</td>
<td>-----</td>
</tr>
<tr>
<td>C01</td>
<td>M</td>
</tr>
<tr>
<td>C02</td>
<td>M</td>
</tr>
<tr>
<td>C03</td>
<td>M</td>
</tr>
<tr>
<td>C04</td>
<td>M</td>
</tr>
<tr>
<td>C05</td>
<td>M</td>
</tr>
<tr>
<td>C06</td>
<td>M</td>
</tr>
<tr>
<td>C07</td>
<td>M</td>
</tr>
<tr>
<td>C08</td>
<td>M</td>
</tr>
</tbody>
</table>

SID, subject identification number; DBS, deep brain stimulation; UPDRS III, unified Parkinson’s disease rating scale-part III (motor scores); H&Y, Hoehn and Yahr scale; LEDD, levodopa equivalent daily dose; M/F, male/female; R/L/B, right/left/both sides; GPi, globus pallidus internus; STN, subthalamic nucleus. All the subjects were right-handed with the exception of P10 (left-handed) and C12 (ambidextrous).
Experiment 1 (hand tasks) was performed as described in section 3.1.1 Hand setup. Prior to each task, participants performed a set of practice trials to get familiar with the task to perform: typically one trial for the MVC task, 1-2 trials for the ramp task, and 5-8 trials prior to the force pulse production task. After testing one hand, there was a 5-min break before testing the other hand. Each participant performed the MVC task two times with visual feedback on the total force ($F_{TOT}$). The trial during which participants produced a higher peak force ($MVC_{TOT}$) was selected to define the maximal forces produced by each individual finger ($MVC_i$, $i = I, M, R, L$). They performed one trial of single-finger ramp task for each of index, middle, ring, and little fingers, and 24 trials of the quick force pulse production task. During the execution of the quick force pulse production task, in case of major errors such as pressing multiple times in one trial, obvious drift in force level prior to the pulse, or a very slow pulse production, the trial was repeated.

Experiment 2 (postural tasks) was performed as described in section 3.1.2 Postural setup. The postural experiment involved three main tasks in the following order: quiet standing (QS), continuous voluntary sway (VS), and load release (LR). Participants performed a set of practice trials prior to each task except for the QS: on average, 2-3 trials for the VS task and 4-6 trials for the LR task. Participants performed one trial of QS task (60 s long) and two repetitions of the VS task (each lasted for 30 s with 30-s rest interval between trials). Participants repeated the LR task for 24 trials with 10-sec rest between trials and a 2-3 min break after each set of 12 trials. During the course of the postural experiment, participants were asked to keep their feet in full contact with the platform and avoid excessive hip and knee joints motion.

7.1.3 Data processing

Inter-trial analysis of variance (as discussed in section 3.3 Data processing) was used to quantify synergy indices and changes in these indices in anticipation of performing a quick action. Within this method the UCM space, for each of hand and postural tasks) was approximated as the null-space of the associated Jacobian matrix ($J$) that links small changes in elemental variables (EVs)
to changes in the selected performance variable (PV). Briefly, inter-trial variance in the space of EVs was quantified in directions that does not affect the task ($V_{UCM}$) and in direction that change the PV ($V_{ORT}$). Knowing these components, a synergy index was computed according to $\Delta V = (V_{UCM} - V_{ORT})/V_{TOT}$, where $V_{TOT}$ means the total variance. Each of these variance components were normalized by its respective dimensionality. ASAs were quantified using two indices: 1) the magnitude of the attenuation in the synergy index ($\Delta V_{ASA}$) in preparation of the task and 2) the onset of this controlled loss of stability ($t_{ASA}$).

7.1.4 Statistics

Results are presented as means ± standard error (SE), unless stated otherwise. SAS 9.4 (SAS Institute Inc, Cary, NC) with mixed linear model (PROC MIXED) and compound symmetrical covariance structure, and Minitab 17.3 (Minitab Inc, State College, PA), were used to perform statistical tests. For Experiment 1, mixed-design ANOVA with repeated measures was used to test effects of $DBS$ (two levels; off and on), $Hand$ (two levels; left and right), and $Space$ (two levels; UCM and ORT) on the main outcome variables ($MVC$, $T_{Peak}$, variance components, $\Delta V_{SS,F}$, and ASA indices). For Experiment 2, a two-way repeated measures ANOVA was used to explore effects of $DBS$ and $Space$ on the inter-trial variance. All other outcome variables such as $R^2$, $t_{APA}$, $\Delta V_{SS,M}$, and ASA indices were compared using Wilcoxon’s signed-rank tests. Correlations between hand and postural synergy indices were explored using Pearson correlation coefficients. ANCOVA statistics were used with the hand synergy index as the continuous variable to explore possible relations between hand and postural synergy indices in more detail. To compare the main outcomes of Experiment 1 and 2 with healthy controls, one-way ANOVAs with factor $Group$ (three levels: DBS-off, DBS-on, and controls) were used. Data were checked to satisfy statistical assumptions of normality and were transformed accordingly if needed. When necessary, degrees of freedom were adjusted using the Kenward-Roger method according to sphericity assumptions. Pairwise
comparisons with Bonferroni corrections were used to explore significant main effects. For all statistical tests, significance level was set at \( p < 0.05 \).

### 7.2 Results

#### 7.2.1 Experiment 1: Hand tasks

**MVC and \( T_{\text{Peak}} \)**

During the MVC task, patients produced similar maximal forces in the DBS-off state (67.3 ± 4.7 N) compared with the DBS-on state (68.0 ± 5.5 N). There was no statistical difference in the magnitude of MVC forces produced by the left hand (65.6 ± 4.9 N) and the right hand (69.8 ± 5.2 N). A two-way repeated measures ANOVA with factors DBS and Hand showed no significant effects. These data are presented in Table 7.2.

**Table 7.2 Performance and synergy indices for hand and postural experiments**

<table>
<thead>
<tr>
<th>Hand tasks</th>
<th>MVC (N)</th>
<th>( T_{\text{Peak}} ) (ms)</th>
<th>( \Delta V_{SS,F} )</th>
<th>( \Delta V_F )</th>
<th>( t_{ASA,F} ) (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD (DBS-off)</td>
<td>Right</td>
<td>68.9 ± 6.9</td>
<td>259 ± 24</td>
<td>2.44 ± 0.14</td>
<td>0.20 ± 0.09</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>65.8 ± 6.7</td>
<td>256 ± 20</td>
<td>2.73 ± 0.20</td>
<td>0.36 ± 0.10</td>
</tr>
<tr>
<td>PD (DBS-on)</td>
<td>Right</td>
<td>70.6 ± 8.3</td>
<td>269 ± 37</td>
<td>2.62 ± 0.10</td>
<td>0.50 ± 0.06</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>65.4 ± 7.8</td>
<td>244 ± 27</td>
<td>2.83 ± 0.18</td>
<td>0.46 ± 0.09</td>
</tr>
<tr>
<td>Controls</td>
<td>Right</td>
<td>80.1 ± 6.4</td>
<td>144 ± 12</td>
<td>2.3 ± 0.10</td>
<td>0.48 ± 0.06</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>75.9 ± 5.8</td>
<td>163 ± 10</td>
<td>2.68 ± 0.13</td>
<td>0.64 ± 0.11</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Postural tasks</th>
<th>APAEMG (ms)</th>
<th>APAM-mode (ms)</th>
<th>( \Delta V_{SS,P} )</th>
<th>( \Delta V_P )</th>
<th>( t_{ASA,P} ) (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD (DBS-off)</td>
<td>-113 ± 15</td>
<td>-137 ± 34</td>
<td>-0.02 ± 0.03</td>
<td>-0.03 ± 0.04</td>
<td>-26 ± 14</td>
</tr>
<tr>
<td>PD (DBS-on)</td>
<td>-123 ± 21</td>
<td>-144 ± 40</td>
<td>0.02 ± 0.05</td>
<td>0.06 ± 0.02</td>
<td>-81 ± 21</td>
</tr>
<tr>
<td>Controls</td>
<td>-122 ± 14</td>
<td>-125 ± 31</td>
<td>0.22 ± 0.07</td>
<td>0.23 ± 0.04</td>
<td>-97 ± 27</td>
</tr>
</tbody>
</table>

MVC, maximum voluntary contraction force; \( T_{\text{Peak}} \), time to peak force; \( \Delta V_{SS} \), synergy index averaged across the steady state (600 to 400 ms prior to task initiation) period; \( \Delta V \), magnitude of anticipatory synergy adjustments; \( t_{ASA} \), time to anticipatory synergy adjustments; APA, time of anticipatory postural adjustments identified based on changes in muscles activity (EMG) or in the magnitude of muscle groups (M-mode). Mean ± SE of performance and synergy indices for the fingers (F) and posture (P).
**Multi-finger synergies and ASAs**

Figure 7.1 represents the mean performance of participants in the quick force pulse test, as well as the log-transformed synergy index averaged across all participants with standard error shades. There was no significant difference in the time ($T_{Peak}$) to reach the peak force between the two DBS conditions. In DBS-off, $T_{Peak}$ values were $256 \pm 20$ ms (left hand) and $259 \pm 24$ ms (right hand), whereas in DBS-on the values were $244 \pm 27$ ms and $269 \pm 37$ ms, respectively.

**Figure 7.1** Performance of the quick force pulse production task. Averaged (across participants) time profiles of the total force ($F_{TOT}$) and the log-transformed synergy index ($\Delta V_Z$) are shown for the DBS-off condition (dashed line) and DBS-on condition (solid line) with standard error shades. $t_0$ represents the task initiation and vertical arrows represent the initiation of anticipatory synergy adjustments (ASAs).

Positive synergy indices during SS ($\Delta V_{SS}$) in Figure 7.1 confirmed larger amounts of inter-trial variance that did not change $F_{TOT}$ ($V_{UCM}$) compared with the inter-trial variance that affected $F_{TOT}$ ($V_{ORT}$). A three-way ANOVA with repeated measures using factors DBS, Hand, and Space on the log-transformed inter-trial variance showed significant main effects of Space [$F_{(1,49)} = 481.2$, $p < 0.001$] and Hand [$F_{(1,49)} = 8.3$, $p < 0.01$] with no other main effect and no interactions. Pairwise comparisons confirmed that $V_{UCM} > V_{ORT}$ ($V_{UCM} = 1.23 \pm 0.39$; $V_{ORT} = 0.012 \pm 0.002$) in both hands and DBS.
conditions, and also a greater amount of total inter-trial variance in the left hand (0.96 ± 0.40) compared to the right hand (0.29 ± 0.09).

Although $\Delta V_{SS}$ was slightly higher in the DBS-on state (2.72 ± 0.10) than in the DBS-off state (2.59 ± 0.12) during SS, this difference was not significant [$F_{(1,21)} = 1.5, p > 0.2$]. In contrast, the drop in the synergy index prior to the force pulse initiation (ASA) showed significant effects of DBS. In particular, ASA started earlier in the DBS-on condition ($t_{ASA} = -84 ± 23$ ms in the DBS-off state and $-174 ± 24$ ms in the DBS-on state), on average a two-fold difference ($F_{(1,21)} = 12.2, p < 0.01$). The overall drop in $\Delta V_z$ during the ASA was larger in the DBS-on state than in the DBS-off state (0.48 ± 0.05 vs. 0.28 ± 0.07; $F_{(1,21)} = 8.1, p < 0.01$). There were no other effects in the $\text{Hand} \times \text{DBS}$ ANOVA. Table 7.2 presents the synergy indices for both hand and postural experiments in each DBS condition.

### 7.2.2 Experiment 2: Postural tasks

**Defining M-modes and the $J_M$ matrix**

Four M-modes were identified using the PCA with rotation and factor extraction procedure applied to integrated EMG indices (see Methods). On average, these M-modes accounted for similar amounts of variance in DBS-off (75.3 ± 2.9%) and DBS-on (75.1 ± 2.9%) states. The first two M-modes involved significantly loaded muscles on the ventral or dorsal side of the body, respectively, and will be addressed as “ventral M-mode” and “dorsal M-mode.” The composition of these M-modes was similar in all participants regardless of the DBS status.

To explore how changes in M-modes would affect $COP_{AP}$ coordinates, linear regression analysis was run using $\Delta M$ as predictors of $COP_{AP}$ shifts for each participant and DBS status. All M-modes were significant predictors of $\Delta COP_{AP}$ regardless of DBS status ($p < 0.001$), and there was no statistically significant difference between adjusted $R^2$ values computed for the regression analysis of DBS conditions (OFF: 0.70 ± 0.06; ON: 0.68 ± 0.07).
**COP displacements, EMG patterns, and APA**

*Figure 7.2* illustrates the average time profile of $COP_{AP}$ across participants, and the ventral and dorsal M-modes across all LR trials performed by a typical participant with standard error shades for the DBS-on (panel A) and DBS-off (panel B) conditions. EMG and M-mode time profiles were highly variable among participants, which made across participant averaging impractical. On average, significant modulation was observed about 115 ms prior to $t_0$ in EMG envelopes (DBS-off: $-113 \pm 15$ ms; DBS-on: $-123 \pm 21$ ms), and about 140 ms prior to $t_0$ in the magnitude of the dorsal and ventral M-modes (DBS-off: $-137 \pm 34$ ms; DBS-on: $-144 \pm 40$ ms). Neither NOVA nor Wilcoxon signed-rank test showed statistically significant difference in $t_{APA}$ between the DBS-on and DBS-off conditions.

**Multi-muscle postural synergies and ASAs**

Inter-trial variance within the M-mode space was quantified in two spaces, $V_{UCM}$ and $V_{ORT}$. There was no statistically significant difference during SS between the two DBS conditions in either $V_{UCM}$ (DBS-off: $0.029 \pm 0.009$; DBS-on: $0.054 \pm 0.026$) or $V_{ORT}$ (DBS-off: $0.029 \pm 0.008$; DBS-on: $0.048 \pm 0.021$). A two-way repeated measures ANOVA ($DBS \times Space$) showed no significant effects. Similar to the finger force pulse production task, $\Delta V_{SS}$ was slightly higher in DBS-on ($0.02 \pm 0.05$) compared to DBS-off ($-0.02 \pm 0.03$), but this difference was not statistically significant (Wilcoxon signed-rank test).

There were, however, significant effects of DBS on ASAs. In particular, there was a drop in $\Delta V_Z$ prior to $t_0$ in DBS-on ($\Delta V_{ASA} = 0.06 \pm 0.02$) that was absent in DBS-off ($\Delta V_{ASA} = -0.03 \pm 0.04$). This effect was confirmed by the Wilcoxon signed-rank test ($p < 0.05$). In addition, ASA in DBS-on was initiated, on average, earlier ($t_{ASA} = -81 \pm 21$ ms) compared to DBS-off ($t_{ASA} = -26 \pm 14$ ms; $p < 0.05$).
7.2.3 Comparisons across the two experiments

Data from the five participants who performed both experiments were used for across-experiment comparisons. For this comparison, we used averaged values across the left and right hands with the equivalent values measured in the postural experiment using both Pearson correlation and ANCOVA. Figure 7.3 presents scatter plots of $\Delta V_{SS}$ (panel A), $t_{ASA}$ (panel B), and $\Delta V_{ASA}$ (panel C) across participants with the least square lines of best fit. Note the correlations between the $\Delta V_{SS}$.
indices ($R^2 = 0.58$) and between the $t_{ASA}$ indices ($R^2 = 0.57$). These correlations were confirmed by two ANCOVAs with DBS as the main factor and multi-finger index as the continuous variable that showed significant effects on $\Delta V_{SS}$ [$F(1,7) = 8.4, p < 0.05$] and $t_{ASA}$ [$F(1,7) = 6.9, p < 0.05$] with no other effects. The correlation coefficient for $\Delta V_{ASA}$ was lower ($R^2 = 0.29$) and not statistically significant.

![Scatter plots of multi-finger synergy indices and multi-muscle synergy indices with the least squares line of best fit. A, Regression between multi-finger log-transformed synergy index ($\Delta V_Z$) and multi-muscle one during the steady state time interval. B, Regression between the initiation of multi-finger anticipatory synergy adjustment ($t_{ASA}$) and multi-muscle one. C, Regression between the magnitude of multi-finger anticipatory synergy adjustment ($\Delta \Delta V$) and multi-muscle one. Data points for the DBS-on condition are shown with a ‘+’ and those for the DBS-off condition are shown with a ‘•’.

Figure 7.3 Scatter plots of multi-finger synergy indices and multi-muscle synergy indices with the least squares line of best fit. A, Regression between multi-finger log-transformed synergy index ($\Delta V_Z$) and multi-muscle one during the steady state time interval. B, Regression between the initiation of multi-finger anticipatory synergy adjustment ($t_{ASA}$) and multi-muscle one. C, Regression between the magnitude of multi-finger anticipatory synergy adjustment ($\Delta \Delta V$) and multi-muscle one. Data points for the DBS-on condition are shown with a ‘+’ and those for the DBS-off condition are shown with a ‘•’.

7.2.4 Comparing results with healthy subjects from earlier publications

**Multi-finger synergies.** MVC forces produced by patients (averaged across the DBS conditions; right: $70.0 \pm 7.4$ N; left: $65.6 \pm 7.0$ N) were slightly lower than the MVC forces produced
by controls (right: 80.1 ± 6.4 N; left: 75.9 ± 5.8 N); the difference was non-significant. Since no effect of Hand was observed on $T_{\text{Peak}}$ and multi-finger synergy indices, averaged data across both hands were used for the following comparison. In the quick force pulses, patients were about 40% slower in reaching the peak force ($T_{\text{Peak}} = 257 ± 18 \text{ ms}$ and $257 ± 31 \text{ ms}$ for the DBS-on and DBS-off, respectively) than controls ($T_{\text{Peak}} = 153 ± 10 \text{ ms}$; $F_{(1,14)} > 10.0$, $p < 0.01$).

Patients showed similar amounts of the log-transformed synergy indices, $\Delta V_Z$, during SS ($2.59 ± 0.15$ and $2.72 ± 0.12$ in the DBS-off and DBS-on, respectively) compared to controls ($2.49 ± 0.09$). In contrast, patients showed significantly smaller and delayed ASAs compared to controls in the DBS-off condition only: $t_{\text{ASA}} = –84 ± 29 \text{ ms}$ and $\Delta V_{\text{ASA}} = 0.28 ± 0.08$ in the patients compared to $t_{\text{ASA}} = –228 ± 17 \text{ ms}$ and $\Delta V_{\text{ASA}} = 0.56 ± 0.07$ in the controls. These differences were large, by about 63% and 50%, respectively, confirmed by the significant effect of Group on $t_{\text{ASA}}$ ($F_{(1,14)} = 18.1$, $p < 0.001$) and on $\Delta V_{\text{ASA}}$ ($F_{(1,14)} = 7.1$, $p < 0.05$). In the DBS-on state, both ASAs indices ($t_{\text{ASA}} = –174 ± 25 \text{ ms}$, $\Delta V_{\text{ASA}} = 0.48 ± 0.06$) were not significantly different from those in controls.

**Multi-muscle synergies.** Patients showed significantly smaller indices of multi-muscle synergies stabilizing $COP_{AP}$ during SS in both DBS-off (-0.02 ± 0.03) and DBS-on (0.02 ± 0.05) conditions compared to controls (0.22 ± 0.07). These differences were confirmed by one-way ANOVAs ($F_{(1,14)} > 5.4$, $p < 0.05$) on $\Delta V_{\text{SS}}$. There also were significant differences in the ASA parameters between the patients and controls. In particular, controls demonstrated significantly larger values of $\Delta V_{\text{ASA}}$ (0.23 ± 0.04) compared to both DBS-off (-0.03 ± 0.04; $F_{(1,14)} = 20.5$, $p < 0.001$) and DBS-on (0.06 ± 0.02; $F_{(1,14)} = 13.1$, $p < 0.01$). The ASAs started earlier in controls ($t_{\text{ASA}} = –97 ± 26 \text{ ms}$) compared to DBS-off (-26.0 ± 14 ms) only ($F_{(1,14)} = 6.5$, $p < 0.05$). The difference between controls and DBS-on ($t_{\text{ASA}} = –81 ± 21$) was non-significant.
7.3 Discussion

Our first hypothesis has been supported only partly. As expected, we saw an increase in indices of anticipatory synergy adjustments (ASAs, Olafsdottir et al., 2005) in the DBS-on state compared to the DBS-off state. On the other hand, effects of DBS on synergy indices computed over the steady-state phases of the tasks were weak and under the significance level. It is possible that chronic DBS, defined as > 4 months treatment, normalized synergy indices because there were no significant differences between DBS-off patients and controls in the hand task. The second hypothesis has been supported by the findings: We observed moderate-to-strong correlations between synergic indices measured in the two tasks, multi-finger force production and multi-muscle whole-body action. This was true for both indices of ASAs, which showed significant effects of DBS, and synergy indices over steady-state task phases (∆V), which showed no significant effects of DBS.

7.3.1 Impaired control of stability in PD and the effects of DBS

Stability of most everyday actions is vital given the unpredictable changes in the environment and intrinsic body states. Indeed, when the brain generates descending signals to perform an action, it is unable to predict excitability of spinal neurons and reactive forces, e.g., if the foot is about to step on a pebble (cf. Bernstein, 1967). This means that all natural actions have to be dynamically stable, i.e. able to return close to a desired trajectory under unexpected changes in conditions. The idea of synergies as task-specific mechanisms ensuring action stability (Schöner, 1995) assumes that the central nervous system (CNS) is able to arrange multiple effectors contributing to any natural action into units that ensure such stable behaviors (reviewed in Latash et al., 2007).

There are, however, situations when high stability of an ongoing action is undesirable, e.g., when one plans to perform a quick change in a salient performance variable. The phenomena of ASAs show that the CNS indeed is able to attenuate synergies in preparation to quick actions (Olafsdottir et al., 2005; Shim et al., 2005). ASAs represent an example of feed-forward control with
the purpose to ensure that the body does not have to fight its own synergies stabilizing a variable to be changed.

PD and a number of other subcortical and systemic neurological disorders are associated with significant changes in both synergies during steady-state tasks and ASAs, i.e. in action stability and agility (reviewed in Latash & Huang, 2015). In contrast, stroke survivors show only minor changes in the synergy index in multi-joint reaching and multi-finger pressing tasks (Jo et al., 2016a; Reisman & Scholz, 2003), whereas ASAs are delayed and reduced significantly (Jo et al., 2016a). These observations suggest that stability and agility, as reflected in indices of synergies and ASAs, involve different neurophysiological mechanisms. Our study corroborates this conclusion by showing differential effects of an acute change in the DBS status on the synergy index of stability (ΔV) and agility (ASAs). In the current study, this differential effect on synergy indices was similar in PD patients who had DBS leads placed in the GP or STN. Further studies with larger samples sizes utilizing patients with both DBS targets might provide deeper insight on the contribution of the STN and GP to synergic control.

Earlier studies of PD patients led to a hypothesis that reduced ASAs may reflect mechanisms that also contribute to freezing of gait and other actions (Falaki et al., 2016; Park et al., 2012). Indeed, if a person is unable to destabilize a salient performance variable with ASA in preparation to action, this variable may be too stable to show a desired change. For example, step initiation is associated with a pattern of relatively quick COP shifts with the purpose to unload the stepping foot and generate moment of force contributing to the desired body motion (Breniere and Do, 1986; Crenna & Frigo, 1991; Halliday et al., 1998). These COP shifts are mechanically necessary to make a step. If the COP coordinate is stabilized by a strong multi-muscle synergy (e.g., Krishnamoorthy et al., 2003b; Wang et al., 2006), the person may be unable to produce COP shifts unless the synergy is attenuated with ASA. As a result, the person may feel “glued” to the floor and unable to initiate the step. Indeed,
young healthy persons show a reduction in the synergy index stabilizing COP coordinate about 200 ms prior to step initiation (Wang et al., 2005, 2006).

A number of studies reported strong positive effects of DBS on freezing in PD (Schlenstedt et al., 2017; Sidiropoulos, 2015; Vercruysse et al., 2014). Whereas other studies reported lack of such effects or even negative effects of DBS (Cossu & Pau, 2017; Marconi et al., 2008; Rocci et al., 2012), the differences likely were due to the location of the stimulation electrodes and frequency of stimulation (reviewed in Xie et al., 2017). Our observations carry an optimistic message showing that a potential contributor to freezing (lack of proper ASAs) can be improved by DBS.

7.3.2 Chronic and acute effects of DBS

To our knowledge, this study is the first to explore the effects of DBS immediately after it is re-engaged on the control of action stability. Earlier studies provided conflicting evidence with respect to the DBS effect on motor coordination. Studies showing no effects of DBS on inter-limb coordination (Daneault et al., 2016) and visuo-motor coordination (Israeli-Korn et al., 2013) contrast with reports on improved digit coordination (Alberts et al., 2004, 2008; Schettino et al., 2009; Gorniak et al., 2013) and improved coordination between the upper and lower limbs (Carpinella et al., 2007). The conflicting reports may have reflected a number of factors including the different effectors and tasks, the ambiguous local effects of DBS on the stimulated structures, and the different definitions of coordination that could emphasize aspects of temporal, spatial, or force coordination. The lack of significant effects of DBS on the synergy index ($\Delta V$) was unexpected and rejects our original hypothesis. This is consistent with several reports of weak or absent positive effects of DBS on such symptoms as postural stability and bradykinesia (Collomb-Clerc & Welter, 2015; Marconi et al., 2008).

One important factor to consider might be the effects of chronic vs. acute DBS (for a recent review see Ashkan et al., 2017). DBS is a chronic intervention, and our patients had it for 4-48 months. It might be expected to lead to relatively stable changes in the functioning of the neural
circuitry affected by the structures with DBS. In such cases, acute DBS withdrawal is not expected to lead to significant effects in variables defined by those circuits. Other circuits, however, may require ongoing DBS to show changes in respective outcome variables. Significant effects of acute DBS withdrawal may be expected on those variables.

It has been reported that some DBS effects (particularly those for dystonic signs) (Merola et al., 2013) need chronic stimulation, whereas others (such as those for tremor) (Lilleeng et al., 2015) respond to DBS immediately. In the past, we demonstrated a significant synergy decrease (ΔV) in PD subjects without DBS treatment. In the current study, we observed this difference only in the postural and not hand tests, suggesting that chronic DBS treatment (> 4 months) already may have normalized the ΔV for the hand. Further studies to test synergy indices before and after DBS implantation, however, are needed to test this hypothesis.

We would like to report potentially important observations that, at this stage, should be viewed as case observations. In our study, the patients with DBS in the GP showed very short ASAs compared to patients with DBS in the STN when tested in the DBS-off condition. This was true for both the postural task (average $t_{ASA}$ for the two subgroups was 1 ms and 34 ms, respectively) and the hand task (average $t_{ASA}$ for the two subgroups was 1.5 ms and 10.5 ms, respectively). In the DBS-on condition, however, the patients with DBS in the GP showed much stronger effects, with an increase in $t_{ASA}$, on average, of 145 ms in the postural task and 19 ms in the hand task. The patients with DBS in the STN showed more modest changes, 25 ms in the postural task and 6 ms in the hand task. These observations suggest that DBS site is an important factor in defining both chronic effects of DBS on ASAs and effects of its acute withdrawal.

### 7.3.3 Systemic effects of PD on motor synergies

The definition of synergies offered in the Introduction implies that different neurophysiological mechanisms may be involved to ensure stability of different performance variables. For example, the system of Renshaw cells may be seen as a tunable mechanism stabilizing
the output of a motoneuronal pool (Hultborn et al., 2004; Mattei et al., 2003). Indeed, if, for any reason, an alpha-motoneuron stops generating action potentials, Renshaw cells excited by the collaterals of that motoneuron’s axon would stop firing and hence reduce the overall amount of inhibition on all the neurons of the pool. This would compensate, partly, for the effect of turning the original motoneuron off, i.e. stabilize the output of the pool. Similarly, negative feedback effects that dominate most spinal reflex loops may be seen as contributors to a synergy stabilizing equilibrium state of the muscle against the external load (Latash, 2010b).

A generic neural scheme has been suggested as a potential mechanism for tunable synergies based on the idea of local back-coupling loops within the CNS (Latash et al., 2005). The scheme is compatible with the widespread short-latency negative feedbacks leading to lateral inhibition and surround suppression leading to characteristic “Mexican hat” patterns of excitability within neuronal pools (Fukai, 1999; Lund et al., 2003; Ozeki et al., 2004; Schoppa & Urban, 2003; Wehr & Zador, 2003). This scheme allows, in particular, for changing stability of the outcome performance variable without a change in its magnitude, i.e. it offers a feasible mechanism for ASA.

The observations of impaired synergic control in patients with subcortical disorders suggest that a different mechanism may be involved in the unimpaired synergic control of voluntary movements. This mechanism is more likely to involve multiple brain structures shared among tasks and effectors, and united into what Bernstein (1935) called operators and Houk (2005) termed distributed processing modules (DPMs). Whereas stability of posture and movement have been linked to the cerebellum and trans-cerebellar loops (reviewed in Manzoni et al., 2004), our observations suggest that loops involving the basal ganglia also may play a crucial role in the neural control of action stability, including its feed-forward control reflected in ASAs. It is also possible that the documented changes in the functioning of cerebellar loops in PD (Lewis et al., 2007; reviewed in Wu & Hallett, 2013; Yu et al., 2007) play an important role in impaired synergic control.
The observations of correlated changes in the synergy indices between the multi-finger force production task and multi-muscle whole-body task are highly significant. Indeed, the neural control mechanisms of prehensile tasks and vertical posture traditionally have been thought to involve different neural mechanisms, with cortical control dominating the hand function but not the vertical posture. Moreover, the definition of a synergy as a task-specific neural mechanism that unites effectors to ensure proper stability of a salient performance variable makes synergies task- and effector system-specific.

The correlations between $\Delta V$ and ASA indices (Figure 7.3) suggest that there are common mechanisms of synergic control shared among tasks and effector systems. Note that the correlation was not caused by similar effects of DBS across the two tasks: indeed, it was seen between the $\Delta V$ indices, which showed no significant improvements under DBS. These observations suggest that indices of synergic control may show natural spread among humans and represent a person-specific “signature” reflected among a spectrum of actions. This hypothesis remains speculative and needs confirmation in a large study of healthy participants.

We would like to emphasize the potential clinical importance of the correlation findings between synergic indices across dissimilar tasks. One of the obstacles on the way to turning studies of synergies into a broadly used and effective clinical tool is the relatively long testing procedure. This is particularly true for studies of multi-muscle synergies because of the requirement for electrode placement. Another problem is the necessity of collecting multiple trials to perform the inter-trial variance analysis. This issue may be resolved using a different proxy of action stability, the index of motor equivalence (Mattos et al., 2011; Scholz et al., 2007), which requires only a handful of trials. Note that the indices of inter-trial variance and motor equivalence show similar effects of PD, drug treatment, and correlated changes within a sway cycle (Falaki et al., 2017b). Our study suggests that it may be possible to use a simple, less time-consuming task (e.g., multi-finger force production) to
obtain indices of synergic control that are valid across other tasks, e.g. those involving postural control that may be more informative for clinicians.

7.3.4 Concluding comments

We would like to emphasize two important conclusions from our study. First, re-engaging DBS following a short withdrawal shows effectiveness with respect to indices of agility (ASAs) but not with respect to indices of stability ($\Delta V$), although we cannot rule out the possible influence of chronic DBS. Second, indices of both stability and agility correlate across dissimilar tasks such as multi-finger action and keeping vertical posture. Whereas the relatively small sample size of our study requires additional independent confirmation of these conclusions, the same small sample size may be viewed as an asset given the statistically significant findings. Indeed, it suggests that the observed effects are not small and may be expected to be of major clinical significance.
CHAPTER 8
The Synergic Control of Gait Initiation in PD

Parkinson’s disease (PD) is usually diagnosed by the presence of bradykinesia and rigidity with or without the presence of rest tremor. Postural problems and associated symptoms, such as freezing of gait (FOG) phenomenon, represent the most disabling symptoms of PD (Marras et al., 2005), which emerge in later stages of PD. Clinically, the presence of postural instability signifies the transition from Hoehn-Yahr (H&Y; Hoehn & Yahr, 1967) stage-II to stage-III.

Transition from standing to locomotion (step or gait initiation) is usually preceded by a complex pattern of center of pressure (COP) shifts that shift the center of mass (COM) towards the stance foot, generate moment of force needed for the desired body motion, and let the stepping leg to come off the ground (Brenier & Do, 1986; Crenna & Frigo, 1991; Halliday et al., 1998). These early postural adjustments (EPAs)—also sometimes addressed imprecisely as anticipatory postural adjustments in the movement science literature— that precede forward stepping typically involve the following pattern: the COP shifts transiently toward the stepping foot and then reverses its motion toward the stance foot; at the same time, the COP shifts backwards. This unloads the stepping leg and allows lifting it off the ground, and generates a moment of force tilting the body forward.

Because of frequent failure in gait initiation in patients with neurological disorders, especially PD, gait initiation and effects of changes in EPA characteristics on gait initiation have been studied extensively in healthy young adults (Brenier & Do, 1986; Elble et al., 1994), healthy elderlies (Hass et al., 2008; Khanmohammadi et al., 2015; Lu et al., 2017; Patchay et al., 2002), and patients with neurological or orthopedic disorders (Halliday et al., 1998; Naugle et al., 2012; Plate et al., 2016). EPAs are reported to be larger in externally elicited steps and be present in patients with FOG (Plate et al., 2016). Although changes in postural adjustments in response to perturbations and in preparation
for gait initiation have been reported in H&Y stage-III patients (Boonstra et al., 2014; King et al., 2010; Nardone & Schieppati, 2010; Rogers et al., 2011), limitations of posturography (also called test of balance) in clinical studies have been highlighted (Visser et al., 2008).

PD is known to affect feed-forward control of motor actions. In particular, delayed and reduced APAs have been reported in patients with PD (Bazalgette et al., 1986; Dick et al., 1986; Latash et al., 1995). However, in our earlier experiments (Falaki et al., 2016, 2017a), in which we quantified only the timing of APAs, we found no significant effects of PD or dopaminergic medication on APAs. These results are consistent with observations that have reported minor or even no effects of dopamine-replacement medications on APAs (e.g., de Kam et al. 2014).

A theory of synergic control of action stability has been developed recently (reviewed in Latash, 2016; Latash et al., 2007). Within this theory, synergies are defined as neurophysiological mechanisms providing for task-specific stability of salient performance variables. In this context, stability refers to the ability of a multi-effector system to limit deviations of a salient performance variable, from a desired time profile or magnitude, in the presence of relatively large deviations of effectors. Agility refers to the ability to change a performance variable quickly, which needs attenuation of the synergies stabilizing the performance variable in preparation of action initiation. Analysis of task-specific synergies has shown that synergies are typically strong during steady-state actions while there is a drop in the synergy index when a person prepares to perform a quick motor task including shifting COP prior to making a first step (Wang et al., 2005, 2006).

The method of quantifying action stability has been used in neurological populations (reviewed in Latash & Huang, 2015), and has shown both impaired stability during steady-state tasks and agility in preparation to a quick action in PD population (Falaki et al., 2018; Jo et al., 2015; Park et al., 2014;), even in patients without clinically identifiable motor impairments (Falaki et al., 2016; Park et al., 2012). In particular, patients at H&Y stage I (PD signs on only one side of the body) demonstrated impaired synergic control of both hands. Reduced synergy indices during steady-state
tasks are interpreted as reflecting decreased stability of the performance variable (e.g., the COP coordinate), while reduced anticipatory synergy adjustments (ASAs; Olafsdottir et al., 2005) are interpreted as reduced agility. It is assumed that ASAs induce gradual destabilization of the performance variable in order to facilitate a planned quick COP shift (Latash & Huang, 2015).

Lack of anticipatory saccades, head movements, and altered sequences of segment reorientation prior to turning and their importance for promoting better coordination during turning and reducing risk of falls have been reported (Ambati et al., 2013, 2016; Reed-Jones et al., 2009). Medication, deep brain stimulation, and rehabilitation may alleviate the frequency of FOG; however, these treatments lack efficacy in PD patients with advanced FOG (Giladi et al., 2001; Latt et al., 2009; reviewed in Nutt et al., 2011). In order to develop a more effective treatment and therapy, better knowledge of the FOG phenomenon is needed. The main goal of this study has been to explore the utility of inter-trial analysis of synergies to quantify indices of COP stability and its modulation in preparation to stepping (agility). This study is potentially important for predicting the emergence of episodes of freezing, a major disabling sign of PD. We had three main aims:

**Aim 1:** To explore whether synergy indices during steady-state (quiet standing) in PD patients before stepping are reduced as compared to healthy controls.

**Aim 2:** To quantify EPAs in PD patients in preparation of gait initiation in comparison to age-matched healthy controls.

**Aim 3:** To explore the effects of quick head rotation on indices of COP stability and agility in PD patients and in controls.

### 8.1 Methods

Similar procedure as those described in Chapter 3 *Common Methods* was used. However, in this experiment, EMGs from 16 muscles on both sides of the body were recorded and synergy indices
were quantified in both AP and ML directions as described in 8.1.2 Procedures and 8.1.3 Data processing.

8.1.1 Subjects

A cohort of 10 PD patients (6 women, aged 65 ± 7 years, mean ± standard deviation) at H&Y stage < II and a cohort of 10 age- and sex-matched controls (CS group, aged 66 ± 7 years) without any other known neurological disorders participated in this study. From each group a male person was removed from data processing due to the problems with the signals from foot switches that were needed to align trials. Patients were referred to the study by neurologists at Penn State Milton S. Hershey Medical Center. Elderly controls were mainly from family members and friend of patients.

Table 8.1 General description of participants

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M/F, male/females; R/L, right/left; LEDD, levodopa equivalent daily dose; UPDRS, Unified Parkinson’s Disease Rating Scale
Table 8.1 presents the general description of participants. The levodopa equivalent daily dose (LEDD) was calculated according to a published article (Tomlinson et al., 2010), and handedness was decided upon the participants’ preferential hand use during eating and writing. All participants gave written informed consent according to the protocol approved by the Institutional Review Board of the Hershey Medical Center.

8.1.2 Procedures

Participants stood barefoot on a force plate with their feet parallel and shoulder width apart. A 16-channel Trigno wireless system (Delsys Inc., MA), with rectangular shaped EMG sensors was used to record EMG of 16 muscles on both side of the body: tibialis anterior (TA), soleus (SOL), gastrocnemius medialis (GM), biceps femoris (BF), rectus femoris (RF), vastus lateralis (VL), tensor fasciae latae (TFL), and lumbar erector spinae (ESL). Two sets of foot switches were placed under each foot (four in total); one under the medial process of calcaneal tuberosity (to define the heel off) and one under the head of the first metatarsal near the big toe (to define the toe off). A square-shaped wooden plate with the exact height as of the force platform was placed in front of the force platform to make stepping as natural as possible. Analog EMG, force platform, and foot switches data were digitized at 1 KHz sampling frequency using a PCI-6225 board and recorded by means of a customized LabVIEW-based program similar to the previous experiments.

A trained rater assessed UPDRS motor scores (UPDRS-III) in PD patients prior to the stepping tasks. The postural experiment involved: quiet standing (QS), continuous voluntary sway in the AP direction (VS\textsubscript{AP}), continuous voluntary sway in the ML direction (VS\textsubscript{ML}), and gait initiation by means of making two steps with and without a quick prior turn of the head (Step and Turn conditions, respectively; counter-balanced); see Common methods. The voluntary sway amplitude was 6 cm peak-to peak (centered about the neutral standing position) for the AP direction and 8 cm for the ML direction, which was shown by two horizontal and two vertical lines, respectively. Except for the QS task, participants performed a set of familiarization trials prior to each task: on average, 2-3 trials for
the VS task and 4-5 trials for the stepping task. There was 10-s rest between trials and 5-10 min break after each of Step or Turn condition.

8.1.3 Data processing

We processed the data offline using a customized Matlab (Mathworks Corp., Natick, MA) program based on the uncontrolled manifold (UCM) hypothesis (Scholz and Schöner, 1999); it included computation of the two components of inter-trial variance ($V_{UCM}$ and $V_{ORT}$) that do and do not affect a specific performance variable (COP$_{AP}$ or COP$_{ML}$) produced by a set of elemental variables (M-modes: muscle groups with parallel changes in activation levels). Stepping trials were aligned by the toe-off signal. EMG signals were normalized ($EMG_{NORM}$) by subtracting the background EMG activity—from the QS tasks—and then dividing by the maximal EMG levels as described in Common methods, Section 3.3.2. The only difference was that $EMG_{MAX}$ was the maximal activity of individual muscles across VS and MS trials (as defined in 3.2.2 Postural tasks).

In this experiment, data analyses for AP and ML directions were performed separately. In particular, two separate sets of M-modes were used: one for analyzing COP shifts in the AP direction and the other one for analyzing COP shifts in the ML direction. The general logic of the inter-trial analysis of variance is as follows: individual trials are aligned; variance in the space of the M-modes is computed across trials for each time sample. The UCM is approximated as the null-space of the mapping between changes in M-mode envelopes to consequent shifts in the COP$_{AP}$ coordinates ($J_{AP}$ and $J_{ML}$). $J$’s were found separately for M-modes and COP displacements in the AP and ML directions using multiple linear regression techniques. Variance in the space of M-modes was quantified within the UCM and within its orthogonal complement, $V_{UCM}$ and $V_{ORT}$, respectively. Further, a metric ($\Delta V$) reflecting the difference between $V_{UCM}$ and $V_{ORT}$ was computed: $\Delta V = (V_{UCM} - V_{ORT})/V_{TOT}$, where $V_{TOT}$ means the total variance and each value was quantified per degree-of-freedom in the corresponding spaces. Note that $\Delta V > 0$ implies presence of a synergy stabilizing COP coordinate by co-variation of M-mode magnitudes. A larger $\Delta V$ implies stronger synergies. $\Delta V \leq 0$
implies no synergy. Prior to running parametric statistics, $\Delta V$ values were $z$-transformed ($\Delta V_z$) to normalize the $\Delta V$ distribution given the limits of this index imposed by its computation.

To quantify the drop in the synergy index prior to the gait initiation (ASAs), the time interval between 1000 to 800 ms prior to the toe-off ($t_0$) was considered as steady state (SS) and was used to compute the mean ($\Delta V_{SS}$) and SD of $\Delta V_z$. $\Delta V_{ASA}$ was defined as the difference between $\Delta V_{SS}$ and the averaged value of $\Delta V_z$ during the 51-ms interval about $t_0$ ($\{t_0-25; t_0+25\}$): $\Delta V_{ASA} = \Delta V_{SS} - \Delta V_0$. We also quantified EPAs as the peak magnitude of COP deviations in the AP and ML directions before gait initiation. These deviations were also used as measures of EPAs (Breniere & Do, 1986; Elble et. al., 1994; Lepers & Breniere, 1995; Sasaki et al., 2001; Naugle et al., 2012; Plate et. al., 2016; Lu et. al., 2017).

8.1.4 Statistics

Results are presented as means ± standard error (SE), unless stated otherwise. SAS 9.4 (SAS Institute Inc, Cary, NC) with mixed linear model (PROC MIXED) and compound symmetrical covariance structure and Minitab 17.3 (Minitab Inc, State College, PA) were used to perform statistical tests. Mixed-design ANOVAs with repeated measures was used to test effects of Group (two levels; PD and CS), Instruction (two levels; Ttep and Turn), Space (two levels; UCM and ORT), and Direction (two levels; AP and ML on main outcome variables (variance components, $\Delta V_{SS}$, $\Delta V_{ASA}$, $\Delta COP_{AP}$, and $\Delta COP_{ML}$). Wilcoxon’s signed-rank test was used to compare $\Delta V_{SS}$, and $V_{ASA}$ between the Step and Turn conditions in each experimental group. $t$-tests and linear regressions were used in the analysis of $J$ matrices. Data were checked to satisfy statistical assumptions of normality and were transformed accordingly if needed. When necessary, degrees of freedom were adjusted using the Kenward-Roger method according to sphericity assumptions. Pairwise comparisons with Bonferroni corrections were used to explore significant main effects when a significant interaction effect was observed. For all statistical tests, significance level was set at $p < 0.05$. 

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8.2 Results

8.2.1 Defining M-modes and J matrices

Two sets of M-modes (\(M_{\text{AP}}\)-modes, \(M_{\text{ML}}\)-modes) and J’s (\(J_{\text{AP}}, J_{\text{ML}}\)) were identified. For each direction, four M-modes were identified using the PCA with Varimax rotation and factor extraction procedure applied to integrated EMG indices (see Common methods). On average, \(M_{\text{AP}}\)-modes and as \(M_{\text{ML}}\)-modes accounted for similar amounts of variance in the original EMG space for PD (AP: 72.4 ± 2.1; ML: 61.3 ± 2.1) and CS groups (AP: 71.5 ± 2.7; ML: 63.7 ± 2.1). A two-way repeated measures ANOVA with factors Group and Direction on the z-transformed amount of variance accounted by M-modes only showed main effect of Direction (\(F_{(1,16)} = 19.66, p < 0.001\)) which confirmed lower amount of variance explained for the ML direction as compared to the AP direction in both groups (AP: 72.0 ± 1.6; ML: 62.5 ± 1.5). The first two \(M_{\text{AP}}\)-modes involved significantly loaded muscles on the ventral or dorsal side of the body, respectively, which shifted the COP in AP direction. The first two \(M_{\text{ML}}\)-modes involved significantly loaded muscles with different signs on the left and right sides, which shifted the COP in the ML direction. The composition of the M-modes was similar in all participants regardless of their Group status.

To explore how changes in M-modes would affect COP coordinates, linear regression analysis was run using \(\Delta M\) as predictors of COP shifts for each participant and disease status. All M-modes were significant predictors of \(\Delta \text{COP}\) across all participants in both groups (\(p < 0.001\)). Although adjusted \(R^2\) values computed for the regression analyses were slightly larger in the CS group, there was no statistically significant difference between groups for either AP (PD: 0.78 ± 0.03; CS: 0.82 ± 0.02) or ML (PD: 0.70 ± 0.04; CS: 0.77 ± 0.02) direction. Only main effect of Direction was observed on the z-transformed adjusted \(R^2\) values for the linear regression analysis (\(F_{(1,16)} = 9.96, p < 0.01\); AP: 0.8 ± 0.02; ML: 0.74 ± 0.02).
8.2.2 COP displacements

Figure 8.1 illustrates the average time profiles of COP\textsubscript{AP} and COP\textsubscript{ML} across participants for each group, for the Step (left panels) and Turn (right panels) conditions with shaded error bars. Both groups showed consistent patterns of COP displacements prior to \( t_0 \) (time of toe-off). Two-way repeated measures ANOVAs with factors Group and Instruction on \( \Delta \text{COP}_{\text{AP}} \) and \( \Delta \text{COP}_{\text{ML}} \) only showed significant main effect of Group on \( \Delta \text{COP}_{\text{ML}} \) (\( F(1,16) = 4.53, p < 0.05 \)): Deviations of COP\textsubscript{ML} prior to \( t_0 \) were smaller in CS (2.12 ± 0.32 cm) as compared to PD (3.47 ± 0.34 cm). There was no statistically significant difference in \( \Delta \text{COP}_{\text{AP}} \) (PD: -2.10 ± 0.45; CS: -2.58 ± 0.41).

![Figure 8.1](image)

Figure 8.1 Averaged across participants time profiles of the center of pressure (COP) coordinates in the anterior-posterior (AP) and medial-lateral (ML) directions for the Step and Turn conditions with shaded standard errors. The solid lines represent time profile of COP in the AP direction and dashed lines represent COP shifts in the ML direction for both control (CS) and patient (PD) groups.
8.2.3 Multi-muscle postural synergies and ASAs

Inter-trial variance within the M-mode space was quantified in two spaces, $V_{UCM}$ and $V_{ORT}$.

*Figure 8.2* and *Figure 8.3* demonstrate inter-trial variance indices in the AP and ML directions, averaged across participants with standard error shades, for the Step and Turn conditions, respectively.

![Figure 8.2](image)

*Figure 8.2* Time profiles of the inter-trial variance indices during the Step condition, quantified within the uncontrolled manifold ($V_{UCM}$) and orthogonal subspace ($V_{ORT}$) averaged across participants with standard error shades for the anterior-posterior (AP) and medial-lateral (ML) directions. The left panels show results of the control (CS) group whereas the right panels show results of the Parkinson’s disease (PD) groups. Solid lines show $V_{UCM}$ and dashed lines represent $V_{ORT}$.

Three-way repeated measures ANOVAs with factors *Group*, *Instruction*, and *Space* were performed on variance indices during SS and at $t_0$ separately for the AP and ML directions. During
SS, a significant main effect of Instruction ($F_{(1,48)} = 4.65, p<0.05$) and no other main effect or interaction was observed on both $V_{UCM}$ and $V_{ORT}$ for the AP direction. Turning the head prior to step initiation, on average, caused a significant increase in variance (Step: $0.0122 \pm 0.0013$; Turn: $0.0180 \pm 0.0037$). Whereas there was no main effects of Space on variance indices during SS for the AP direction, we observed significant main effects of Space for ML direction.

![Figure 8.3](image)

Figure 8.3 Times profiles of inter-trial variance during the Turn condition, quantified within the uncontrolled manifold ($V_{UCM}$) and the orthogonal subspace ($V_{ORT}$) averaged across participants with standard error shades for the anterior-posterior (AP) and medial-lateral (ML) directions. The left panels show results of the control (CS) group and the right panels show results of the Parkinson’s disease (PD) groups. Solid lines represent $V_{UCM}$ and dashed lines represent $V_{ORT}$.

For the ML direction, there were significant main effect of Instruction ($F_{(1,48)} = 20.57, p < 0.001$), Space ($F_{(1,48)} = 23.14, p < 0.0001$), a two-way Instruction $\times$ Space interaction ($F_{(1,48)} = 15.86, p < 0.001$), and a three-way Group $\times$ Instruction $\times$ Space interaction ($F_{(1,48)} = 6.07, p < 0.05$). However,
pairwise comparisons for the three-way interaction did not show any significant difference. With respect to the two-way Instruction $\times$ Space interaction, V_{ORT} (0.008 $\pm$ 0.002) during Step condition was significantly smaller than V_{ORT} during Turn condition (0.181 $\pm$ 0.006) or V_{UCM} in both conditions (Step: 0.014 $\pm$ 0.002; Turn: 0.018 $\pm$ 0.006). V_{UCM} (0.016 $\pm$ 0.003) was larger than V_{ORT} (0.013 $\pm$ 0.003) for the ML direction, and the Turn condition showed larger variance compared to the Step condition (Step: 0.011 $\pm$ 0.001; Turn: 0.018 $\pm$ 0.004). Three-way repeated measures ANOVA on V_{UCM} and V_{ORT} at t_0 did not show any significant main effects in the AP or ML directions.

There were significant main effects of Group ($F_{(1,16)} = 26.13, p < 0.001$), Instruction ($F_{(1,48)} = 9.1, p < 0.01$), and Direction ($F_{(1,48)} = 17.57, p < 0.001$) on the synergy index during the steady-state ($\Delta V_{SS}$). CS showed, on average, significantly larger $\Delta V_{SS}$ (0.20 $\pm$ 0.03) as compared to the PD group (0.04 $\pm$ 0.03). Both groups showed larger synergy indices for the ML direction (PD: 0.12 $\pm$ 0.04; CS: 0.29 $\pm$ 0.04) as compared to the AP direction (PD: -0.04 $\pm$ 0.05; CS: 0.12 $\pm$ 0.03). Turning the head prior to the gait initiation caused a significant drop in $\Delta V_{SS}$ (Step: 0.18 $\pm$ 0.03; Turn: 0.06 $\pm$ 0.03).

There were significant effects of Turn on $\Delta V_{SS}$ in PD in both AP (Step: 0.03 $\pm$ 0.06; Turn: -0.10 $\pm$ 0.08) and ML directions (Step: 0.18 $\pm$ 0.04; Turn: 0.06 $\pm$ 0.06) as confirmed by Wilcoxon’s signed-rank test ($p < 0.01$). However, this effect in CS was statistically significant only for the ML direction (Step: 0.39 $\pm$ 0.04; Turn: 0.18 $\pm$ 0.05), but not AP (Step: 0.13 $\pm$ 0.04; Turn: 0.11 $\pm$ 0.04).

Figure 8.4 represents ASAs for the PD and CS groups for both Step and Turn conditions in the AP and ML directions. Only CS showed statistically significant ASAs for both stepping conditions and both directions as confirmed by non-parametric sign tests. There were significant main effects of Group ($F(1,16) = 31.79, p < 0.001$), Instruction ($F(1,48) = 7.91, p < 0.01$), Direction ($F(1,48) = 5.64, p < 0.05$), and Group $\times$ Direction interaction ($F(1,48) = 5.02, p < 0.05$) on $\Delta V_{ASA}$, in the three-way repeated measures ANOVA.
CS, on average, demonstrated statistically significant positive ASAs (0.28 ± 0.05) that were larger compared to PD (-0.01 ± 0.03). ASAs magnitudes were larger for the ML direction (AP: 0.08 ± 0.03; ML: 0.19 ± 0.05) and they became smaller in the Turn condition (Step: 0.20 ± 0.04; Turn: 0.07 ± 0.04). Pairwise comparisons confirmed significantly smaller $\Delta V_{ASA}$ in PD during the Turn condition (-0.07 ± 0.03), as compared to CS in both conditions (Step: 0.35 ± 0.06; Turn: 0.21 ± 0.06).

Wilcoxon’s signed rank test confirmed significant effect ($p < 0.05$) of turning on $\Delta V_{ASA}$ in PD in both AP (Step: 0.07 ± 0.04; Turn: -0.08 ± 0.04) and ML direction (Step: 0.04 ± 0.06; Turn: -0.05 ± 0.04).

There was a difference for CS, but for the AP direction only (Step: 0.28 ± 0.07; Turn: 0.07 ± 0.04), not for the ML direction (Step: 0.43 ± 0.10; Turn: 0.35 ± 0.10).
8.3 Discussion

In this study, we expected PD to result in lower synergy indices stabilizing the vertical posture during the quiet standing prior to the gait initiation (lower stability; Hypothesis 1) and smaller anticipatory synergy adjustments (ASAs) in preparation to step initiation (Hypothesis 2). We also expected that changes in visual scene caused by head rotation prior to the step initiation would reduce ASAs in PD patients, not necessarily in healthy controls (Hypothesis 3). Our first and second hypotheses have been supported by the findings. In particular, we observed statistically significant lower synergy indices computed over the steady-state phase and smaller indices of anticipatory synergy adjustments in PD. However, the third hypothesis has been supported only partly. As expected, we saw smaller or even absent ASAs in the Turn condition compared to the Step condition. On the other hand, turning the head resulted in smaller ASAs in healthy controls, albeit for the anterior-posterior (AP) direction only. Head rotation prior to step initiation also affected the stability indices in PD and in controls (during steady state), but the effect in controls was seen only in the medial-lateral (ML) direction.

8.3.1 Feed-forward control of gait initiation and FOG phenomenon in PD

Anticipatory postural adjustments (APAs, Belen'kiĭ et al., 1967; Massion, 1992) consist of changes in muscular activity with the purpose of generating forces and moments directed against those expected from an upcoming perturbation. PD is expected to affect the feed-forward adjustments across motor actions. In particular, delayed and reduced APAs have been reported in PD patients during postural tasks (Bazalgette et al., 1986; Dick et al., 1986; Latash et al., 1995). Step or gait initiation is also associated with a relatively complex sequence of COP shifts which is assumed to shift the center of mass (COM) towards the stance foot and generate moment of force contributing to the step of the swing foot (Breniere & Do, 1986; Crenna & Frigo, 1991; Elble et al., 1991; Halliday et al., 1998; Lepers & Breniere 1995). These preparatory postural adjustments, which are seen several hundred ms prior to the take-off of the stepping foot, have been addressed as APAs or early postural
adjustments (EPA) in movement science literature (Breniere & Do, 1986; Crenna & Frigo, 1991; Lu et al., 2017; Patchay & Gahery, 2003; Patchay et al., 2002; Naugle et al., 2012).

Freezing of gait (FOG) is an important disabling clinical phenomenon characterized by brief episodes of freezing, during which the patient is unable to step or makes extremely short steps. These phenomena typically occur during gait initiation or during turning while walking. Frequent trembling of legs during FOG episodes exists and there is significant variability in gait metrics between normal walking and FOG episodes (reviewed in Nutt et al., 2011). As gait initiation failure is frequent in PD patients and patients with other neurodegenerative disorders, and because EPAs seems to be crucial to initiate a step, EPAs preceding gait initiation have attracted extensive attention (Brenier & Do, 1986; Elble et al., 1994; Halliday et al., 1998; Hass et al., 2008; Khanmohammadi et al., 2015; Lu et al., 2017; Naugle et al., 2012; Patchay et al., 2002; Plate et al., 2016).

However, effects of PD on EPAs prior to making a step have been ambiguous with some studies reporting reduced magnitude and longer EPAs (Lee at al., 1995; Burleigh-Jacobs et al., 1997; Mancini et al., 2009; Rocchi et al., 2006, 2012). In contrast, another recent study—investigating the influence of several external parameters (age and type of step initiation including externally elicited steps or self-timed steps) on gait initiation in PD patients, with and without the FOG phenomenon, and healthy controls—showed an overall slightly but not significant reduced EPAs, even in patients with FOG (Plate et al., 2016). In line with these results, we found no effect of PD or dopaminergic medication on the timing of APAs initiation in our earlier studies (Falaki et al., 2016, 2017a), which is consistent with earlier observations of minor or lacking effects of dopamine-replacement drugs on APAs (e.g., de Kam et al. 2014). As a result, explaining FOG by the absence of or significant reduction in EPA characteristics during step initiation is questionable.
**8.3.2 Impaired control of stability in PD and effects of turning**

Considering the unpredictable changes in the environment and imperfect knowledge of the intrinsic body states, stability of actions is vital. This study was based on the concept of multi-element synergies stabilizing salient performance variables in a hierarchical system (reviewed in Latash, 2010b, 2016, 2017). In this context, synergies are defined as task-specific mechanisms that ensure action stability (Schöner, 1995) assuming that the central nervous system (CNS) organizes multiple task effectors into units ensuring stable behaviors (reviewed in Latash et al., 2007; Latash, 2012a). Within this concept, an index of multi-muscle synergies is quantified within the framework of the uncontrolled manifold (UCM) hypothesis (Scholz & Schöner, 1999) that represents the relative amount of inter-trial variance that does not affect and the variance that does affect shifts of COP in the total amount of inter-trial variance variance (Krishnamoorthy et al., 2003a, 2003b). However, there are situations in which high stability of an ongoing action is undesirable, e.g., when a person prepares to perform a quick action such as step initiation. As a result, although maintenance of movement stability is crucial, yet it is equally important to possess agility. Movement agility requires controlled loss of stability and lack of this loss of stability may lead to such consequences as difficulty with action initiation including the FOG phenomenon.

Typically there are strong synergies during steady-state tasks. However, in healthy individuals, task-specific synergies are attenuated in preparation for making a quick action including COP shifts prior to the step initiation (Wang et al., 2005, 2006), known as ASAs (Olafsdottir et al., 2005; Shim et al., 2005). ASAs are typically seen 200-300 ms prior to the action initiation. It has been assumed that ASAs lead to gradual destabilization of the current task space, which aims to facilitate desired quick changes (Latash & Huang, 2015). In some recent studies, PD patients have shown lower stabilizing synergy indices during steady-state performance, and smaller in magnitude and delayed ASAs in preparation of changes in the amount of force produced by fingers (Jo et al., 2015; Park et al., 2012) or in preparation of a postural task (Falaki et al., 2016, 2017a). These observations
led to a hypothesis that reduced or lack of ASAs may reflect mechanisms contributing to FOG and difficulties with the initiation of other actions (Falaki et al., 2016; Park et al., 2012). In line with this idea, it has been reported that PD patients do not make anticipatory saccades and head movements, and show altered sequence of segments reorientation ahead of turning, which emphasize their importance for promoting better coordination and reduced falls risk (Ambati et al., 2013, 2016; Reed-Jones et al., 2009). Our study corroborates the idea that ASAs are related to movement agility and disabling episodes of freezing by showing reduced ASAs in PD. Changes in the visual scene just prior to initiating a step resulted in more reduction in or lack of ASAs. The latter observations are in line with the observation of greater risk of falling in PD patients during the tasks that are more challenging for the motor control system (Morris et al., 2001), e.g., PD patients show greater rate of postural instability when turning while walking compared to walking straight forward (Hong et al., 2009; Huxham et al., 2008; Mellone et al., 2016; Stack & Ashburn 1999). Turning has been reported to increase the risk of falling and rate of injuries in PD patients (Stack & Ashburn, 1999). The increased in the frequency of FOG when turning or passing through a narrow doorway in patients may be related to the reduction or disappearance of ASAs. Our observations of reduced ASAs can be related to changes in visual scene or vestibular signals associated with head rotation.

**8.3.3 Analysis of synergies as a sensitive clinical tool**

A variety of methods have been used to study the movement stability during whole-body tasks in different patient population (Cavanaugh et al., 2005; Hausdorff et al., 1985; Riva et al., 2013; van Emmerik et al., 2014); in particular, analysis of postural sway during quiet standing (Visser et al., 2008), responses to unexpected postural perturbations (Boonstra et al., 2014), and postural preparation to self-initiated tasks (King et al. 2010; Rogers et al. 2011) have been used to study patients with postural problems. Some of these studies produced indices sensitive to postural problems and treatment effects. Quantifying multi-muscle synergies during postural tasks has the following advantages. (1) It is theory-based and linked to the principle of abundance, theory of
controlling actions with time-varying referent configuration, and to the concept of uncontrolled manifold. (2) In addition to its sensitivity to effects of changes in visual scene on preparation for step initiation that can be directly related to disabling episodes of freezing, this approach shows high sensitivity to early stages of PD, e.g., patients in H&Y stage I (Park et al., 2012, 2014), and even in persons at elevated risk for parkinsonism (Lewis et al., 2016). (3) It seems to provide high sensitivity to subcortical neurological disorders (reviewed in Latash & Huang, 2015). Other approaches are not as sensitive to disease-related symptoms and are mainly based on behavioral indices.

Although there are positive effects of medication, deep brain stimulation (DBS), and rehabilitation techniques on reducing FOG in some patients (Collomb-Clerc & Walter 2015; reviewed in Nutt et al., 2011; Schlenstedt et al., 2017; Sidiropoulos, 2015; Vercruysse et al., 2014), other patients, especially with advanced PD, show no such effects (Giladi et al., 2001; Marconi et al., 2008; Rocchi et al., 2012; Cossu and Pau, 2017). Our observations of reduced ASAs in PD, carry a clinical potential in developing treatments or rehabilitation techniques that would increase ASAs in patients, which might lead to reduced risk of falling. Although, a more detailed experiment with a larger number of participants is needed to confirm this idea.

There are observations that suggest involvement of different neurophysiological mechanisms in controlling movement stability and agility (Falaki et al., 2018; Jo et al., 2016; Reisman and Scholz, 2003). Our study corroborate, partly, this idea by showing significant changes in the index of stability ($\Delta V_{ss}$), as a result of turning the head for the ML direction only, whereas significant changes in the agility index were seen for the AP direction only. Changes in the timing of rotating different body segments and anticipatory saccades have been reported during turns while walking (Ambati et al., 2016). However, simultaneous drop in both stability and agility indices, especially in the healthy elderly, suggests some interconnections between these two neurophysiological substrates, which needs to be studied in more details.
8.3.4 Concluding comments

This study has utility for both basic and clinical research. It provides more details on neurophysiological mechanisms of synergic control of movements, the FOG phenomenon, and suggests a method to quantify effects of treatment to help with development of new therapies to improve balance in PD patients. If more comprehensive studies with broader range of participants confirm our results, stability and agility indices has a clinical utility to be used as biomarkers to objectively assess postural balance, and predict the emergence of postural instability and episodes of freezing.

We would like to acknowledge two obvious limitations of this study, which are the relatively small number of participants and lack of control for potential contribution of the vestibular system. Some of the aforementioned results can be partly attributed to signals from vestibular system during head turning. Impaired central processing of vestibular information is generally considered in combination with other sensory or motor systems (reviewed in Cronin et al., 2017). Normal vestibular function (Frenklach et al., 2009) or unrelated to the postural problems dysfunction of this system in moderately affected PD patients (Pastor et al., 1993) has been reported. Impaired kinesthesis, i.e., impaired proprioception for a kinesthetic map of the body, has also been suggested as a contributor to balance problems, e.g., as reflected in difficulties with perceiving changes in the inclination (Wright et al., 2010). It would be highly desirable to perform an experiment that explores effects of changes in visual and vestibular information on synergistic control of movements in healthy and PD populations.

To summarize, the current study provides evidences of relations between indices of stability and agility—obtained from EMGs recorded on both side of the body and quantified for the AP and ML directions—that may reflect early dysfunction of mechanisms of preparation to step initiation that may later lead to FOG symptoms. The effects of turning the head (changes in visual scene) on these
indices are consistent with the known effects of visual scene on FOG. It would be highly desirable to conduct a study with a larger number of participants that include PD patients with and without the FOG phenomenon to fully assess these relations using a broader range of clinical indices, and evaluate the efficacy of synergy indices in quantifying postural instabilities and predicting the emergence of FOG.
CHAPTER 9
Summary and Concluding Remarks

The major goal of this dissertation is to evaluate the utility of multi-muscle synergies in quantifying different aspects of postural balance impairments in patients with Parkinson’s disease (PD). Over the course of this dissertation, we analyzed effects of PD (all studies), dopaminergic medication (Chapter 5), and deep brain stimulation (DBS, Chapter 7) on multi-muscle synergic control of vertical posture. In Chapter 6, we compared indices computed from inter-trial variance to those computed from the recently developed motor equivalence method. In Chapter 8, we explored relations between synergy indices of stability and agility during preparation to step initiation in PD. Also, we tried to link changes in the synergic control of actions with underlying neurophysiological mechanisms (Chapters 7 and 8), especially by comparing synergy indices across dissimilar whole-body postural and multi-finger force production tasks (Chapter 7). Such synergy indices were quantified with respect to the structure of inter-trial variance (all chapters) and motor equivalent motion (Chapter 6) in the space of hypothetical elemental variables (muscle modes, M-modes) manipulated by the central nervous system (CNS).

One of the distinct features of the motor control system is its ability to provide stability of actions given the poorly predictable environment and varying internal states. Postural instability and its associated symptoms, such as episodes of freezing, are among the most disabling features of PD. One of the main problems in treating PD is due to the fact that signs of the disease become identifiable during clinical examination only when about 70% of nigrostriatal neurons have already degenerated (Zigmond & Burke, 2002). As a result, discovery and development of early biomarkers of PD capable of quantifying postural impairments or predicting their emergence is highly important. The current clinical evaluation tools for PD are mainly phenomena-based, qualitative, and subjective, which may not always be successful in predicting clinical outcomes (e.g., Weaver et al., 2009). The
framework of synergic control of movements has been used in all of the presented studies, which allows quantifying a major aspect of movement coordination, the flexible involvement of elements reflecting stability of important performance variables, and might provide insights into the neurophysiological substrates of synergies.

The first and second studies have confirmed impaired control of synergic control in H&Y stage II (without any clinically identifiable balance instability) and stage III patients. Based on our observations: PD is associated with two problems of postural control. First, stability of posture is compromised (compared to age-matched controls). Second, PD patients are impaired in their ability to attenuate postural stability in preparation to a quick action, which may be causally related to the disabling episodes of freezing. These differences were seen in early-stage PD (H&Y stage II) patients suggesting that analysis of multi-muscle synergies may be a sensitive biomarker of PD, possibly predictive of future problems with postural stability. Observations also confirmed positive effects of dopaminergic medications on both aspects of impaired synergic control in PD. Changes in steady-state synergy indices and anticipatory adjustments of these indices (ASAs) have been reported even in H&Y stage I patients using multi-finger force production task (Park et al., 2012). In contrast, there was no difference between patients and controls, and between patients tested off- and on-medication with respect to the initiation of anticipatory postural adjustments (APAs).

Analysis of inter-trial variance needs multiple trials, which may be problematic in patient populations. Recently, analysis of motor equivalence (Mattos et al., 2011, 2013; Scholz et al., 2007) has been developed within the framework of synergy analysis, which theoretically can be performed in single trials. While the two methods have been introduced earlier to estimate stability of salient performance variables, they have never been compared directly. From purely statistical considerations, the two methods are expected to produce correlated results, but this is a theoretical prediction based on assumptions including the assumption of perfectly normal data distributions (which is commonly violated in practical data sets). In the third study, for the first time, we compared
indices from inter-trial (inter-cycle) variance and motor equivalence analyses, and showed that both methods result in correlated metrics sensitive to effects of PD and medication.

Analysis of synergies has been already used in several studies and showed sensitivity to changes in movement coordination resulting from normal aging (Olafsdottir et al., 2007a, 2007b; Shinohara et al., 2003), fatigue (Singh et al., 2010, 2011, 2012), exercise (Wu et al., 2013), and some neurological disorders (Falaki et al., 2016, 2017a; Jo et al., 2015, 2016a; 2017; Park et al., 2012, 2013a, 2014). However, synergy indices, obtained from different tasks involving different sets of effectors, have never been compared with each other. In the fourth study, we explored effects of DBS on the synergic control of both the hand and the whole body. Results suggest that synergy indices reflect systemic neural mechanisms shared across tasks and effectors. The contrasting effects of DBS on indices of stability and agility suggest that these indices and their changes in PD reflect different functional neural subsystems that could be selectively affected in different neurological disorders.

This conclusion has also been supported partly by our fifth study, in which we explored synergy indices prior to gait initiation and effect of changes in visual scene on indices of stability and agility. PD patients showed reduced stability and agility in preparation of stepping when they turned their head prior to making step. The indices of stability and agility in the healthy elderly were affected differently for different directions of motion, i.e., the indices of agility decreased only for the anterior-posterior direction, while the index of stability was reduced for the medial-lateral direction. This study corroborate the idea that controlled loss of stability is an important component of movement agility and impairments in anticipatory adjustments in synergies stabilizing the vertical posture may lead to consequences such as episodes of freezing.

Although we did not directly targeted cerebellum in this dissertation, observations of impaired control of synergies in patients with disorders affecting subcortical structures, such as the basal ganglia and the cerebellum (reviewed in Latash and Huang, 2015), suggest that different neurophysiological mechanisms might be involved in the synergic control of voluntary movements.
Park and his colleagues tested effects of olivo-ponto-cerebellar atrophy (multisystem atrophy with cerebellar involvement) on finger coordination and observed similar changes in synergy indices to those seen in PD patients (Park et al., 2013b). This group of patients demonstrated a mixture of parkinsonian and cerebellar symptoms. Whereas stability of posture and movement have been linked to the cerebellum and trans-cerebellar loops (reviewed in Manzoni et al., 2004), our observations taken together with the contrast in synergy indices between PD patients and stroke survivors (Jo et al., 2016a; Reisman and Scholz 2003) suggest involvement of basal ganglia loops in controlling action stability. However, changes in the functioning of cerebellar loops are documented in PD patients (Yu et al., 2007, reviewed in Wu & Hallett, 2013), which may have significant contribution to impaired synergies. It is highly desirable to perform experiments designed to disambiguate roles of the cerebellum and basal ganglia in the synergic control of movements.

The methodology used in these studies to quantify synergy indices might detect problems in postural control in PD patients before such problems are recognized based on clinical tests. Our findings suggest potential utility of task-specific synergy analysis to develop a quantitative biomarker of PD that might identify problems with different aspects of motor coordination in patients. Whereas freezing is typically described for walking tasks, we believe that impaired ability to prepare for a quick action is a more general deficiency in PD. Loss of agility as a potential contributor to freezing can be measured by the lack of proper ASAs, as it was observed in our study exploring step initiation and in more challenging condition involving changes in the visual scene prior to stepping. Our observations suggest developing motor rehabilitation techniques to improve ASAs. Having a comparably powerful method based on a few trial (or even single trials) would signify an important step toward making analysis of synergies a broadly used test for early diagnosis of neurological motor disorders, for tracking effects of medications, disease progression, and effects of other treatments including motor rehabilitation.
Analysis of synergies is based on the concept of multi-element systems stabilizing important, task-specific variables in a hierarchically organized control system (reviewed in Latash, 2010, 2016, 2017). Few-to-many mappings allow for controlling a few variables to produce a stable behavior, which may have important implications in the analyses of large-scale neural data. Recently a similar method based on many-to-few mapping has been used to explore mechanisms of control when neural circuits produce a joint output and when they are functionally decoupled (Kaufman et al., 2014; reviewed in Scott, 2017). Within this method, two subspaces are defined: output-null which allows variability in the neural population without changing the net result, and output-potent where activity of the neural population would change the net output. This method assumes that important movement parameters are encoded at the neuronal population level and the neuron firing is determined by the behavior at the population-level (Georgopoulos et al., 1982). Considering highly redundant cortical neural data (Gallego et al., 2017; Stavisky et al., 2017), it might be reasonable to apply the principle of abundance at the level of neural populations. Asking questions about movement coordination at the level of neural population may lead to a deeper understanding of neurophysiological mechanisms of movement stability and agility. These analyses also may result in better understanding of basic principles of neural plasticity, to foster more efficient treatment programs, including neuro-rehabilitation techniques.
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