Corticomuscular Contributions to the Control of Rhythmic Movement in Humans

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Corticomuscular Contributions to the Control of Rhythmic Movement in Humans

by

Hendrik Simon Enders

A THESIS
SUBMITTED TO THE FACULTY OF GRADUATE STUDIES
IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE
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Abstract

The inherent simplicity of human locomotion is deceiving in nature and its complexity becomes apparent when we observe children as they learn to walk or patients suffering from neuromuscular disorders. Human movement requires inputs from supraspinal and spinal centers as well as sensory afferent feedback. However, little is known about the interaction between cortical and muscular activity during whole body movement. This thesis aimed to investigate neuromuscular control at the muscular level, the cortical level and ultimately to link recordings from muscles and the cerebral cortex. Experiments were conducted on a cycling ergometer to mimic the rhythmic movement of limbs that is common to various forms of human locomotion such as walking, running, and cycling. Recordings of muscular activity showed that the coordinated activation of muscles reduces to a few number of critical components when the pedaling load increases. This reduction in the solution space of the task was accompanied by a more precise execution (i.e. less variability) of the chosen solutions. Recordings of electrical activity of the cerebral cortex during the pedaling movement showed that activity was located in the frontal, parietal and motor areas. The time-dependent activity in the motor areas of the cortex were linked to specific phases in the pedaling cycle. Lastly, simultaneous recordings of muscular and cortical activity showed a significant coherence between EEG signals and EMG signals. This corticospinal coupling was weakened as fatigue developed throughout the pedaling exercise. On the contrary, the information flow from the muscles to the cortex was enhanced with the development of fatigue. In summary, our results show that muscular activation patterns can be used to make inferences about neuromuscular control strategies. Further, activity in the cerebral cortex plays a role for rhythmic movement in humans and is linked to muscle activation patterns of the lower limbs.
Preface

Each of the following chapters is based on scientific manuscripts:


Chapter 6 is based on Enders H., Leibold A., Nigg BM. (in preparation for submission) Corticomuscular coherence of the primary motor cortex and lower limb muscles during a rhythmic pedaling task.

This dissertation is based on a collection of manuscripts, and therefore, has some repetition in the introduction and methods sections of chapters three to six.
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To M. & D.
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List of Symbols, Abbreviations and Nomenclature

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<table>
<thead>
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<th>Symbol</th>
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<tbody>
<tr>
<td>EMG</td>
<td>Electromyography</td>
</tr>
<tr>
<td>EEG</td>
<td>Electroencephalography</td>
</tr>
<tr>
<td>PCA</td>
<td>Principal Component Analysis</td>
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<td>ICA</td>
<td>Independent Component Analysis</td>
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<tr>
<td>IC</td>
<td>Independent component</td>
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<td>$\theta$</td>
<td>Theta</td>
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<td>$\gamma$</td>
<td>Gamma</td>
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<td>CMC</td>
<td>Corticomuscular coherence</td>
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<tr>
<td>MAP</td>
<td>Maximum aerobic power</td>
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<tr>
<td>TDC</td>
<td>Top dead center</td>
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<td>RPM</td>
<td>Revolutions per minute</td>
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<td>RPE</td>
<td>Rating of perceived exertion</td>
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<td>TA</td>
<td>Tibialis anterior</td>
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<td>SOL</td>
<td>Soleus</td>
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<td>GM</td>
<td>Gastrocnemius medialis</td>
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<tr>
<td>MMP</td>
<td>Multi muscle pattern</td>
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<td>CV</td>
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<td>Principal activation vector</td>
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<td>Principal muscle activation pattern</td>
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<td>TTE</td>
<td>Time-to-exhaustion</td>
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<td>ERSP</td>
<td>Event-related spectral perturbation</td>
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<td>ERD</td>
<td>Event-related desynchronization</td>
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<td>ERS</td>
<td>Event-related synchronization</td>
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<td>BA</td>
<td>Brodmann area</td>
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<tr>
<td>SMA</td>
<td>Supplementary motor area</td>
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<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<tr>
<td>RDS</td>
<td>Right down stroke</td>
</tr>
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<td>LDS</td>
<td>Left down stroke</td>
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<td>PDC</td>
<td>Partial directed coherence</td>
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The improver of natural knowledge absolutely refuses to acknowledge authority, as such. For him, scepticism is the highest of duties; blind faith the one unpardonable sin.

Thomas H. Huxley, 1866
Chapter One: **INTRODUCTION**

As humans, we can move limbs in a purposeful manner, whether it is a rather simple cyclical task such as walking or fine manipulations of objects such as using a key to open a door. While these tasks may appear simple to a naïve observer, the inherent complexity of performing such tasks becomes apparent when we see the clumsy movements of toddlers as they learn to walk or movements produced by patients with sensorimotor deficits (e.g. stroke). This demonstrates that completing any of these tasks successfully requires a precise interaction between the central nervous and the musculoskeletal system. In fact, planning and executing a movement efficiently requires the sophisticated integration of volitional commands, sensory feedback, force production and limb movement. To understand how humans perform complex movements on a macroscopic level requires an understanding of (a) the muscular system, (b) the nervous system and (c) the interactive processes between the muscular and the nervous system.

The first mention of the human brain is believed to date back to the 17th century BC on a papyrus roll that contained reports about medical information of 48 severely injured individuals. The human brain was first described in a case of a person that had an open skull fracture which allowed doctors to observe the tissue below the skull. Given that medicine was largely based on herbal treatments and ointments, it is not surprising that the doctor’s prediction was that the fracture was “an ailment not to be treated”. The notion that the brain is largely responsible for understanding and perception was first proposed by the Greek philosopher and scientist Alcmaeon of Croton around the 5th century BC. Since then, many scientists have contributed to our modern understanding of the human brain. The belief that its primary role is the computational hub of the human body that allows for the unparalleled cognitive abilities of humans in the animal kingdom remains intact. While scientists agree on its relevance for
planning, executing and controlling movement, the primary attention of modern neuroscience has focused on cognition and perception.

The muscular system has been identified as the biological system that powers movement and human locomotion for more than a century. Leonardo da Vinci (1452 - 1519), the famous Italian polymath, devoted a significant amount of time to studying human anatomy and drawing numerous pictures of the human musculoskeletal system in order to understand the function of the skeleton and the forces applied to it through muscles and tendons. He might be considered one of the first biomechanists and if his studies of the human body had been published at the time, they would have most likely made a significant impact on research and medical science. While da Vinci investigated the musculoskeletal system mostly from an anatomical perspective, Giovanni Alfonso Borelli (1608 - 1679) was the first scientist to relate animal movements to machines using mathematical and engineering principles, laying the foundation for what is known today as the field of biomechanics. Research focusing on the mechanisms of muscle contraction and force production, however, did not accelerate until the 1950s when a paradigm shifting observation was made by two independent laboratories (A. Huxley & Niedergerke, 1954; H. Huxley & Hanson, 1954). This pivotal research has motivated scientists to further explore the topic of muscle contraction. As a result, there has been an accumulation of research attempting to unravel the mechanisms of force production in skeletal muscle (Ostap et al., 2004).

Another famous Italian scientist of the 20th century was Luigi Galvani (1737 – 1798). He discovered that the leg of a frog preparation twitches in response to the external stimulus when exposed to electrical impulses. The work of Galvani in the late 18th century laid the foundation for the field of muscle electrophysiology. The complex nature of electrical excitation and inhibition within nerves was discovered much later in the middle of the 20th century by Hodgkin,
Huxley and Katz (Hodgkin, Huxley, & Katz, 1952) and was awarded with a Nobel prize in physiology or medicine in 1963. Since then, many researchers have focused on the electrical activity that can be measured from skeletal muscles during force production. In the more recent past, the field of electrophysiology branched into the field of neuroscience with many researchers attempting to make inferences about the neural control of human movement based on electrical recordings of skeletal muscles (Farina, Merletti, & Enoka, 2004, 2014).

Understanding the neuro-motor control of human movement is of great significance for both engineering technologies as well as health outcomes. Engineers have created incredibly light and realistic prosthetic limbs with many degrees of freedom. Developing and utilizing these technological masterpieces, however, requires a detailed understanding of the neuro-motor control mechanisms of the intact human body. While the control of such devices has proven successful, it requires invasive surgery to record cortical control signals that will interact with the device (Moritz, Perlmutter, & Fetz, 2008; Hochberg et al., 2012; Hargrove et al., 2013). For many patients, such as those that have suffered from a stroke, a cortical implant is not an appropriate treatment option. In the US alone, almost 800,000 people have suffered from a stroke, with over 600,000 of these being new or first strokes according to the Centers for Disease Control and Prevention (Mozaffarian et al., 2014). One pillar to improve motor recovery for stroke patients is to increase our understanding about cortical contributions to movement. This will allow for the development of corresponding rehabilitation programs that facilitate cortical activation and functional reorganization. Even more important, it is critical that information about cortical and muscular contributions is obtained in a non-invasive manner since open brain surgery is not an option for patients suffering from stroke or spinal cord injury.
Studying the neuro-motor control of human movement lies at the interface between the function of the central nervous system and the muscular system. Scientists can measure similar properties of the two systems by simultaneously recording the electrical activity generated by neurons in the cerebral cortex and the corresponding electrical activity in the muscles. Measurements of the electrical activity can be used to understand how descending projections (i.e. corticospinal and corticobulbar pathways) excite spinal motor neurons, produce an action potential across the muscle, and ultimately cause a muscle contraction. In humans, electrical activity of the skeletal muscles can be measured in a non-invasive fashion using surface electromyography (EMG). Similarly, electrical activity of the cerebral cortex can be measured noninvasively using electroencephalography (EEG). The majority of EEG recordings in humans has focused on upper limb or hand movements. Few studies have utilized EEG in humans during voluntary rhythmic lower limb locomotor tasks.

As introduced previously, voluntary locomotion requires the integration of cortical, subcortical and peripheral information for efficient and accurate movement. Research dealing with vertebrate movement and locomotion is often conducted based on two different approaches. First, a large portion of motor control research has focused on the central pattern generator hypothesis as a model for rhythmic movement and typically compares bursts of rhythmic muscle activation patterns using EMG in intact and spinal animals or healthy and injured humans. Second, the motor neuroscience community has largely focused on discrete, goal-directed movements that are often visually guided and are controlled based on a cortical contributions that can be quantified using EEG. Very few studies have combined the two approaches for either rhythmic or discrete movement tasks. Given the fact that humans are incapable of independent locomotion when the spinal cord is completely disrupted, there seems to be a rationale to
investigate the cortical contribution more deeply in addition to the muscular component of neuro-motor control. Therefore, there is a need to quantify both the cortical and muscular contribution in healthy humans in rhythmic movement due to its ubiquitous presence for all locomotor patterns (e.g. walking, running, cycling, and swimming).

Accordingly, this thesis is based on three conceptual approaches to address neuro-motor control. Muscular and cortical contributions to locomotion will be investigated individually by using (1) isolated EMG recordings as well as (2) isolated EEG recordings. Furthermore, this thesis will attempt to address the cortical contribution to muscle activation patterns during locomotion using (3) a combined analysis of EEG and EMG recordings. Based on this outline, the studies will contribute to the current literature using isolated EMG recordings but also expand this line of research to incorporate a combination of EMG and EEG measurements during rhythmic movements. Ultimately, the goal of this dissertation is to quantify neuro-motor control strategies in the EMG or EEG signal and attempt to quantify the cortical and muscular contribution for the neuro-motor control during a pedaling task.

1.1 Thesis outline

The general objectives of this thesis were to attempt to gain an understanding of the contribution of the cerebral cortex and lower limb muscles to the control of rhythmic locomotor tasks in healthy humans.

1.1.1 Muscle

Scientists studying human movement often quantify muscle activity, with the primary variables of interest being the timing and magnitude of the recorded EMG signals. Such signals are typically characterized by a significant amount of fluctuations within and between trials and subjects. In the past, this variability has often been considered random error and has largely been
neglected. For this thesis, variability is used to describe fluctuations in the amplitude or magnitude of a signal or a variable. It is known from kinematic studies, that variability is not simply noise or error but may actually play an important role in the context of motor control. Therefore, the variability present in muscle activation patterns during human movement may actually reflect neuro-motor control strategies of the system rather than unwanted noise. Little research has been conducted in the area of muscle activation variability and its role in motor control for human locomotor tasks. Therefore, the specific aim #1 of this thesis was to quantify the variability with respect to magnitude and temporal features of the EMG signal as part of the neuromuscular strategy of lower limb muscles during a cycling task. Investigating the variability in the EMG signal will provide information about neuro-motor control strategies of the nervous system. Changing the pedaling task by increasing the mechanical load will give insight if such control strategies are adapted as task difficulty is altered. Ultimately, this will show if signals recorded from the muscular system contain information that is believed to reflect neuro-motor control processes.

1.1.2 Brain

Many studies using surface EMG recordings attempt to make inferences about contributions of the cerebral cortex or specific areas of the cortex to the neural control of movement. While these studies provide valuable information, they lack a direct real-time measurement of cortical activity during whole body movement. Advancement in hardware and software have made it possible to obtain real-time EEG recordings while humans are performing whole body exercises (J. Gwin, Gramann, Makeig, & Ferris, 2011). Therefore, the specific aim #2 of this thesis was to (a) test which cortical areas are activated during a cycling task, (b) identify the temporal activation patterns of the regions of interest and (c) quantify the changes in
cortical activity as fatigue develops throughout the course of an exhausting exercise bout. This objective addresses a lack of knowledge with respect to the spatial and temporal features of cortical contribution to continuous rhythmic locomotion. Understanding the contributions of different regions of the cerebral cortex to human locomotion has potential implications to better understand motor impairments after injury and to improve rehabilitation programs aimed at motor recovery.

1.1.3 Brain-muscle interaction

A significant correlation between cortical activity (EEG) and muscular activation (EMG) has been demonstrated by many different researchers (Mima & Hallett, 1999a; Stephan Salenius & Hari, 2003). These measurements, however, were primarily done using isometric contractions or slowly varying levels of force. These experimental paradigms are not well suited to mimic dynamic locomotor activities such as walking or cycling that occur in everyday life. Additionally, many researchers suggest that rhythmic locomotor tasks rely very little on supraspinal control. Nevertheless, lesions to cortical or subcortical structures have dramatic consequences for human locomotion. While rhythmic muscle activation patterns can be observed, independent spinal locomotion has yet to be demonstrated in humans (Wirz, Columbo, & Dietz, 2001). This suggests that the cerebral cortex might play a much more important role for human locomotion than previously thought. In fact, a much larger cortical contribution to locomotion has been observed in cats as soon as precise stepping movements are required (Liddell & Phillips, 1944; Amos, Armstrong, & Marple-Horvat, 1990; Beloozerova & Sirota, 1998). Therefore, the specific aim #3 of this thesis was to test if there is a significant correlation between the EEG and EMG during a high-intensity cycling task. The significance of this objective is to directly quantify the degree of cortical contribution to specific muscle activation
patterns during rhythmic locomotion. It will provide researchers with information about whether the cerebral cortex directly influences muscle activation strategies in the lower limb during a repetitive locomotor task. If this were the case, it would suggest that the EMG signal does in fact encode cortical information and might be useful to infer about cortical contribution to the neural control of movement.

1.2 Overview of dissertation

This thesis continues with a review of the relevant literature (Chapter two) in order to provide a historical perspective and framework for the studies included in this dissertation. Further, it attempts to offer relevant background information with respect to neuro-motor control of locomotor tasks with specific emphasis on the role of the cerebral cortex and lower limb skeletal muscles. Specific aim #1 is addressed in chapter 3 and 4. Specific aim #2 is addressed in chapter 5. Specific aim #3 is addressed in chapter 6. Chapters 3 to 6 are written as separate manuscripts for publication in peer-reviewed journals. The dissertation is closed with a summary of the findings of the previous chapters and finished with an outlook for further research directions and questions.
Chapter Two: LITERATURE REVIEW

2.1 The Bernstein problem

One of the most common characteristics of human movement is the concurrence of high task accuracy in conjunction with substantial movement variability. In other words, a task can be completed successfully (e.g. shooting a basketball free throw) with many different movement strategies (e.g. movement of the arm, muscle activation pattern) that lead to a combination of ball release variables (e.g. angle, velocity, spin) that result in a successful free throw attempt. This observation was first documented in the early 20th century by the Russian scientist Nikolai Aleksandrovich Bernstein (1896 – 1966). Bernstein used a slowly moving film in combination with a high speed lens shutter to capture small lightbulbs, which he placed on specific points of his subjects’ bodies (Bernstein, 1927). By recording the light emitted by the lightbulbs, Bernstein was able to calculate the motion of the limbs and joints in time and space. In one of his classical experiments, Bernstein studied the movement of blacksmiths hitting the chisel with a hammer (Bernstein, 1923). The blacksmiths were extremely well trained in this task, as they complete this movement hundreds of times per day for several years. Bernstein observed that the movement variability of the tip of the hammer was much smaller than the movement variability of the limbs and joints of the blacksmiths’ arm holding the hammer. He described this phenomenon as ‘repetition without repetition’. Bernstein, as well as many other scientists who followed, concluded that the central nervous system is not concerned with finding a unique solution to the movement of limbs or activation of muscles, but rather is concerned with a stable and accurate performance of the task to be completed (Bernstein, 1967; M. Latash, Scholz, & Schöner, 2002). Since then, the field of motor control has evolved enormously, and many researchers have studied this phenomenon typically referred to it as the ‘Bernstein problem’,


‘redundancy problem’ or ‘degree of freedom problem’. These studies try to understand how the human body controls the many muscles and joints in the human body while maintaining a stable and accurate task outcome.

2.2 Abundance in the human body

It is well known that the human body has a large number of joints that provide many kinematic degrees of freedom, which typically exceed the degrees of freedom required for a task to be solved. Furthermore, the musculoskeletal system has numerous muscles crossing a given joint. As a result, there are an infinite number of theoretical solutions to complete a given task. Typically, this leads to a muscle redundancy, or having more muscles available than kinematic degrees of freedom. This known abundance in degrees of freedom led researchers to study how the central nervous system can control the many available solutions to produce stable and accurate task performance. In the motor control community, the words motor redundancy and motor abundance are used interchangeably (M. Latash, 2000, 2008). The term redundancy can express (a) the fact that a unit is not needed or no longer useful or (b) refer to additional units that allow a system to adjust and compensate in case a functional unit is eliminated or lost (e.g. injury or failure). The term motor abundance implies that utilizing a muscle or joint is based on a set of multiple equivalently acceptable choices. Therefore, the principle of abundance (i.e. multiple options leading to equivalent task outcomes) is often viewed as a potential solution for the problem of motor redundancy (i.e. more degrees of freedom than needed) (M. Latash, 2008). Redundancy and abundance can be found across all levels of motor control. As outlined above, there are many more kinematic degrees of freedom that can be controlled than the degrees of freedom of a task outcome. In Bernstein’s classical blacksmith experiment, there are three major joints (shoulder, elbow and wrist) with 7 degrees of freedom (e.g. three for both the shoulder and
the wrist joints, and one for the elbow joint), while there are only three degrees of freedom to
determine whether the task is solved successfully (x, y and z coordinates of the hammer).

Similar observations can be made on the level of the muscular and nervous systems. For
example, the elbow flexor muscle group includes the brachialis, biceps brachii and the
brachioradialis. All three muscles act to flex the elbow joint by decreasing the angle between the
forearm and upper arm. As a result, there are a theoretically infinite number of muscle activation
patterns that will produce a given moment to achieve a preferred elbow angle. Furthermore, the
central nervous system, specifically the human cerebral cortex, contains a large number of
neuronal cells. While the popular science literature typically quotes 100 billion neurons in the
average human brain, a recently peer-reviewed study estimates the number to be closer to 86
billion neurons (Azevedo et al., 2009). Based on such immense numbers of cells in the human
brain, it is not surprising that research suggests that cells within neuronal ensembles have a
largely redundant function, especially with increasing numbers of neurons in an ensemble in the
motor cortex (Narayanan, Kimchi, & Laubach, 2005).

It is often suggested that neural redundancy is one of the key reasons why behavior can be
conserved or recovered despite significant brain damage (Glassman, 1987). Furthermore, the
redundancy in neuronal cell assemblies may enhance signal-to-noise ratio during behavior
(Barlow, 2001). These brief examples illustrate how redundancy is considered a typical
characteristic of most biological systems within the human body. With respect to motor control,
it can be observed at the level of the nervous system, within muscles acting on joints, as well as
in kinematic trajectories and force output. This variability has been an ongoing topic of research
with a large focus on kinematic and behavioral variability as it relates to motor task performance.
The following section will highlight the most relevant studies related to movement variability in human motor tasks.

2.3 Movement variability

The majority of studies regarding whether variability is structured to guarantee a stable task performance were performed in the upper limb. One of the key studies demonstrating the idea of structured variability was performed during pistol shooting (J. Scholz, Schöner, & Latash, 2000). There are three angles (pitch, yaw and roll) describing the orientation of a pistol in space. At the time when the trigger is pulled, only the pitch angle (vertical deviation from the axis through the pistol’s barrel) and the yaw angle (left and right deviation from the axis through the pistol’s barrel) will affect the accuracy of the shot. The roll angle (rotation around the axis through the pistol’s barrel), however, will not influence whether the target is hit or missed. Therefore, any variation in the roll angle at the time of the trigger pull will not affect the task outcome. Indeed, researchers were able to show that pitch and yaw angles were tightly controlled by the participants, while the roll angle varied to a larger extent (J. Scholz et al., 2000).

Typically, these observations are referred to as the uncontrolled manifold hypothesis (J. Scholz & Schöner, 1999), the minimal intervention principle (Valero-Cuevas, Venkadesan, & Todorov, 2009), or optimal feedback control (Scott, 2004). The common feature of these theories is the observation of small variance in task-relevant variables compared with larger variance in task-irrelevant variables. This characteristic feature has been observed in a wide range of movement and behaviors, such as upper limb kinematics (Bernstein, 1967; J. Scholz et al., 2000), bimanual pointing tasks (Domkin, Laczko, Jaric, Johansson, & Latash, 2002), finger force production (M. L. Latash, Scholz, Danion, & Schöner, 2001; J. P. Scholz, Danion, Latash, & Schöner, 2002; Valero-Cuevas et al., 2009), center of pressure movements to control posture (Krishnamoorthy,
Latash, Scholz, & Zatsiorsky, 2003), as well as saccadic eye movements and goal-directed arm movements (Harris & Wolpert, 1998). All of these studies conclude that the human body selectively minimizes the variance of the task outcome (i.e. final eye, arm or finger position, joint configuration or total force and moment produced by multiple digits) and allows variance that does not interfere with the reliable achievement of the task at hand. This observation is often interpreted as one possible model of how the motor system plans, creates and controls coordinated motor behavior in the context of redundancy and an abundance of degrees of freedom.

2.4 Muscle coordination strategies

The majority of the previous studies were restricted to behavioral and kinematic measurements. Even though these control strategies are present on the movement output level, the origin of structured variability might stem from muscle forces and muscle activation patterns. While there are a few studies that apply variability analysis to EMG measurements (Krishnamoorthy et al., 2003; Valero-Cuevas et al., 2009), the movements are very constrained and simplified (e.g. index finger force production, center of pressure shifts) and it is questionable how much they reflect the coordination challenges underlying whole body locomotor control. A clear link between the observation of structured variability in behavior and kinematics and EMG measurements and muscle coordination is lacking.

Despite the fact that little research has been done with respect to the structure of variability within EMG measurements, a large body of research has focused on the role of muscle activity in the context of neuromuscular control of locomotion. While this research is motivated by a similar question, namely how the central nervous system controls the multiple muscles available for movement, the focus has largely been on the simplification of motor control by grouping
muscles into synergies or modules that allow for the production of rhythmic and coordinated movement patterns.

During a simple walking task, it is estimated that more than half of the lower limb’s muscles are activated in order to control the leg movement in the sagittal plane (Winter, 1991). In theory, the central nervous system could control each of these muscles and each degree of freedom individually. Indeed there is some evidence that for specific situations, the human body might employ such strategies (Kutch, Kuo, Bloch, & Rymer, 2008). However, there are several reasons why individual motor control is impractical and complex (Lacquaniti, Ivanenko, & Zago, 2012). Many muscles in the human body span more than one joint, and therefore act on multiple degrees of freedom simultaneously when activated. Activation of such muscles leads to combined movements of multiple joints and limbs, thereby establishing a mechanical coupling between these segments. This biomechanical coupling is embedded within a system of neural coupling. Many of the sensorimotor pathways of the human nervous system are highly divergent. For example, corticospinal axons project to motor neuron pools of multiple muscles (Shinoda, Yokota, & Futami, 1981). Similarly, sensory afferent feedback from proprioceptors project up to the first segment of the lumbar spine, even though the density is much higher at lower lumbar spine segments (Jankowska, 1992). This shows that there seems to be an inherent neural coupling in descending commands as well as afferent feedback that will typically affect the state of multiple muscles simultaneously. Therefore, establishing a system that controls muscles and motor units individually seems counter intuitive given the biological coupling inherent to the human body. This coupling would most likely present an obstacle to a system that is geared for the control of individual units. Instead, it is expected that a control strategy has evolved to deal and utilize the coupling between the many different muscles involved in typical locomotor tasks.
A widely researched hypothesis is that basic patterns of muscle activation have evolved that represent the elementary building blocks for the generation of limb movement (Ivanenko, Cappellini, Dominici, Poppele, & Lacquaniti, 2007; Bizzi, Cheung, d’Avella, Saltiel, & Tresch, 2008; Tresch & Jarc, 2009; Lacquaniti et al., 2012). This hypothesis is based on the idea that few basic patterns are shared between multiple muscles for a given task. It follows that a single command could be used to activate multiple muscles simultaneously at specific time points within a movement cycle. If correct, this hypothesis would simplify the control significantly by reducing the degrees of freedom to be controlled for the central nervous system. Instead of controlling thousands of individual motor units or dozens of muscles, the central nervous system would only be concerned with the control of the few basic patterns that are sufficient to construct coordinated multi-segment movements (Tresch & Jarc, 2009). This hypothesis is typically referred to as ‘muscle synergies’ or ‘muscle modules’. The term muscle synergy will be used for this dissertation. A muscle synergy typically consists of two components. The first is a basic temporal activation pattern, and the second is a weighting factor that determines the contribution of each basic pattern for different muscles.

The literature delivers a large body of evidence for such patterned control in different animal species. Researchers have shown that many natural motor behaviors, such as jumping, swimming, walking, kicking and reflex responses, can be explained by muscle synergies in frogs (Tresch, Saltiel, & Bizzi, 1999; d’Avella, Saltiel, & Bizzi, 2003; d’Avella & Bizzi, 2005; Kargo & Giszter, 2008; Cheung, d’Avella, & Bizzi, 2009) and postural control tasks in cats (Ting & Macpherson, 2005; Torres-Oviedo, Macpherson, & Ting, 2006). Interestingly, there was little difference in the muscle synergies in frogs before and after deafferentation, suggesting that
synergies rely more strongly on spinal or supraspinal commands rather than sensory inputs (Cheung, D’Avella, Tresch, & Bizzi, 2005).

The concept of muscle synergies is also well researched and supported in humans. In agreement with the muscle synergy hypothesis, many studies are able to show that muscle activity in the lower leg and the trunk can be reconstructed as a linear combination of typically four to five basic sets of muscle activation patterns (Lacquaniti et al., 2012). Early on, it was shown that pattern recognition techniques are able to extract common features in muscle activation patterns (Patla, 1985; Davis & Vaughan, 1993; Olree & Vaughan, 1995). The authors speculated that the nervous system controls these basic building blocks rather than each muscle individually, and they suggest that modifications to locomotion speed and stride length are controlled by modulating the timing and amplitude of these basic patterns.

It has further been shown that these basic patterns during human locomotion are quite robust with respect to task constraints. The overall shape of the few basic patterns seems to be quite similar, independent of modulations in task or environmental constraints. For example, it was shown that five basic patterns can account for the EMG activity of up to 16 leg and trunk muscles while subjects were walking on a treadmill at varying walking speeds ranging from 1 – 5 kmh⁻¹ (Ivanenko, Poppele, & Lacquaniti, 2004). This work has been extended to the analysis of over 30 muscles and treadmill speeds of up to 12 kmh⁻¹ (Cappellini, Ivanenko, Poppele, & Lacquaniti, 2006). The authors found that speed changes were associated with increases in the magnitude of the basic muscle activation patterns and only minor changes in timing. However, the transition from walking to running was associated with a phase shift in the activation of muscle synergies (Cappellini et al., 2006), which are thought to reflect the altered cycle length of swing and stance phase between walking and running (Mann & Hagy, 1980).
Changing from forward to backward walking is known to substantially alter EMG patterns (Thorstensson, 1986; Cipriani, Armstrong, & Gaul, 1995; Grasso, Bianchi, & Lacquaniti, 1998). Nevertheless, decomposing a set of EMG patterns recorded during backward walking results in five basic muscle synergies that are highly correlated to those extracted from forward walking (Ivanenko, Cappellini, Poppele, & Lacquaniti, 2008). This suggests that despite different EMG waveforms, these locomotor modes are based on the same underlying motor programs. Changes in environmental constraints such as unloading of the human body, and thereby mimicking gravitational changes, also did not affect the basic muscle synergies (Cappellini et al., 2006). However, the contribution of the basic patterns providing body weight support and propulsion forces were altered depending on the level of body weight support (McGowan, Neptune, Clark, & Kautz, 2010). It is theorized that the tuning of the basic patterns allows the body to quickly and efficiently adapt to altered environmental constraints by adjusting the activation strength for each basic pattern instead of learning and controlling new sets of muscle synergies. Lastly, it is suggested that the development and control of muscle synergies play a significant role for the learning of locomotor function in childhood development. It was shown that newborn babies exhibit only two patterns, which are augmented by more patterns during early childhood development, and are fine tuned in complexity until adulthood (Dominici et al., 2011). The observed patterns in humans were remarkably similar to other species, such as rats or monkeys. The authors therefore suggested that locomotion is built from common motor primitives, which may be the result of common neural networks (Dominici et al., 2011).

Walking, running and postural control are arguably the most well studied activities with respect to muscle synergies. However, the concept has also been applied to various other activities, and coordinated activation of specific groups of muscles has been confirmed in cycling...
(J. Wakeling & Horn, 2009; Hug, Turpin, Couturier, & Dorel, 2011; De Marchis, Castronovo, Bibbo, Schmid, & Conforto, 2012; Barroso et al., 2014), rowing (Shazlin Shaharudin, Zanotto, & Agrawal, 2014; S Shaharudin & Agrawal, 2015), drop-jump landing (Kipp et al., 2014) and even the back ward giant swing in gymnastics (Frère & Hug, 2012). Cycling presents itself as a great model for rhythmic movements, as the task is highly constrained to the sagittal plane, with robust kinematics that are mostly independent of cadence or the produced torque (Takaishi, Yamamoto, Ono, Ito, & Moritani, 1998). This allows researchers to study the response of the musculoskeletal system in terms of muscular coordination when altering one specific aspect of the cycling task, such as the pedaling cadence or the mechanical power output. A systematic comparison between cadence and load was applied to ten muscles, and the most dominant activation patterns were extracted using Principal Component Analysis (PCA) (J. Wakeling & Horn, 2009). The cadence and load-specific results were consistent among the tested muscle groups spanning the ankle, knee and hip joints. With a fixed cadence (60 revolutions per minute), the intensity of the measured EMG signals increased significantly from when 6.5 Nm to when 40 Nm of torque was applied to the crank (J. Wakeling & Horn, 2009). This is not surprising as motor unit recruitment and rate coding (motor unit firing rate) will increase with a higher pedaling load. It was further shown that for a fixed crank torque of 6.5 Nm, a higher EMG intensity was observed in all muscles as the cadence was increased from 60 to 140 revolutions per minute. This finding can be explained by the force-velocity relationship, which predicts that the force that can be produced by a muscle decreases as the shortening velocity increases. As the pedaling cadence increases, so does the velocity of muscle shortening, which results in a decreased force production capacity of the lower limb muscles. In order to produce the same amount of torque, the central nervous system will recruit more motor units and potentially increase motor unit firing rate. These
changes in motor unit recruitment strategies have been confirmed in cycling as the speed of contraction changes (J. Wakeling, Uehli, & Rozitis, 2006).

In summary, this section highlights some of the most relevant manuscripts that have contributed to our understanding of modular control of muscles, specifically during rhythmic locomotor tasks, such as walking, running or cycling. The results suggest that muscle synergies might play an important role in simplifying the control of the many muscles utilized for locomotion. It is suggested that these muscle synergies are shared between different species (Dominici et al., 2011), as well as different locomotor tasks, such as running and cycling (Barroso et al., 2014). Therefore, muscle synergies are commonly interpreted as the fundamental building blocks for efficient and accurate human movement.

2.5 The role of the cerebral cortex in human locomotion

There have been numerous studies suggesting that control through muscle synergies might be an efficient strategy to simplify motor control. This is supplemented by few studies suggesting that structured variability, similar to the level of movement output, is also a characteristic of neuromuscular activation patterns. This leads to the question how such motor control principles on the muscular level are controlled in real-time to generate adaptive and efficient locomotion. One possibility of an online controller is the human cerebral cortex, the highest control center of the hierarchically organized nervous system.

Given the evidence that deafferentiation resulted in little change to the muscle synergies (Cheung et al., 2005), thereby limiting the role of a strong sensory contribution, there is a rationale for investigating the cortical involvement in the generation of limb movement. In fact, some researchers have shown that the discharge behavior of motor cortical neurons represent functional synergies of muscles in the upper limb (Holdefer & Miller, 2002). Others speculate
that ‘neural loops’ connect the motor cortex and muscle synergies, and suggest this as a potential explanation for the synchronous activity observed in sensorimotor areas and muscles (Aumann & Prut, 2015).

There is clear evidence that the cerebral cortex, specifically the motor cortex, is heavily involved in the generation and guidance of goal-directed upper limb movements (Georgopoulos, Kalaska, Caminiti, & Massey, 1982; J Sanes, Donoghue, Thangaraj, Edelman, & Warach, 1995). It is further supported by clinical studies that lesions in the motor cortex result in significant impairment, for instance for distal upper limb movement (Hoffman & Strick, 1995). However, the role of the motor cortex, and the cerebral cortex in general, is less well studied for locomotor type movements in humans. Goal-directed upper limb reaching movements are typically described as discrete movements, whereas locomotor type movements such as walking or pedaling are typically referred to as rhythmic movements. Discrete movements have an unambiguously identifiable start and end points, and are bound by distinct limb postures (Hogan & Sternad, 2007). Contrarily, rhythmic movements are periodic or cyclical. However, researchers often distinguish between different periodic movements types (e.g. strictly periodic, almost periodic, or quasi-periodic). According to Hogan and Sternad, (2007) a movement is almost periodic if all of its values recur at approximately regular intervals. Arguably, this is a relatively accurate representation of the movement trajectory of the lower limbs in the sagittal plane during locomotor activities such as walking, running and cycling.

Rhythmic and discrete movements do not only differ in movement dynamics, but also in their underlying neural principles. Brain imaging studies have shown that different brain areas are involved in motor control for rhythmic and discrete movements (Schaal, Sternad, Osu, & Kawato, 2004). It is generally accepted that rhythmic movements require substantially less
cortical and subcortical involvement compared to discrete movements. In fact, rhythmic movements are typically associated with neural circuitry in the spinal cord and/or brainstem, which is able to generate rhythmic locomotor patterns (S Grillner & Zangger, 1979; S Grillner, 1985). The neural networks located in the spinal cord are often referred to as central pattern generators. It has repeatedly been shown that quadrupeds demonstrate locomotion even if the spinal cord is transected from the brainstem (Armstrong, 1988). Typically, significant weight support is required for the animal to remain in a standing position. The locomotor pattern is often triggered pharmacologically or by afferent inputs as the treadmill is turned on (Rossignol, Barrière, Alluin, & Frigon, 2009). The observation of a locomotor pattern after complete spinal cord injury is typically referred to as spinal locomotion, since all commands from higher brain centers have been transected. While spinal locomotion is well described in quadrupeds, human spinal locomotion is controversially discussed.

There are several studies ranging from infant locomotion to micro-stimulation of patients with spinal cord injuries that support the concept of a pattern generator in humans at the level of the spinal cord and/or the brainstem (Dimitrijevic, Gerasimenko, & Pinter, 1998; Pinter & Dimitrijevic, 1999; Lamb & Yang, 2000). However, independent spinal locomotion without functional descending pathways has yet to be proven in humans (Dietz, Colombo, Jensen, & Baumgartner, 1995; Wirz et al., 2001; Ferris, Gordon, Beres-Jones, & Harkema, 2004). There is significant evidence that neural networks located in the spinal cord are capable of producing rhythmic patterns of muscle activation, which can lead to some form of locomotion in animals. Furthermore, it is suggested that force production and limb movement during walking is to a certain degree produced by spinal reflexes (J. Yang & Stein, 1990; Stein, Misiaszek, & Pearson, 2000). However, some research suggests that the firing behavior of motor neurons in the spinal
cord of decerebrated cats is fundamentally different compared to intact cats (Hoffer, O’Donovan, Pratt, & Loeb, 1981). This suggests that motor neuron behavior is compromised without functional descending pathways, however, some locomotor patterns can still be generated using spinal neural networks. While such spinal neural circuits are also available in humans, their function alone does not seem to be sufficient to achieve independent locomotion without functional descending input from supraspinal levels.

This raises the important question of whether the cerebral cortex plays a more significant role in the human species for rhythmic movements. In order to answer this question, real time recordings of the cerebral cortex are needed that measure the electrical activity in humans during full body movements. Capturing rapid movement dynamics with periodicity of less than one second requires a neuroimaging tool that has a sufficiently high time resolution. Doing so in healthy intact humans further requires a non-invasive procedure. Selecting the optimal neuroimaging tool typically involves a trade-off between temporal and spatial resolution, direct or indirect measurements of neuronal activity and substantial differences in equipment and operating costs (Lystad & Pollard, 2009). Positron emission tomography and single-photon emission computerised tomography are both invasive tools and measure neuronal activity indirectly as a haemodynamic response in the brain. Their spatial resolution is quite good, however, their time resolution is in the order of minutes, and is therefore completely impractical for quantifying neural activity during movement. Functional magnetic resonance imaging is a non-invasive neuroimaging tool that also measures the haemodynamic response in the brain. It has a good spatial resolution, however, has an insufficient time resolution (>1 s) for movement, and requires a participant to remain as still as possible while lying down. Magnetoencephalography measures neuronal activity directly by quantifying the neuromagnetic
field as a result of electrical current flow in the brain. It is a non-invasive technology and has the best combination of temporal and spatial resolutions. The limitation to this technology is the fact that measurements can only be made in a confined space, as the participant has to remain quietly seated during the measurements. Electroencephalography is a non-invasive neuroimaging tool that quantifies neuronal activity directly through the measurement of electrical potentials. EEG has an excellent time resolution (<1 ms), however is limited in its spatial resolution. Based on the neuroimaging tools described above, it is the only tool that allows a participant to move as freely as possible, thereby allowing movements close to reality.

Despite its theoretically great features for motor neuroscience, EEG has historically been considered too noisy and prone to a variety of artifacts to provide useful information about neural activity during whole body movement. Only in the last decade have people started using EEG in studies dealing with human movement. Arguably, this is the result of considerable advancements in hardware and software for EEG recording and processing (Makeig, Gramann, Jung, Sejnowski, & Poizner, 2009; Gramann et al., 2011; Reis, Hebenstreit, Gabsteiger, von Tscharner, & Lochmann, 2014). Owing to the technical advancements in the field of EEG analysis, researchers have made some initial progress in quantifying neural activity during a variety of human movements. One of the first studies utilizing EEG during a postural control task showed a clear cortical response of about 200 ms prior to reaching the stability boundary and before participants initiated a movement correction (Slobounov, Hallett, Stanhope, & Shibasaki, 2005). However, a constrained postural control task, such as self-initiated oscillatory movements in the anterior-posterior direction, is far from real world whole body locomotion. Another early study showed a frequency-specific response in the cerebral cortex after an
exhaustive treadmill run (Schneider, Askew, Abel, Mierau, & Strüder, 2010), however did not quantify any neural dynamics during the actual exercise protocol.

In the first study that reported EEG recordings during human upright locomotion, researchers were able to show that neural activity during treadmill walking can be localized to specific areas of the cerebral cortex (J. Gwin et al., 2011). This was done by utilizing a sophisticated cleaning protocol that was largely based on Independent Component Analysis (ICA), a signal processing technique aimed to address the blind source separation problem (Jung et al., 2000; J. Gwin, Gramann, Makeig, & Ferris, 2010). ICA has proven to be successful in parsing multichannel EEG signals into cortical components reflecting actual neural activity, as well as noise and artifact components that can be rejected for further analysis. The neural activity was primarily localized to frontal, motor and parietal areas of the cortex as well as parts of the limbic system in the brain. Furthermore, it was shown that the neural activity showed oscillations between increased and decreased activity in these brain areas, which were coupled to the gait cycle (J. Gwin et al., 2011).

Since this first successful study, other studies have utilized similar techniques that allowed researchers to expand upon the initial findings. For example, a comparison between active and passive walking provided evidence that EEG activity in the $\alpha$ (alpha, 8 – 12 Hz) and $\beta$ (beta, 12 – 30 Hz) bands over the central midline of the brain were significantly suppressed (Wagner et al., 2012). This is in agreement with an EEG study that observed suppression of EEG amplitude during active compared to passive cycling trials (Jain, Gourab, Schindler-Ivens, & Schmit, 2013). Suppression of EEG activity is often the result of event-related desynchronization and characterizes a desynchronization between neurons within the cortex. Typically, desynchronization in the cortex is interpreted as active information processing and
communication between cortical areas. Therefore, suppression of EEG activity due to neural desynchronization was interpreted as increased neural information processing during the active walking, compared to the passive movement, conditions (Wagner et al., 2012; Jain et al., 2013). The timing of strong desynchronization, i.e. neural information processing, was related to the transition between stance and swing phase within the gait cycle.

The study of neural activity during walking was expanded to varying visual feedback conditions. Participants walked on a treadmill while looking at a black screen, watching themselves in a mirror, and watching a person walk in a virtual environment in third or first person view (Wagner, Solis-Escalante, Scherer, Neuper, & Müller-Putz, 2014). Gait cycle modulations of EEG activity in motor and parietal areas showed increased neural activity when participants received visual feedback through the virtual environment system. This was particularly prominent in the β and γ (low gamma, 30 – 50 Hz) frequency bands. The authors speculated that increased neural activity may have been the result of additional motor planning and visuomotor processing (Wagner et al., 2014). These findings suggest a stronger cortical involvement in human gait when provided with movement related visual feedback, and could be useful for the design of improved rehabilitation programs for gait recovery after stroke or brain injury.

A more detailed investigation revealed two phenomena when comparing standing to walking. First, the authors observed sustained suppression of oscillations in the α and β frequency bands that were focally located over the sensorimotor areas (Seeber, Scherer, Wagner, Solis-Escalante, & Muller-Putz, 2014). Second, γ band amplitudes were modulated within a gait cycle. The authors speculated that changes in γ frequency range represent movement dynamics during the gait cycle, while the sustained suppression of α and β oscillations over the whole gait...
cycle might represent a change in cortical excitability that is altered between standing and walking (Seeber et al., 2014). A follow up study by the same group further observed that, in addition to low $\gamma$ band amplitudes, there are also amplitude modulations in the high $\gamma$ frequency band (around 70 – 90 Hz) that are coupled to the gait cycle (Seeber, Scherer, Wagner, Solis-Escalante, & Müller-Putz, 2015). Interestingly, the amplitude modulations between the low and high $\gamma$ bands were negatively correlated.

It can be summarized that amplitude modulations have been found in $\alpha$, $\beta$ and low and high $\gamma$ frequency bands. Nevertheless, their function seems to be different with respect to movement. While modulations of $\alpha$ and $\beta$ band amplitudes seem to reflect an overall change in neural state, such as transitioning from standing to walking, the modulations in the $\gamma$ band are thought to reflect neural modulations related to the movement dynamics during gait. Therefore, cortical involvement during locomotor tasks in humans seems to be frequency specific, and the authors suggest that different neural networks may contribute to modulation of $\alpha$, $\beta$ and $\gamma$ frequencies during human movement (Seeber et al., 2014, 2015).

The studies discussed above shared the combined objective to unravel the spatial and temporal characteristics of the cortical involvement in human gait, in order to understand which regions of the brain are involved, and how neural activity is modulated throughout a locomotor task. A few other studies have utilized EEG to test the hypothesis that neural rhythms can be used to predict kinematics of a movement. For example, a group of researchers observed that the low frequency component within the EEG signal contains information that can be used to encode sagittal plane kinematics of ankle, knee and hip joints with just a few number of electrodes (Presacco, Goodman, Forrester, & Contreras-Vidal, 2011; Presacco, Forrester, & Contreras-Vidal, 2012). Similar results were found during upper limb movements (Bradberry, Gentili, &
Contreras-Vidal, 2010; Dipietro, Poizner, & Krebs, 2014). Despite these promising results, there is ongoing debate about the applied methods and the encoded information (Bradberry, Gentili, & Contreras-Vidal, 2011; Poli & Salvaris, 2011; Antelis, Montesano, Ramos-Murguialday, Birbaumer, & Minguez, 2013). One of the main criticisms is based on the fact that similar correlation results between EEG and angular kinematics can be achieved even when corresponding EEG and kinematic trials are randomized or surrogate signals are used (Antelis et al., 2013). Therefore, it is unclear whether encoding performance of kinematics based on EEG signals exceeds probabilities of pure chance, and therefore the results of these studies should be interpreted carefully.

While the majority of recent studies have investigated the cortical contribution during relatively slow walking movements, a few studies have also investigated EEG dynamics during other movements. For example, it was shown that EEG components focally located over the frontal and parietal cortex increased during a 10 second preparation period for a drop jump (Baumeister et al., 2013). In this study, however, EEG activity was not quantified during the actual landing of the jump, as the impact introduced too much noise into the system.

Other studies have used cycling as a very controlled model of rhythmic locomotor exercise, and have utilized EEG recordings to study neural activity during pedaling (Brümmer, Schneider, Strüder, & Askew, 2011; Jain et al., 2013; Schneider, Rouffet, Billaut, & Strüder, 2013). It was shown that systematically increasing exercise intensity on a bicycle ergometer, starting at 50 W until subjective exhaustion, results in a significant increase in EEG activity in the primary motor cortex (Brümmer et al., 2011). Immediately after the last exercise stage was finished, the authors measured a one minute resting state EEG. They observed that activity within the primary motor cortex after the exercise resulted in values similar to those during a
resting state measurement prior to the beginning of the incremental test. It was concluded that elevated EEG activity was primarily related to the active movement and force output regulation during the pedaling exercise (Brümmer et al., 2011). Similar results were confirmed in a follow up study; however, only the highest pedaling intensity (5 W/kg) showed a significant increase in EEG power (Schneider et al., 2013).

A more comprehensive analysis was provided in a study comparing active and passive cycling on a stationary recumbent bicycle (Jain et al., 2013). The authors showed a neural activity pattern that was coupled to the crank cycle during the pedaling movement. Similar to the studies performed in walking, EEG amplitude was significantly suppressed in the active pedaling condition. This was particularly evident for oscillations in the β frequency range for electrodes overlaying the leg area of the sensorimotor cortex. Despite the fact that amplitude differences occurred between active and passive cycling, the overall temporal pattern appeared to be similar between active and passive movements. Based on this observation, the authors concluded that the observed activity has a strong component dedicated to the processing of sensory information, which is required during active and passive pedaling independent of whether active force production occurs (Jain et al., 2013). Analyzing the timing of cortical activity, the authors concluded that cortical involvement appeared to be strongest during the recruitment of muscles that were critical in the transition from flexion to extension during the pedaling cycle (Jain et al., 2013). A similar observation was made in another study, where the summed EMG activity across multiple lower leg muscles showed a significant correlation with EEG signals recorded from scalp electrodes during a cycling exercise (Schneider et al., 2013).

This fairly new line of research attempts to link the cortical contribution during rhythmic human locomotor exercise to the muscle activation patterns measured at lower limb muscles.
involved during force production. Providing evidence for a direct coupling between the cortical involvement measured with EEG, and the muscle activation patterns measured with EMG could be one of the strongest supporters for the hypothesis that the cerebral cortex directly contributes to the activation of lower limb muscles in order to generate and control rhythmic human movement.

2.6 Corticomuscular coupling

Oscillatory activity within the human nervous system has been known and studied for hundreds of years and is, arguably, one of the most basic characteristics of neural and muscular activity. In the early 19th century, William Wollaston discovered the rhythmic discharge behavior of muscles in the $\beta$ frequency range (Wollaston, 1810). Later on, in the early 20th century, Hans Piper observed rhythmic discharge behavior in the $\gamma$ frequency band around 40 Hz (Piper, 1907). Oscillatory activity in the human brain has been researched ever since Hans Berger discovered a strong rhythm in the $\alpha$ frequency range that was modulated by closing or opening of the eyes (Berger, 1929). It is generally believed that neural oscillations that can be picked up using EEG measurements reflect the summation of synchronous activity of thousands of neurons within the cerebral cortex (Kandel, Schwartz, & Jessel, 2000). While the oscillatory behavior of neural and muscular activity has been known for decades, it was only about 25 years ago when researchers discovered that the rhythmic discharge of muscles is governed by the central nervous system. The discovery sparked a series of experiments that confirmed that oscillatory activity within the cerebral cortex contributes to the rhythmic discharge behavior of motor units in primates (Murthy & Fetz, 1992, 1996a, 1996b; JN Sanes & Donoghue, 1993) and humans (McLachlan & Leung, 1991; Farmer, Bremner, Halliday, Rosenberg, & Stephens, 1993).
Investigating the cortical contribution to the activation of skeletal muscles requires one signal originating in the cerebral cortex (e.g. scalp EEG or local field potentials) and EMG recordings as a second signal. The interaction between cortical and muscular signals is most commonly quantified using frequency analysis to reveal the synchrony within different parts of the nervous system. In the frequency domain, the correlation between two physiological signals is most often assessed using coherence. Studying the coherence between the cortex and skeletal muscles is typically referred to as corticomuscular coherence (CMC). While CMC is the most frequently used method, it should be noted that other measures such as the wavelet cross-spectrum or granger causality are also used (Granger, 1969; Pereda, Quiroga, & Bhattacharya, 2005; Bigot, Longcamp, Dal Maso, & Amarantini, 2011). The focus of this section, however, will be on discussing studies that utilize CMC as the analysis tool to investigate interactions between the cortex and muscles. CMC is defined as the squared magnitude of the cross spectrum of two signals $x$ and $y$ divided by the auto spectrum of each signal (Equation 2.1). It is mathematically constrained between zero and one, where one indicates a perfect linear relationship and zero indicates the absence of any linear relationship between $x$ and $y$ (Rosenberg, Amjad, & Breeze, 1989). The phase relationship between the two signals is commonly used to address the temporal association and the direction of information flow (Mima & Hallett, 1999a, 1999b).

$$|R_{xy}(\lambda)|^2 = \frac{|f_{xy}(\lambda)|^2}{f_{xx}(\lambda)f_{yy}(\lambda)}$$ \hspace{1cm} \text{Equation 2.1}
Many researchers have used CMC to assess the cortical contribution to the activation of muscles in monkeys and humans. The first observation of CMC was made in a case study of a patient suffering from seizures, where researchers observed a movement related rhythm that was present at the level of the cortex and the muscles (McLachlan & Leung, 1991). A systematic investigation was published in 1995 showing a significant coupling between cortical and muscular recordings in the $\beta$ frequency range (Conway et al., 1995). This observation has been confirmed by many different researchers using different recording techniques in animals and humans. For example, significant coherence (20 – 30 Hz) was found between local field potential recordings and rectified EMG signals of the hand and forearm in monkeys during a precision grip task (Baker, Olivier, & Lemon, 1997). The authors observed that the timing of coherence coincided with the holding phase (i.e. stationary force production) of the gripping task. Another study utilized MEG to record neural activity in one participant during self-paced finger movements (S Salenius, Salmelin, Neuper, Pfurtscheller, & Hari, 1996). They showed that a rhythm around 40 Hz was observed over the hand area in the motor cortex that demonstrated a significant correlation with the rectified EMG signal recorded from extensor muscles. A different group utilized EEG and EMG recordings of five participants during sustained periods of wrist extension and flexion (Halliday, Conway, Farmer, & Rosenberg, 1998). They showed coherent activity in the frequency range of 15 – 30 Hz between EEG and rectified EMG during periods of isometric muscle contraction. The initial findings of $\beta$ band coherence during low level maintained contractions were expanded to stronger contractions (60 – 80 % of maximal contraction) resulting in a frequency shift of the observed CMC into the $\gamma$ frequency band (Brown, Salenius, Rothwell, & Hari, 1998; Brown, 2000). The agreement between the results obtained from studies utilizing different techniques and species led to the view that rhythmic
Oscillations in the sensorimotor cortex in the $\beta$ and $\gamma$ band are associated with volitional motor tasks, predominantly during periods of sustained muscle contraction.

Based on these results, the initial mechanism responsible for CMC was believed to be a descending drive from the sensorimotor area. This was strongly supported by the observed phase differences (i.e. temporal relationship) between cortical and muscular signals. There was a consistent positive time lag between the cortical signal and the muscular signal for both the upper and lower limb muscles (Brown et al., 1998). Furthermore, the time lag differed between cortical signals and upper or lower limb muscles by approximately 15 ms (Brown et al., 1998), which is in good agreement with known conduction velocities of the pyramidal tract (Rothwell, Thompson, Day, Boyd, & Marsden, 1991; Gross et al., 2000) and the additional distance that needs to be travelled to reach lower limb muscles.

Further support of a descending cortical drive as the primary mechanism for CMC is based on clinical studies involving patients with neurological movement disorders. For example, patients suffering lesions to the central nervous system showed significantly altered motor unit synchronization (Farmer, Swash, Ingram, & Stephens, 1993). Motor unit synchronization in the first dorsal interosseous muscle was reduced from 96% on the unaffected side to about 66% on the stroke-affected side. The study also showed that recovery of hand function (from 0/7 to 7/7 on a hand function test) in four subjects was paralleled by a successive increase in motor unit synchronization (Farmer, Swash, et al., 1993). Other studies also support the idea of a relationship between coherence and motor unit synchronization, specifically in the frequency range of 15 – 30 Hz (Semmler, Sale, Meyer, & Nordstrom, 2004; Moritz, Christou, Meyer, & Enoka, 2005; Lowery, Myers, & Erim, 2007). However, it has to be noted that coherence is generally sensitive to common inputs across a variety of frequencies while motor unit
synchronization is most strongly affected when the common input is closely linked to the mean motor unit firing rate (Lowery & Erim, 2005; Lowery et al., 2007).

Further evidence is based on a study that investigated patients with abnormal corticospinal tracts that project to both contralateral (normal) and ipsilateral (abnormal) distal muscles of the upper limb (Farmer et al., 2004). When these subjects attempt to voluntarily activate their right or left hand there is clear activation of muscles on the other side of the body resulting in mirror movements. In healthy subjects no coherence is seen between EEG recorded over the sensorimotor areas ipsilateral to the voluntarily activated muscles (Conway et al., 1995; S Salenius et al., 1996; Brown et al., 1998). However, in patients with corticospinal projections to motor neurons that activate ipsilateral muscles, there was a significant coherence between EEG activities of the sensorimotor area with EMG activity of the first dorsal interosseous muscle on the ipsilateral side (Farmer et al., 2004). This study provided evidence that corticospinal projections to motor neurons innervating skeletal muscles are involved in producing CMC. It supports the initial proposal of a descending cortical drive from sensorimotor areas as the primary mechanism contributing to CMC. The effect of sensory feedback as a mechanism for CMC in the $\beta$ and $\gamma$ frequency bands is believed to be small. This is based on the fact that muscle tendon vibrations during isometric contractions alter afferent proprioceptive feedback but did not affect CMC compared to unperturbed isometric contractions (Mima, Steger, Schulman, Gerloff, & Hallett, 2000). In summary, there is good evidence that CMC results from a descending cortical drive from the sensorimotor areas that innervate and synchronize motor units.

Most of the studies described above have focused on the upper limb and are limited to static or quasi-static contractions. There are few studies that investigate CMC in lower limb muscles. One study compared CMC between EEG and EMG of the tibialis anterior muscle
before and after a maintained isometric contraction that resulted in fatigue (Ushiyama et al., 2011). The majority of subjects showed an increase in the magnitude of CMC while two subjects only displayed significant levels of CMC in the post fatigue condition. While this study addressed the lower limb muscles, it did not overcome the limitation that isometric contractions are not ideal to replicate activation and force production of muscles during locomotor tasks. Comparisons between isometric and isotonic lower limb muscle contractions showed greater coherence in the $\alpha$ and $\beta$ bands during isometric contractions, while gamma band coherence was higher during isotonic contractions (J. T. Gwin & Ferris, 2012). To date, however, there has only been one study investigating CMC in humans during locomotor tasks (Petersen, Willerslev-Olsen, Conway, & Bo Nielsen, 2012). The results showed significant CMC between the motor cortex and the TA muscle in the frequency range of 24 – 40 Hz, however, the magnitude of coherence was lower compared to isometric contractions. The timing of coherence occurred during the swing phase while subjects were slowly walking on a treadmill, indicating a direct cortical contribution to human gait function.

### 2.7 Summary

A great deal of research has focused on the control of human movement over the past decades. The structure in motor variability has been largely confined to the level of motor behavior and kinematics, thereby, neglecting the muscular system as a potential origin of structured variability. Regarding the muscular system, more focus has been given to the construction of movement based on muscle synergies, a functional organization of muscles into groups that might simplify motor control, specifically for rhythmic locomotor tasks. There is some evidence that such muscle synergies are linked to cortical areas in the motor cortex and are modulated by cortical input. The actual research investigating this cortical contribution is sparse.
Most research utilizing EEG is focused on voluntary upper limb movements and only little is known about rhythmic locomotion. Similarly, the correlation between cortical and muscular signals, quantified as coherence, has focused mostly on upper limb muscles and almost exclusively on low level isometric contractions. This leaves a large gap in the area of the cortical contribution to lower limb function during rhythmic movement and to the muscle activation pattern of leg muscles during dynamic contractions. This thesis will attempt to address some of these shortcomings by utilizing EMG and EEG in isolation and combination during whole body rhythmic locomotor exercise in humans.
3.1 Introduction

The observations made by Bernstein (Bernstein, 1967) showed that a repetitive task or movement is characterized by a non-trivial amount of variability. This suggests that movement variability is not just a random error but may be an inherent property of the control system itself. It is often suggested that this variability is due to the redundancy of the musculoskeletal system where multiple muscles cross a single joint. However, with respect to muscular control mechanisms, the redundancy of the musculoskeletal system has been questioned (Loeb, 2000) and recent studies provide compelling evidence that each muscle may be needed for a given task (Kutch & Valero-Cuevas, 2011).

Several theories have been proposed dealing with the existence of redundancy and variability in the human body (J. Scholz & Schöner, 1999; Todorov & Jordan, 2002; Scott, 2004; Valero-Cuevas et al., 2009). A theory that has attracted a lot of attention is the idea of muscle synergies (Tresch et al., 1999; d’Avella et al., 2003). Instead of controlling multiple muscles or motor units that may have redundant functions, the control function is simplified to a small number of variables (see (Tresch & Jarc, 2009) for a review). However, recently, the concept of muscle synergies and its relation to a neural control strategy has been challenged (Kutch et al., 2008; Valero-Cuevas et al., 2009; Kutch & Valero-Cuevas, 2012) and is still debated in the scientific community.

Other theories propose that task-oriented movement components are accurately controlled because any deviations in these components interfere with the task goal (Todorov & Jordan, 2002), whereas the motor output is minimally affected by fluctuations in irrelevant movement.
components (J. Scholz et al., 2000). As a result, movement variability is typically low for certain aspects of a movement task, whereas other aspects fluctuate to a larger degree (J. Scholz & Schöner, 1999; J. Scholz et al., 2000; M. L. Latash et al., 2001; Todorov & Jordan, 2002; Scott, 2004; Valero-Cuevas et al., 2009). Arm and eye movement trajectories can be accurately predicted using such variability optimising theories (Harris & Wolpert, 1998). This idea of optimal feedback control is typically measured in behavioral or kinematic variables. Studies dealing with variability during dynamic muscular control are limited thus far.

Variability may be found in different subsystems within the human body (joint angular displacement, muscle function, nervous system). Kinematic variability mainly characterizes fluctuations in the positioning and movement of limbs, i.e., the movement execution. However, the control of these movements through muscle activation may be characterized by a nontrivial amount of variability itself. Therefore, it is of interest to apply variability analysis to the activation of muscles that govern the motor output. Electromyography (EMG) studies in the past were primarily performed in static or quasi-static situations such as the evaluation of center of pressure sway (Krishnamoorthy et al., 2003) or muscle activity of fingertip force exertion (Valero-Cuevas et al., 2009).

In a repetitive moment such as walking or cycling, muscles are used dynamically given a variety of different scenarios with respect to force generation. For example, it is known that during cycling, changes in cadence or torque primarily affect the kinetics (Takaishi et al., 1998), whereas kinematics appear to be unchanged. For this reason, kinetic changes during cycling may affect primarily muscle activation patterns and their variability. Some people have argued that synergistic activation patterns could be identified for cycling (Hug et al., 2011). However, people
have not yet tested the idea of optimal control theories in the context of muscle activation during cycling.

Additionally, the limited EMG studies that have been completed thus far focus on purely time-dependent intensity patterns. To describe all information within a waveform, the time-dependent amplitude and the frequency content of the wave are needed. Splitting a signal into several frequency bands allows one to test if the variability is different for the general activation pattern (low frequency components) compared to the detailed fine structure of the activation pattern (high frequency components). Investigating EMG signals in this two-dimensional fashion can be accomplished using time-frequency analysis such as wavelet transforms (Vinzenz von Tscharner, 2000). It has to be noted that the time-frequency-dependent analysis might not be suited in order to make inferences about the neuromuscular recruitment strategies of motor units and or different fibre types. It is generally controversially debated if spectral properties of the surface EMG provide reliable information about recruitment strategies (Farina, 2008; Vinzenz von Tscharner & Nigg, 2008). As stated previously, the frequency-dependent analysis was primarily used to quantify the variability of the general activation pattern compared to the more detailed fine structure within the EMG signal.

In summary, studies dealing with optimal control theory typically observed that the trial-to-trial fluctuations in the data are on average greater in task-redundant motor parameters than fluctuations in task-relevant parameters (Todorov & Jordan, 2002; Scott, 2004; Valero-Cuevas et al., 2009). However, little research in this area was made during whole body exercise when muscles are used dynamically. Although the existence of muscle synergies has been argued to exist in movements like cycling (Hug et al., 2011), researchers have not yet explored the idea that motor variability during cycling is structured and constrained to specific movement
parameters. Therefore, it is suggested that further insight about motor control strategies in cycling can be obtained when variability analysis is applied to the EMG data and the non-stationary EMG signal is considered in the time and frequency domain. Therefore, the purpose of this study was to investigate the variability of muscle activation patterns of several lower limb muscles during a dynamic cycling task under different mechanical loading scenarios in the time and frequency domain.

The hypotheses to be tested were:

H1: Muscle activity can be divided into low- and high-variability components.

H2: Variability within the solution space decreases as the mechanical demand for the limb increases.

3.2 Methods

3.2.1 Experimental Design

Fifteen active male subjects (27.3 ± 4.1 years, 76.3 ± 4.0 kg, 178.1 ± 6.6 cm, mean ± SD) volunteered to participate in this study. All subjects were experienced athletes in endurance type sports and were actively exercising at least three times a week at the time of data collection. Maximum aerobic power (MAP) ranged from 386 – 437 W corresponding to an average of 5.6 W·kg⁻¹ body mass. Before data collection, each participant gave written informed consent in accordance with the University of Calgary's policy on research using human subjects and completed a Physical Activity Readiness Questionnaire. This study was approved by the University of Calgary Conjoint Health Research Ethics Board.

A Velotron Dyanfit Pro cycle ergometer (RacerMate, Inc., Seattle, WA, USA) was used for data collection. The pedal position was determined using a magnetic pedal switch that was activated when the right pedal crank was 90° counter clockwise from the top dead center (TDC).
Mechanical power output and the crank revolutions per minute (RPM) were monitored using the Velotron Coaching Software. Both values were continuously provided as feedback for the participants throughout the testing session. For each participant and testing session, the cycle ergometer was calibrated to guarantee accurate and reliable power output. Participants were seated on the cycle ergometer ensuring a comfortable position with a knee flexion angle at the bottom dead center of 5 ± 1°.

Before data collection, subjects were given a 10 minute warm-up period because it is generally considered to be beneficial for performance (Bishop, 2003). Two conditions with fixed mechanical power output were tested in a randomized fashion. The target power outputs tested were 150 W and 300 W. Between the two testing conditions, participants were given a 5 minute rest period to avoid confounding results due to fatigue. In addition, the Borg scale (Borg, 1998) was used as an assessment tool to quantify the subjective rate of perceived exertion (RPE). Subjects were instructed to hold the cadence as close as possible to the target value of 90 RPM. For each condition, 60 s of data were continuously recorded and stored on a computer for offline processing. EMG signals from the middle 70 consecutive pedal revolutions were extracted and cut into individual cycles according to the signal of the magnetic switch.

3.2.2 EMG Recordings

Muscle activity was recorded from seven lower limb muscles using EMG at a sampling frequency of 2400 Hz. Bipolar Ag/AgCl surface electrodes were placed on the muscle bellies of the tibialis anterior (TA), soleus (SOL), gastrocnemius medialis (GM), biceps femoris long head (BF), vastus medialis (VM), rectus femoris (RF) and vastus lateralis (VL) of the right leg according to the recommendations of the SENIAM guidelines (Hermens, Freriks, Desselhorst-Klug, & Rau, 2000). A single ground electrode was placed on the tibial tuberosity. All
electrodes, cables and amplifiers (Biovision, Wehrheim, Germany) were securely attached to the skin using medical tape to minimize movement artifacts. EMG signals were amplified (2500) and bandpass filtered (10-500 Hz) during data acquisition.

3.2.3 Analysis

EMG analysis was performed using a filter bank of 13 non-linearly scaled wavelets (Vinzenz von Tscharner, 2000) that can be flexibly adapted to analyse a variety of biophysical signals (Beck et al., 2008; Enders, von Tscharner, & Nigg, 2012). The result of the wavelet transform is a time-dependent intensity pattern for each frequency band where the sum of the power of all frequency bands conserves the entire power of the signal (Vinzenz von Tscharner, 2000). In this study, EMG signals were separated into nine frequency bands (wavelet center frequency, 19-330 Hz) and normalized to one pedal revolution.

Each cycle was represented by a multi-muscle pattern (MMP) with 360 rows (pedal position) and 63 columns (seven muscles by nine frequency bands). For both experimental conditions, a matrix $M$ was generated consisting of MMPs of all trials and subjects. The MMPs of different trials and subjects were appended row-wise (Figure 3.1). The EMG intensities for each muscle and subject were normalized to the mean intensity of the 150 W condition. A mean activation pattern was calculated from the original input matrix $M$ as the average over all trials and all subjects per load condition. The mean activation pattern was subtracted from the matrix $M$ to derive a matrix $M'$ as this was shown to be better suited to investigate neural control strategies of EMG data (Ranganathan & Krishnan, 2012). We also calculated the mean coefficient of variance (CV) across the crank revolution for each muscle-frequency band combination to get an understanding of the overall amount of variability of the raw data.
Figure 3.1: The left panel shows a raw EMG signal (A) and its representation in time-frequency space (B) with white and black representing high and low intensity, respectively. These time–frequency plots are organized in a matrix $M$ that is used as an input for the PCA (C).

Each matrix $M'$ was subjected to a principal component analysis (PCA) to decompose the muscle activity into eigenvectors sorted by their explained variance. The eigenvectors can be viewed as principal activation vectors (PAV). The PAVs form a base defined by the intensities of the frequency bands of all muscles, with a dimensionality that is limited to the rank of the covariance matrix of $M'$. The solution space was defined as the subspace spanned by the first PAVs that explained at least 90% of the variance. Thus, the solution space can be interpreted as the combination of solutions that are actually used by humans rather than the theoretical number of possible solutions available to the task. The PCA approach was also applied individually for each subject. This was used to check if the individual subjects showed similar characteristics with respect to muscle activation and variability.
The PAVs of the solution space do not contain the time information of the muscle activation as their vector components (variables) do not include the timing of the EMG. The matrix $M'$ that was used as an input to the PCA contains the time information of the recorded signals. Therefore, the time dependent principal muscle activation patterns (PMAC) were obtained by projecting $M'$ onto the PAVs (similar to (J. Wakeling & Horn, 2009)). For a review of the computational background the reader is referred to classic pattern recognition literature (Theodoridis & Koutroumbas, 2008).

The principal angle between all base vectors of the two load conditions was calculated and can be interpreted as a measure of the similarity between the two subspaces (Knyazev & Argentati, 2002). The principal angle was calculated as the projection of one vector onto another vector. If these vectors are parallel, the projection would be one. In our case, these two vectors are represented by principal axes in the two solution spaces. If the first principal axis in the 150 W solution space is parallel to a principal axis in the 300 W space, the principal angle between these two axes would be one. As the value of the principal angle approaches zero, the two vectors become orthogonal. We used the principal angle to investigate the possibility of modular muscle activation often referred to as muscle synergies (d’Avella et al., 2003; Tresch & Jarc, 2009; Lacquaniti et al., 2012). In the case that muscular synergies are present during the cycling task, one would expect that at least some of the base vectors of both conditions are parallel indicated by a principal angle close to one (Cheung, Piron, et al., 2009). This would indicate that similar vectors span the subspaces of the 150 W and 300 W condition.

3.2.4 Computation of the relative variability (RV)

The time-normalized PMACs were used to calculate means across all trials (PMAC$_M$) and standard deviations (PMAC$_{SD}$) at each time point. We then calculated the root mean square
of the $\text{PMAC}_M$ using Equation 3.2.1 yielding the effective amplitude of the time series. This resulted in an effective amplitude ($EA$) value for each subject, load condition and PMAC.

$$EA = \sqrt{\sum PMAC_M(t)^2} \quad \text{Equation 3.2.1}$$

The absolute variability between different pedal revolutions was then calculated as the root mean square for the standard deviation of all trials, $\text{PMAC}_{SD}$. The relative variability (RV) was obtained by normalizing the absolute variability by the effective amplitude for each PMAC as indicated by Equation 3.2.2.

$$RV = \frac{\sqrt{\sum PMAC_{SD}(t)^2}}{EA} \quad \text{Equation 3.2.2}$$

This normalization procedure allows for direct comparison between different PMAC irrespective of their absolute magnitude.

3.2.5 Statistics

Analysis of variance (ANOVA) was used to test for statistical differences. A $2 \times 2$ factorial design was used. The first factor was the load condition with the levels 150W and 300W. According to our second hypothesis, a second factor was used indicating the grouping of the variability into low- and high-variability components. Adjustments of the type I error rate were ensured using a Bonferroni correction where appropriate. Statistical tests were considered significant using $\alpha = 0.05$. All data is presented as mean and standard deviation (SD).
3.3 Results

3.3.1 Mean activation pattern

Activation increased for the 300 W condition for all muscles, however, the timing of the muscle activation appeared unchanged (Figure 3.2). Generally, the quadriceps muscles were active in a time window slightly before the crank passed the TDC until about 90° past the TDC. The activation of the soleus muscles overlapped with the quadriceps muscles but lasted longer and was followed by the activation of the knee flexors (gastrocnemius medialis and biceps femoris). The tibialis anterior was active when the crank approached the TDC. The general activation pattern of all recorded muscles (Figure 3.2) was well aligned with previous studies that analyzed EMG data for constant load cycling (Ryan & Gregor, 1992). The CV was higher in the 150 W condition compared to the 300 W condition (Figure 3.2). The most dominant changes occurred for the three quadriceps muscles.
Figure 3.2: A, Mean activation pattern (subtracted before PCA) of the seven measured muscles for the 150 W (top) and the 300 W (bottom) condition across all subjects. The EMG signal of each muscle is composed of nine frequency bands ranging from 19 to 330 Hz. The gray scale represents the relative EMG intensity normalized to the mean activation during the 150 W condition. B, Mean CV of the nine frequency bands for all seven muscles tested. Note that the CV compared between the 150 W and 300 W condition decreases across all muscles especially for the lower frequencies and most significantly for the quadriceps muscle. C, Time-dependent EMG intensity of all muscles for comparison with the traditional EMG intensity analysis. Black line, 150 W; gray line, 300 W. All muscles increase the activity in the 300-W condition ($P < 0.05$).

3.3.2 Solution space

The solution space obtained from the input matrix $M'$ was spanned by 21 and 10 PAVs for the 150 W and 300 W condition, respectively (Figure 3.3). The individual analysis showed that the solution space was on average spanned by 17.57 (SD, 1.65) and 7.64 (SD, 3.27) PAV for the 150 W and 300 W condition, respectively.
3.3.3 Relative Variability (RV)

Visual inspection revealed that for both load conditions, the RV started to increase substantially for higher order PMAC (Figure 3.4). This was consistently observed for individual subjects as well as for the analysis across subjects. For the 150 W and 300 W condition, the RV started to increase after the first four and first three PMAC, respectively. Therefore, the PMACs were split into a group of low-variability and high-variability components. The low variability group explained 55.8% and 68.6% of the movement for the 150 W and the 300 W conditions, respectively.

Statistical analysis showed that there was a significant group main effect \( (P < 0.001) \) as well as a significant load main effect \( (P < 0.01) \). Post-hoc analysis confirmed that for both the 150 W condition as well as for the 300 W condition, the low-variability group was significantly lower \( (P < 0.001) \) compared to the high-variability group (Figure 3.4). Similarly, the load effect
was present for both the low-variability ($P < 0.05$) and high-variability ($P < 0.001$) group, showing a lower variability for the 300 W condition compared to the 150 W condition (Figure 3.4).

**Figure 3.4:** A, The horizontal axis shows the cumulative variance accounted for (VAF). The vertical axis shows the RV. Each dot represents one principal activation component and indicates the cumulative VAF and the individual RV. As an example, the third dot indicates how much variance is explained by the first three components together but only shows the RV for the third component. The dashed line shows the 90% threshold of the explained variance. Both the 150 W (gray) and the 300 W (black) condition show an increase in RV after 4 and 3 PAC, respectively. Comparison of the RV of the low-variability subspace (B) and the high-variability subspace (C) between both conditions. *300W significantly lower compared with 150 W ($P < 0.05$). **300 W significantly lower compared with 150 W ($P < 0.001$).
Across both load conditions, the highest loadings within the low-variability subspace occurred on wavelets one, two and three corresponding to center frequencies of 19, 37 and 62 Hz. The loadings of the high-variability subspace included higher ordered wavelets as well.

3.3.4 Principal angle

The maximum absolute principal angle that was found between the solution spaces of the two conditions was 0.88 referring to an angle of about 28°. The average principal angle of the two subspaces was 0.4 (SD, 0.19) referring to an average of 66°, which is below the values (> 0.75) that are typically found in studies supporting the existence of muscular synergies (Cheung, Piron, et al., 2009).

3.3.5 Rating of perceived exertion

Subjective assessments for the RPE for the 300 W condition showed an average of 13.5 with a maximum of 15 corresponding to an activity that is perceived “somewhat hard”. This was significantly higher ($P < 0.01$) compared to the 150 W condition that had an average RPE of 10.1.

3.4 Discussion

3.4.1 Variability Analysis

The analysis of the entire subject pool demonstrated similar results to the analysis of individual participants. Therefore, the group results will be discussed in the following paragraphs.

This study showed that the solution space decreased as the muscular demand of the task increased (Figure 3.3). This is well aligned with the basic principles that the number of solutions decreases when a task needs to be completed in a specific manner (Hasson, Shen, & Sternad, 2012) to optimize performance. In addition, the variability within the solution space got smaller
when the mechanical power output increased (Figure 3.4). This indicates that the probability to execute a chosen solution is reduced when performance is increased by an athlete. Arguably, the ability to sustain this high performance level requires a transition into a regime where the task specifies more precisely the recruitment and activation pattern of specific muscles (Figure 3.5). The muscle activation data could be split into a low-variability and a high-variability portion (Figure 3.4). The variability analysis indicates that certain muscle activations are more accurately controlled when the muscular demand increased (Figure 3.5). This suggests to us that there is an aspect of structured trial-to-trial variability in lower limb muscle activation patterns that is well aligned with the structure found in within-trial variability in hand muscle EMG (Valero-Cuevas et al., 2009).
Figure 3.5: Projection of the input data on the low-variability subspace (A and B) and the high-variability subspace (C and D) for the 150 W (left) and the 300 W (right) condition. Note that the intensity scales are different between the 150 W and the 300 W condition. The low-variability subspace shows more structure with respect to the muscle activation compared with the high-variability subspace. The low-variability subspace of the 150 W condition shows an activation pattern of all muscles similar to the mean pattern, whereas the 300 W condition shows an activation pattern focusing on all three quadriceps muscles and the soleus.

This result may be interpreted that the low variability muscle activation patterns are tightly controlled by the nervous system while high variability muscle activation patterns are allowed to fluctuate. Because the low-variability subspace was mainly characterized by the activity of the lower ordered wavelets (low frequency), it seems that the general muscle activation is tightly controlled by the body. Higher ordered wavelets were mostly found in the high-variability subspace, indicating that quick oscillations of the time-dependent intensity pattern are less controlled.
The structured organization of muscle activation components confirms our first hypothesis. Because of this structure, the solution space was decomposed into two subspaces that are represented by the low-variability and high-variability group (Figure 3.4). The reconstruction of the muscle activation within each subspace (Figure 3.5) yielded two main insights. First, it seems that when switching from 150 W to 300 W the biomechanical constraints of the cycling task specify more precisely the muscular coordination pattern of the movement (Loeb, 2000). Second, it seems that as muscular demand increases, the body switches into a regime of necessary muscles and specifies the control strategy on these task-relevant movement parameters similar to the idea of the minimal intervention principle (Valero-Cuevas et al., 2009). This task-oriented control becomes evident in the low-variability subspace of the 300 W condition. Within one cycling revolution, the main power is typically produced shortly before the crank reaches the TDC until the crank angle reaches about 90° from the TDC (Faria & Cavanagh, 1978). Earlier studies on EMG found that this phase is characterized by a strong activation of the quadriceps muscle (Houtz & Fischer, 1959; Ryan & Gregor, 1992), which could be confirmed by our analysis (Figure 3.2). It is well accepted that the quadriceps muscles are one of the main power producing muscles in cycling. Our analysis showed that the activation of the quadriceps muscles, in particular the rectus femoris, during the power production phase was captured in the low-variability subspace during the 300 W condition (Figure 3.5). This lends compelling support to the idea that the body switches into a regime of a task-oriented control strategy in order to reach and sustain a high power output. We speculate that this transition is partly biomechanically dictated as the task reduces the solutions used by the cyclists (Figure 3.3). However, this transition might also be neurally chosen as the 300 W conditions is also characterized by a stronger use of necessary muscles to sustain this level of power production.
The results of this study mark a first step in indicating a task-oriented control of muscle activation patterns during cycling. This physiological evidence on the muscular level may be a consequence of a control strategy in analogy to the minimal intervention principle (Todorov & Jordan, 2002) that suggest a preferential control of task-oriented parameters by the nervous system (Valero-Cuevas et al., 2009).

Other research has shown that muscle activation during cycling may also be characterized by a synergistic control of muscle activation (Hug et al., 2011). In the case that muscle activation is organized in a synergistic manner as proposed by the muscle synergy theory, one would expect that the synergies are the same when extracted from the same task even though some external conditions (e.g. load) may change. If the same synergies can be extracted from different load conditions, the identified low-dimensional subspaces would be very similar, which can be tested by calculating the principal angle (Knyazev & Argentati, 2002). We were not able to support this idea based on our principal angle results of the two tested conditions.

Generally, one has to be careful with the interpretation of the low-dimensional subspaces that are typically found in muscle synergy studies. It may well be that this is a result based on the method itself rather than neural control strategies since PCA or non-negative matrix factorization are often used as dimensionality reducing algorithms. Because of this inherent feature of these algorithms, it is challenging to prove or reject the hypothesis of muscle synergies.

However, several other potential explanations can be made as to why a low-dimensional subspace has to be found when analyzing muscular coordination (Kutch & Valero-Cuevas, 2012). As an example, Valero-Cuevas et al. (Valero-Cuevas et al., 2009) pointed out that locomotion is a very complex behavior. However, locomotion can be reduced to a very low-dimensional repeating cycle. This may explain why linear decomposition methods typically find
a low-dimensional subspace that explains most of the variance within the data. Another previously unnoted possibility of finding a low dimensional subspace was provided by cadaver experiments in combination with computational models. In this study, it was shown that dimensionality reduction may also arise from pure task constraints and mechanical coupling of the musculoskeletal system (Kutch & Valero-Cuevas, 2012). Therefore, it remains a challenging question to prove the existence of muscle synergies arising from neural origin. In order to do so, the experimenter needs to rule out the possible non-neural origins for these low-dimensional subspaces (Kutch & Valero-Cuevas, 2012) before concluding that muscle synergies are a reflection of the muscular control of the central nervous system.

3.5 Conclusion

The current study showed that muscle activity during constant load cycling can be split into low-variability and high-variability components after a PCA is applied to the entire data set. This structured variability found with dynamic muscle use is similar to observations made during static EMG measurements. The reconstruction of the muscle activation patterns based on the low-variability and high-variability subspace allowed for a physiological interpretation of the result. It seems that the body switched from a generic control mechanism to a task-oriented control as performance and mechanical power increased. The structured aspect in combination with a task-oriented control may be interpreted as support to the minimum intervention principal. In contrast, no evidence was found for the muscle synergy theory when the EMG signal was considered in a time-frequency-dependent manner.
Chapter Four: **NEUROMUSCULAR STRATEGIES DURING CYCLING AT DIFFERENT MUSCULAR DEMANDS**

4.1 **Introduction**

Cycling has been widely studied by scientist as a repetitive activity requiring coordinated muscle recruitment to apply force to the pedals. Understanding the neuromuscular mechanisms of pedaling requires quantification of the timing and magnitude of lower limb muscle activation. It allows quantifying the function of individual muscles and their contribution to characteristic phases within the repeating movement cycle. This was first accomplished by Houtz and Fisher (Houtz & Fischer, 1959) and has been repeated by several independent laboratories (for a review see (So, Ng, & Ng, 2005; Hug & Dorel, 2009)).

The musculoskeletal system has typically more muscles available than required to complete rhythmic movement tasks. This leads to a variety of solutions, which we refer to as solution space, to solve a specific task without changing the result (Müller & Sternad, 2009). Due to the musculoskeletal redundancy, the precise coordination between multiple muscles is an important characteristic in addition to the magnitude and timing of muscle activation, especially for high levels of power output (J. Wakeling, Blake, Wong, Rana, & Lee, 2011). The timing of activation refers to the onset and offset when a muscle is active during a movement. Muscle coordination describes the contributions of individual muscles and/or muscle groups to the movement of interest (Zajac, Neptune, & Kautz, 2002) by analyzing the entire neuromuscular activation pattern instead of treating muscles as independent units. Zajac et al., (2002) have proposed a model of muscle coordination with a synergistic behaviour between knee and hip extensors as well as ankle plantar flexors. While knee extensors are well suited to produce leg
power, the ankle plantar flexors are co-activated to stiffen the ankle joint keeping the foot stable in order to transfer the leg energy into a tangential pedal force for propulsion (Zajac et al., 2002). This coordinated behaviour for force production is load dependent during pedaling as lower limb joint power production increases in a joint specific manner with increased mechanical demand (Elmer, Barratt, Korff, & Martin, 2011). Such an altered challenge for the musculoskeletal system may affect muscle coordination patterns similarly as the relative power production for the task changes (Elmer et al., 2011). In fact, it was shown previously that changes in power production are accompanied by changes in co-activation of muscle pairs (O’Bryan, Brown, Billaut, & Rouffet, 2014). Extending this work to study muscle co-ordination of multiple muscles may prove useful to understand how the musculoskeletal system solves the same task with altered mechanical demands from a neuromuscular perspective.

A more conceptual rationale for studying muscle coordination is the proposal that muscles do not work as independent units. However, researchers have typically taken a reductionist approach with the analysis focused on the individual muscle. While this approach has been successfully used in the past it fails to provide a comprehensive analysis of the complexity of the neuromuscular strategy employed by the musculoskeletal system during movement. Addressing the coordinative aspects of muscle activation may offer advantages to understand neuromuscular strategies without splitting it into individual anatomical units.

One tool that appears to be useful for studying muscle coordination is Principal Component Analysis (PCA). This analysis method has been used in cycling to assess changes in muscle activity with fatigue (Vinzenz von Tscharner, 2002) and different workloads (J. Wakeling & Horn, 2009). It was suggested that increasing the power output not only results from increased magnitude of muscle activation but also from changes in specific muscle coordination
patterns (J. M. Wakeling, Blake, & Chan, 2010). PCA can be used as an efficient tool to investigate if muscle specific contributions and temporal muscle coordination are adjusted in a load dependent fashion similar to lower limb joint power production (Elmer et al., 2011).

One aspect that has received little attention is the variability of muscle coordination and if this variability changes with different muscular demands. While variability of waveforms (Ryan & Gregor, 1992) and of muscle coordination between cyclists (Hug, Turpin, Guével, & Dorel, 2010) has been assessed previously, nobody has investigated the trial-to-trial variability of muscle coordination as well as the short-term fluctuations in the EMG signal of one pedal revolution. Analysis of variability in human movement is important as it reflects and allows for the quantification of the neuromuscular control processes (Harris & Wolpert, 1998; Hausdorff, Zemany, Peng, & Goldberger, 1999). Previously, we have shown a structured trial-to-trial amplitude variability of the EMG signal during cycling which was interpreted as a neuromuscular adjustment to the altered environmental task constraints (Enders, Maurer, Baltich, & Nigg, 2013).

In addition to the amplitude variability, there are short-term fluctuations within the EMG power (envelope of the raw signal) during each pedal cycle that may provide valuable information. These fluctuations describe the adjustment of muscle activation within each pedal revolution. A random superposition of motor unit firing would result in random short-term fluctuations without organized structure. However, similar to the structure within the amplitude component of muscle activation strategies, an underlying structure may be present in the short-term temporal fluctuations of the EMG signal during cycling. If increased muscular demand leads to different motor unit firing rates, which is commonly the case (De Luca, Roy, & Erim, 1993), one may expect differences in the regularity of the short-term fluctuations in the EMG
signal during cycling. Regularity typically describes structure in a signal or a waveform and is related to the probability of predicting future time points in the signal. Finding increased structure in the short-term fluctuations may be an indicator of neuromuscular control processes. In fact, it has been suggested previously that correlated firing of motor units may be a mechanism by which the central nervous system reduces the individual degrees of freedom to be controlled (Farmer, 1998; Semmler et al., 2004).

To the best of our knowledge, nobody has quantified the short-term fluctuations in the EMG signal during cycling. Ordered structure in these short-term fluctuations may be indicative of neuromuscular control and can be assessed using a newly developed method (Zandiyeh & von Tscharner, 2013) based on sample entropy calculations (SampEn) (Richman & Moorman, 2000; Costa, Goldberger, & Peng, 2002). The obtained result, the entropic half-life (EnHL), was shown to be able to sensitively detect changes (Baltich, von Tscharner, Zandiyeh, & Nigg, 2014) and can be compared to a phase-randomized surrogate signal. Using a phase-randomized surrogate signal allows for the power spectrum of the measured signal to be unchanged while randomizing the structure encoded in the phase of the signal.

Therefore, the purpose of this study was twofold. The first purpose was to identify muscle activation strategies at different power outputs using PCA to quantify muscle coordination during cycling. The second purpose was to explore the identified strategies with respect to variability and regularity of the principal component scores (PC) reflecting the correlated muscle activation while pedaling. We hypothesized (H1) that muscle coordination will change with increased power output similar to the redistribution seen with joint power production (Elmer et al., 2011) and changes in muscle co-activation (O’Bryan et al., 2014). It was further hypothesized (H2) that the regularity of the short-term fluctuations of the correlated
muscle activation assessed with the EnHL increases with the increased mechanical demand. Based on the second hypothesis we further propose (H3) that the experimental EMG signal is characterized by a higher regularity compared to phase-randomized surrogate data for both load conditions.

While the first hypothesis addresses our understanding how humans adapt muscle coordination to achieve high power output, the second two hypotheses deal with a novel way to extract neuromuscular control strategies from the surface EMG signal. Typically, frequent fluctuations in the EMG signal are treated as random, thus, not providing any information. However, if our third hypothesis is confirmed one may conclude that the fluctuations in the EMG are a result of a non-random neuromuscular control process in the human body. To the best of our knowledge this would be the first measure of the regularity of neuromuscular control based on the surface EMG during dynamic tasks in humans.

4.2 Methods

4.2.1 Experimental Protocol

Fourteen healthy, active male participants (27.7 (4.0) years, 77.1 (4.0) kg, 181.1 (7.5) cm, mean and SD) were recruited. Participants had to be free from injury for at least six months prior to data collection. Participants were active endurance type athletes exercising at least three times a week at the point of data collection. Participants were not limited to cyclists but had also competitive experience in soccer, cross country skiing and running, in order to capture a variety of endurance type athletes. Each participant gave written informed consent in accordance with the University of Calgary’s policy on research using human subjects and completed a Physical Activity Readiness Questionnaire. The study was approved by the University of Calgary Conjoint Health Research Ethics Board.
Electromyographic signals were recorded while subjects were pedaling on a calibrated Velotron Dynafit Pro cycle ergometer (RacerMate Inc., Seattle, WA). Participants were comfortably seated on the ergometer allowing a knee flexion angle of approximately 5° at the bottom dead center. After a standardized 10 minute warm up, data were collected at 150 W and 300 W power output in a randomized fashion while participants were pedaling at a frequency of 90 revolutions per minute (RPM). Participants were provided visual feedback of their cadence and instructed to keep it as close as possible to the target cadence of 90 RPM. Therefore, the difference between both experimental conditions is the force applied to the pedals by the lower limb muscles. Between both conditions, a 5 minute rest period was allowed to avoid fatigue. The pedal position was determined using a magnetic switch that sent a square wave pulse when the right pedal crank passed 90° counter clock-wise from the top dead center (TDC). For each condition, 60 seconds of data were recorded and the middle 70 pedal revolutions were used for further analysis.

4.2.2 EMG Recordings

Surface EMG signals were recorded from seven leg muscles. Bipolar Ag/AgCl electrodes (10 mm diameter, 22 mm inter-electrode distance) were placed after removal of the hair, abrasion with sandpaper and cleaning with isopropyl wipes on the muscle bellies of the tibialis anterior (TA), soleus, (SOL) gastrocnemius medialis (GM), biceps femoris long head (BF), vastus medialis (VM), rectus femoris RF, and vastus lateralis (VL) on the right leg according to the recommendations of the SENIAM project guidelines (Hermens et al., 2000). A ground electrode was placed on the tibial tuberosity and all electrodes, cables and amplifiers were taped to the skin in order to reduce movement artifacts. EMG signals were amplified (Biovision, Wehrheim, Germany) with an amplification factor of 2500, band pass filtered (10 – 500 Hz) and recorded with a sampling frequency of 2400 Hz via a 12-bit A/D converter (National Instruments, Austin, TX).
4.2.3 EMG Processing and PCA

For each of the seven muscles, the myoelectric signals were resolved into the power extracted by 9 frequency bands (19 – 330 Hz) using a wavelet analysis (Vinzenz von Tscharner, 2000). Individual trials corresponding to one full crank revolution were selected based on the signal from the magnetic pedal switch. For the PCA each trial was time normalized to 720 samples corresponding to the 360° crank revolution. The total power summed across all frequency bands (EMG power) of the myoelectric signal was represented as a vector with seven components representing the EMG power of all seven muscles at each position in the pedaling cycle. These column vectors were appended forming a matrix of $N = 705600$ (14 subjects x 70 pedal revolutions x 720 crank angles) EMG power vectors that span a 7-dimensional vector space. The EMG power for both conditions was normalized to the mean EMG power obtained for each muscle during the 150 W condition across all trials. For each condition the mean of the vectors was subtracted from the matrix. Applying PCA to the input matrix results in a set of PC-vectors and their corresponding eigenvalues of the matrix. The PC-vectors were numbered (PC$_{#}$-vector) in decreasing order of the eigenvalues. The eigenvalues represent the explained variance by each component number and is expressed as a percentage of the sum across all eigenvalues. Therefore, the first PC-vector indicates which muscles contribute most strongly to the overall EMG pattern during the movement. The elements of the PC-vectors are called the PC-loadings. The projections of any EMG power vector on a PC-vector are called a Principal Component (PC) indexed with the component number; they are often called PC-weights or PC-scores. PCs were visualized as a function of pedal revolutions (720 crank angles) and formed a waveform for each component number. Coordination and trial-to-trial variability of muscle activation was visualized as trajectories in the plane spanned by the first two PCs.
4.2.4 Entropy calculation

Information theory defines entropy and sample entropy (SampEn) as the rate of information generation within a signal and quantifies the regularity in the signal (Richman & Moorman, 2000). It can be conceived that points measured at short time intervals (small scales) may show non-random amplitude differences and points measured at very large time intervals (large scales) are uncorrelated or represent random amplitude differences. Thus, with increasing time intervals between adjacent measured values (increasing scale) a transition from correlated to randomness between neighboring points occurs. A freely available software package (Goldberger et al., 2000) was used to calculate SampEn for each time series. A new reshape scale method was used to compute a reshape scale transition of SampEn (Zandiyeh & von Tscharner, 2013). As an example, a reshape scale of three of the example time series of [1 2 3 4 5 6 7 8 9 10 11 12] will result in a new time series consisting of blocks [1 4 7 10 2 5 8 11 3 6 9 12], in this example the block size is four elements long. Thus, increasing the reshape scale will result in an increasingly larger time interval (Δt) between adjacent points in the reshaped time-series (Zandiyeh & von Tscharner, 2013). In this study the reshaping procedure was expanded by randomizing the blocks within the reshaped time series which represents a necessary addition to prevent the reordering of the elements which occurs at large scales. For each individual signal, the SampEn was normalized to the maximum SampEn that was obtained by averaging the SampEn of four completely randomized signals. A reshape scale SampEn transition was obtained by computing the SampEn for gradually increasing scales. The EnHL was quantified as the scale at which the normalized SampEn equals 0.5.
4.2.5 Application of reshape scale SampEn transitions

The cycling movement induces an underlying basic repetitive temporal structure to the PCs seen in the waveforms that is caused by the pedaling rate. In order to analyze the structure of the short-term fluctuations in the EMG power, the PCs were filtered using a wavelet high pass filter (3dB cut-off frequency: 2.5 Hz) to remove the underlying base structure induced by the pedal revolution (90RPM = 1.5 Hz).

EnHL was used to assess the regularity in the high pass filtered PCs temporal structure. EnHL was computed for the 150 W and 300 W conditions for each subjects using the high pass filtered PCs(t) in absolute time units (not normalized to crank angle) of all 70 consecutive pedal revolutions.

4.2.6 Phase-randomized surrogate data

One surrogate signal was generated for the 150 W and 300 W condition of each subject for comparisons with the original, high pass filtered PCs. The original signal was Fourier transformed, then the phase was randomized and a surrogate signal was obtained by applying an inverse Fourier transform. Thus, the surrogate signal has the same power spectrum and autocorrelation as the original signal, however, the structure encoded in the phase has disappeared.

4.2.7 Statistics

Analysis of variance (ANOVA) was used to assess statistical differences of the EnHL between the four conditions (150 W, 300 W, 150 W surrogate, 300 W surrogate). A factorial design was used when assessing differences in the EnHL for individual PCs. Inflation of type I error rate was avoided using a Bonferroni correction. A one-way ANOVA was used when comparing the overall EnHL between the four tested conditions. All tests were considered significant at $\alpha = 0.05$. 

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4.3 Results

4.3.1 Principle Component Analysis

The result of submitting the EMG-vectors (7 components each) to the PCA showed that the PC of the first 6 and 4 PC-vectors were sufficient in order to explain more than 95% of the variance of the data set for the 150 W and the 300 W pedaling condition, respectively. This indicates a reduction of the dimensionality of the solution space for the 300 W condition that was required to explain 95% of the variance. In the 150 W condition the first two PC-vectors explained 30.9% and 26.7% of the total variance, respectively. The 300 W condition was strongly dominated by PC1, which explained 71.3% of the total variance. This is roughly equal to the cumulative variance explained by the first three component numbers in the 150 W condition.

Visual inspection of the PC1-vector loadings of the 150 W condition and the PC2-vector of the 300 W condition showed largest loadings for BF, GM, and SOL (ankle and knee flexor muscles) (Figure 4.1 A and H). The loadings of the PC2-vector of the 150 W condition and the PC1-vector of the 300 W condition were largest for VM, RF, VL (knee extensor muscles) (Figure 4.1 B and G). This demonstrates that the strategies (knee/ankle flexor and knee extensor) represented by the first two PC-vectors are reversed for the 150 W and the 300 W condition (Figure 4.1). This inversion was considered for the remainder of the analysis. Additionally, PC2-vector of the 150 W condition is split into two different strategies in the 300 W condition. The first strategy is represented by the activation of the biarticular rectus femoris (PC1-vector) and the second strategy groups the monoarticular VM and VL (PC3-vector).

Although the loadings of PC1-vector and PC2-vector for both conditions grouped similar muscles, a difference can be observed in the distribution of the PC-loadings between the two conditions. In the 150 W condition three muscles (BF, GM, SOL for PC1-vector and VL, RF,
VM for PC$_2$-vector) show about equal loadings on the first two PC-vectors. In the 300 W condition, the first two PC-vectors are dominated by loadings of the RF and BF, respectively. Beyond the first two components the PC-loadings between the two conditions diverge. The PC$_3$-loadings in the 150 W condition are strongly dominated by the activation of the TA, a muscle that plays almost no role in the 300 W condition, while the PC$_3$-loadings indicate a correlated activation of the VL, VM and SOL in the 300 W condition. In the 150 W condition, all three knee extensor muscles are grouped in PC$_2$-vector while a decoupling between the RF (PC$_1$-vector) and the VL and VM (PC$_3$-vector) can be observed in the 300 W condition (Figure 4.1).

Figure 4.1: Principal component loadings (horizontal axis) of the seven muscles (vertical axis) on the first six PCs (from left to right) for the 150 W (top) and 300 W (bottom) conditions. All horizontal axes have the same scaling as indicated by the lower left example. The number on top of the boxes indicates the explained variance in percent for each PC$_n$-vector.
The PCs are visualized as waveforms (PCs for 720 crank angles) in Figure 4.2. The waveforms change in a similar way as the crank angle progresses in each of the pedal revolutions. The average waveforms across all pedal revolutions form an average waveform for each component number (Figure 4.2). The second and first waveforms in the 150 W and 300 W conditions, respectively, are similar with a clear peak activity during the power production phase after the crank passes the top dead center (TDC). The first and second components in the 150 W and 300 W conditions, respectively, show a slightly later peak during the down stroke of the pedaling movement. The waveforms of the first two components are reversed for the 150 W and 300 W conditions, thus, confirming the reversal shown for the corresponding PC-loadings.

While the first waveform and the second waveform for the two conditions, respectively, are very similar, the explained variance corresponding to this waveform is much higher in the 300 W condition. In contrast to the first two waveforms, the higher ordered waveforms showed no similarity. The third waveform can be seen in Figure 4.2 to illustrate the lack of similarity that was found for all higher waveforms.
**Figure 4.2:** The first three average waveforms (solid black line) of 70 pedal revolutions for the 150 W condition (left) and 300 W condition (right). The horizontal axis describes the crank angle where the dashed line indicates when the crank passes the TDC. The gray shaded area represents the 95% confidence interval.

### 4.3.2 Entropic Half-life of the Principal Components

Visual inspection of the waveforms showed that there were short time fluctuations on top of the individual waveforms. The fluctuations reflect the variation of the activation of the muscles during the cycles of the pedal revolutions. The high pass filtered PCs(t) that reflect these fluctuations over time showed a distinct transition from an ordered, correlated relation between consecutive time points to a random relationship between neighboring points when computing the SampEn for different scales (Figure 4.3).
Figure 4.3: Transition curve of SampEn for different reshape scales ranging from $\Delta t$ 1.7 ms to 40 s. The entropic EnHL is the reshape scale for which the normalized sample entropy is 0.5 (gray dot). Reshape scales on the horizontal axis are shown as a log plot for better visualization.

The EnHL of this transition was computed for each of the PC ($t$) for the 150 W and the 300 W and their surrogates (Figure 4.4). A significant main effect of the EnHL of all PC-vectors was found when comparing all four tested conditions ($F_{1,13} = 2856.4, P < 0.001$). Significant differences in the EnHL for the 150 W, the 300 W and their surrogates were consistently found for each individual component number (Figure 4.4). All individual PCs showed a significantly longer EnHL in the 300 W experimental condition compared to the 150 W experimental condition ($P < 0.001$). Both the 150 W and 300 W experimental conditions showed significantly longer EnHL compared to each surrogate condition ($P < 0.001$). However, there was a significant difference ($P < 0.001$) in the EnHL of the respective surrogate data for PC₁, PC₃ and PC₅ while PC₂, PC₄ and PC₃ did not show statistically significant differences ($P > 0.05$).
Figure 4.4: The EnHL for temporal PC fluctuation corresponding to individual component numbers for the 150- and 300-W experimental conditions (circles) as well as their corresponding surrogate conditions (squares). The lines of the 150 W and 300-W conditions are shown in gray and black, respectively. Each data point represents the mean across subjects (N = 14), with the error bars indicating the 95% confidence interval.

The ANOVA of the overall EnHL (EnHL averaged across all PC-weights of the 95% solution space) showed a significant main effect of the tested conditions (F₁,₁₃ = 2582.72, P < 0.001). Post-hoc comparisons showed that across all fourteen subjects the overall EnHL was significantly longer in the 300 W condition compared to the 150 W (P < 0.001). In detail, the transition from being more regular to more random with increasing scale occurred at EnHL =16 ms in the 300 W condition and at EnHL = 9 ms in the 150 W condition (Figure 4.5). This represents an increase in the EnHL of 68.4% as power output doubled.
The overall entropic half-life for the 150 W surrogate and 300 W surrogate data were 4.1 ms and 4.7 ms, respectively. However, the mean EnHL of the surrogates, although they are not very different in absolute terms, are significantly different \( (P < 0.01) \). Both the 150 W and 300 W experimental conditions had a significantly longer entropic half-life compared to the 150 W surrogate and 300 W surrogate data \( (P < 0.001) \).

4.3.3 Muscle coordination

Muscle coordination was visualized as trajectories of the PCs in the plane spanned by the first two PC-vectors of each condition (Figure 4.6). This plane represents the two dominant coordinated recruitment patterns while performing the cycling task in each condition. The zero
crossover point represents the mean muscle activity. As mentioned previously, the first two component numbers were reversed in the 300 W condition compared to the 150 W condition. As a result the horizontal axis describes a correlated activation of the biceps femoris, gastrocnemius medialis and soleus muscles while the vertical axis represents the correlated activation of the vastus medialis, vastus lateralis and rectus femoris muscles. It can be seen that the general activation pattern, represented by the loop trajectories, is similar in both conditions although there appear to be major differences in magnitude and variability of these trajectories.

In the 150 W condition, the initial activation as the crank passes the TDC is a coordinated activation of knee extensor (PC1), knee flexor and ankle flexor (PC2) muscles indicated by an angled positive slope (light blue to yellow). Contrary to this behaviour, the 300 W condition is initially characterized by an almost vertical slope (light blue to green) indicating a dominant muscle activation of the knee extensors (PC1), primarily the RF muscle. After the upper turning point in Figure 4.6 (green to yellow) in the 300 W condition the PCs show a negative slope (yellow to orange) indicating a coordinated relaxation of the knee extensor and simultaneous activation of the knee flexor muscles. As the knee extensors are fully relaxed the knee flexors develop their full activation around 120° past the TDC (orange). A similar pattern is seen in the 150 W condition during the transition from 90° (yellow/orange) to 180° (red). In the 300 W condition the knee flexor muscles relax while activity of the knee extensor muscles is unaffected until slightly before the crank passes the TDC. This results in an almost horizontal line (red to purple) for the 300 W condition in Figure 4.6 indicating again a dominant pattern of the knee flexors (PC2) with the knee extensors being relaxed. In contrast, during the 150 W condition the last half of the crank revolution (red to light blue) is characterized by a slope indicating an activation of the knee
extensor muscles (PC₂) during the relaxation phase of the knee flexor and ankle flexor muscles (PC₁)

**Figure 4.6:** Coordination plots visualized as loop trajectories in the solution space spanned by the first two principle components for 150 W(left) and 300 W(right). The color code represents the crank angle at each time point and is visualized in the top right corner. The x-axis (PC₁ for the 150 W condition and PC₂ for the 300 W condition) describe the activation of the BF, GM and SOL. The y-axis (PC₂ for the 150 W condition and PC₁ for the 300 W condition) describe the activation of VL, VM and RF.

4.4 Discussion

This study investigated muscle activity during cycling using a PCA approach that has previously been used for the analysis of gait kinematics (Daffertshofer, Lamoth, Meijer, & Beek, 2004; Federolf, Tecante, & Nigg, 2012; Maurer, von Tscharner, Samsom, Baltich, & Nigg, 2013; V von Tscharner, Enders, & Maurer, 2013). Similar to these studies, we were able to identify
main activation patterns reflected in the EMG power, thus showing the coordination of muscle activity while cycling. The muscle coordination in this study was visible in the loadings of the PC-vectors (Figure 4.1). This approach expanded on studies that reported the onset and end of muscle activity and global waveforms of muscle activity while cycling (Ryan & Gregor, 1992; Baum & Li, 2003).

The results of this study showed that specific muscle activation profiles (e.g. RF) take over a more dominant role as power output increases and that the knee extensors and ankle plantar flexors had more distinctly separated times of activation at higher effort levels. Increasing the power output was also characterized by a reduction in the solution space as seen by the lower number of PC-vectors necessary to capture 95% of the variance of the data in the high power condition. We suggest that this result is primarily due to the increased mechanical task constraints that decrease the number of options for the musculoskeletal system to solve the pedaling task. This result confirms a basic physical principle that completing a task in an unspecified manner allows for a theoretically infinite number of solutions. However, an increase in task constraints (e.g. completing a task as fast as possible, approaching maximum power output), results in a decreased number of available solutions for the system in order to complete the task successfully (Müller & Sternad, 2009). Previous studies on pedaling support this reduction in the solution space as the task becomes more constrained when considering the magnitude characteristics of an EMG signal (Enders et al., 2013).

4.4.1 Muscle function during pedaling

The reduced solution space in the 300 W condition was strongly characterized by an activation of knee extensors (RF), knee flexors (BF) and ankle plantar flexors (SOL), however, the knee joint muscles played a dominant role. It was previously shown that lower limb joint
power production increases substantially as mechanical power production increases (Elmer et al., 2011) with the knee extensor and flexor muscles providing more relative joint power compared to the ankle muscles (Elmer et al., 2011) and the RF muscle activation being strongly associated to the produced power output (O’Bryan et al., 2014). In fact, it was shown that muscular efficiency increases with higher levels of power output at a given cadence (Zameziati, Mornieux, Rouffet, & Belli, 2006). This suggests that the observed changes in neuromuscular strategy during the 300 W condition may be one of the mechanisms how efficiency is optimized. In support of this argument, Rouffet, Mornieux, Zameziati, Belli, & Hautier, (2009) reported changes in EMG activity and timing of the RF and BF muscles (PC₁ and PC₂ in the 300 W condition) when subjects pedaled at a low power output (i.e. unloaded cycling exercise). This change in neuromuscular strategy was associated with increased oxygen consumption (Rouffet et al., 2009). Combining the results in this study and previously reported findings suggest that power-induced changes in the neuromuscular strategies during cycling seem to involve the RF and BF muscles leading to different outcomes depending on the power produced by the individual.

The coordination between muscles in the high power output condition also confirms a mechanical model that was proposed for the pedaling movement (Zajac et al., 2002) where the knee and hip extensors contract during leg extension to produce substantial leg power. However, the knee and hip extensors do not deliver much of this energy to the crank. Instead, the plantar flexor muscles that produce little leg power are active to redistribute the power by reducing leg energy and concurrently increasing energy delivered to the pedal to produce a tangential pedal force (Zajac et al., 2002). This synergistic behaviour of hip and knee extensors and the ankle plantar flexors permits the foot to remain nearly horizontal allowing efficient energy
redistribution from the leg to the crank (Zajac et al., 2002). This mechanical synergistic
behaviour was confirmed based on the EMG results of this study.

The 300 W condition showed a main pattern that was very close to the EMG profile of
the RF. This biarticular muscle acts as a hip flexor and knee extensor and is crucial for power
production during the propulsion phase but also for power transfer between the hip and the knee
joint (Ryan & Gregor, 1992). This suggests that energy redistribution between the hip and the
knee joint seems to be an important characteristic in the muscle activation strategy during high
power output. In fact, it was proposed that power produced by monoarticular muscles is
transferred to adjacent joints by their biarticular antagonists (Van Ingen Schenau, 1989). Others
have suggested a unique role for biarticular muscles due to their capability of redistributing
energy among different body segments rather than transferring power between joints (Zajac et
al., 2002). A common core to these concepts is the unique role of acting on multiple joints and
segments and thereby offering solutions different to a single or even multiple monoarticular
muscles. This suggests that the RF muscle plays a key role for segment coordination between
pelvis and thigh and redistributing the energy produced by knee and hip muscles.

4.4.2 PCA reveals coordination strategies

Similar to the studies done on kinematics (Daffertshofer et al., 2004; Federolf et al.,
2012), the PC-loadings provided a holistic picture on the correlated activation of different
muscles and the proportional contribution of individual muscles to the overall EMG activity. In
the 150 W condition we observed that ankle and knee flexors were grouped into PC1-vector,
indicating a correlated activation of the BF, GM and SOL. Similarly, the three quadriceps
muscles were grouped into PC2-vector, indicating a correlated activation of all three muscles.
Both PC-vectors contributed almost equally to the overall muscle activation strategy, indicating a
balanced role from the knee and ankle muscles. The 300 W condition was characterized by two systematic changes in the loadings of the first two PC-vectors. First, the loadings on PC$_1$-vector and PC$_2$-vector were clearly dominated by the RF and BF, respectively, thereby reducing the role of the ankle flexors. Secondly, the proportional contribution of PC$_1$-vector was approximately five times higher than PC$_2$-vector in the 300 W condition indicating a clear dominance of the knee extensor muscles over the knee flexor muscles. In summary, the changes from 150 W to 300 W can be described as a proportional increase in knee muscle activation compared to the ankle activation. With higher mechanical demand knee muscle activation increases substantially for leg power production while the demand for a stiff ankle joint necessary for efficient energy transfer to the crank is similarly relevant in the 150 W and 300 W conditions. Lastly, the activation of the biarticular RF and both monoarticular VL and VM were decoupled in the 300 W condition, indicating different roles during the movement cycle. This uncoupling supports the idea for different roles of biarticular and monoarticular muscles during cycling (Van Ingen Schenau, 1989).

4.4.3 Variability of the neuromuscular strategy

Previous studies have shown structured components in the amplitude trial-to-trial fluctuations (Enders et al., 2013) indicating a non-random control that may be involved during pedaling. However, only the amplitude fluctuations were considered in the analysis neglecting the information encoded in the phase. It is known that the phase of the signal contains information (Oppenheim & Lim, 1981), which gave rationale to the analysis of the EMG signal in this study to quantify the short-term fluctuations within a pedal revolution using SampEn.

These short-term fluctuations in the overall EMG power of one pedal revolution may be caused by muscle activity that is responsible for the fine tuning of the movement. To quantify
numerically the properties of EMG power fluctuations we hypothesized that a new variable, the EnHL which is based on the reshape scale transition of SampEn (Zandiyeh & von Tscharner, 2013), would be able to reveal that the short-term fluctuations of EMG power were non-random but had a structure. In our case, structure may be interpreted as signal regularity where EMG power might be more consistently regulated by descending motor commands and/or other sensory inputs or reflexes. The first major result of the SampEn analysis showed that there was a significant increase in the EnHL for all subjects and components indicating a greater amount of structure in the EMG power encoded in the phase of the signal. Secondly, this study proved that a large amount of the regularity is encoded in the phase of the EMG power and changes with the power output during cycling. The combination of these two results leads to two main interpretations. First, we conclude that structure in the signal increases with task-difficulty most likely due to a more constrained solution space that allows for less randomness in the execution of a movement task. Secondly, the structure encoded in the phase of the short-term fluctuations of the EMG power might be indicative of neuromuscular control mechanisms within the human body. This is based on the observation that randomizing the phase while keeping all other aspects of the signal unaltered, particularly the autocorrelation, resulted in a substantial drop of the EnHL. It shows that the observed structure in the EMG power is significantly different from an uncontrolled random process.

Entropy has been widely used as an analysis tool to assess physiological signals such as the electrocardiogram (Richman & Moorman, 2000; Costa et al., 2002). SampleEn has not yet been used in the context of EMG signals during rhythmic locomotion. EMG signals are a superposition of motor unit action potentials from numerous motor units in the muscle. A random firing of motor units located under the electrode will result in a random EMG signal with
no underlying structure and no regularity in the short-term fluctuations of the EMG power. It was previously shown that single motor unit discharge variability continuously decreases with increasing force output (Vaillancourt, Larsson, & Newell, 2003). As a result of increased motor unit discharge regularity the overall EMG signal and, thus, the short-term fluctuations within the signal may become more regular. Our results suggest that motor unit firing during both low and high power output cycling is non-random in support of previous comparisons of the time-dependent EMG structure to surrogate data during isometric force production (Vaillancourt, Larsson, & Newell, 2002). The further increase in regularity in the 300 W condition suggests increased neuromuscular control that may be a result of increased synchrony in the firing of the motor units. However, the recordings in this experiment were superficial and do not allow to measure specific motor unit populations. Therefore, the translation of muscle tissue under the electrode, which might be different in the two experimental conditions due to muscle gearing and fascicle mechanics, should be considered as a limitation of surface EMG recordings in this study.

It is well described that increased motor unit synchronization is an important factor for muscle activation and force development (Semmler, 2002). It is further argued that a great benefit of motor unit synchronization is the coordination of multiple muscles (Semmler, 2002) resulting in skilled muscle synergies. We might speculate that our increased regularity is based on this altered motor unit firing in order to improve muscle coordination for increased force development. Some studies speculate that increased motor unit synchronization may be a result of an enhanced descending drive from cortical areas (Milner-Brown, Stein, & Lee, 1975). If motor unit synchronization is dependent on a functional descending corticospinal pathway, which is supported by studies using neurologically impaired subjects (Farmer, Swash, et al., 1993), then it might be speculated that the descending drive to the motor units and muscles is
enhanced in the 300 W compared to the 150 W condition. However, this speculation needs careful evaluation using measurements that combine electrophysiological signals of muscles and cortical areas.

4.5 Conclusions

This study evaluated inter- and intra-trial variability of myoelectric signals during pedaling at different power outputs. Overall, the result suggest that the solution space becomes more defined as task-difficulty increases which leads to a more regular signal with respect to the short-term fluctuations. Additionally, alterations in muscle activation strategy were apparent as there was a redistribution of the importance of muscles contributing to the movement.
Chapter Five: **CHANGES IN CORTICAL ACTIVITY MEASURED WITH EEG DURING A HIGH INTENSITY CYCLING EXERCISE**

5.1 Introduction

Coordinated motor skills require the integration of information from peripheral sensors, spinal locomotor networks as well as supraspinal commands (Sten Grillner, Wallén, Saitoh, Kozlov, & Robertson, 2008). However, only in the last decade, researchers have begun to investigate the function of the human brain with respect to voluntary, rhythmic locomotor tasks in real time. Owing the dynamic nature of human locomotion, a primary requirement to quantify cortical dynamics during locomotion is a time resolution that allows the recording of modulations in cortical activity within one cycle of a repeating movement sequence. Classical neuroimaging tools such as functional magnetic resonance imaging or positron emission tomography are not well suited to resolve such rapid modulations of activity. Contrary, electroencephalography (EEG) is a mobile brain imaging technique with more than sufficient time resolution to capture cortical dynamics during human locomotion. While historically, EEG has been considered too prone to noise and artifacts for dynamic recordings, recent advancements in hardware and software have opened the possibility for mobile brain imaging using EEG (Makeig et al., 2009; Gramann et al., 2011).

In the last decade, researchers have begun to study time-dependent cortical dynamics in locomotor and exercise-related situations with the majority of studies focusing on upright human walking and slow jogging. It was proposed that the low frequency component (0.1 – 2 Hz) of EEG recordings can be used to infer the overall time-dependent, linear and angular kinematics of the ankle, knee and hip joints during walking (Presacco et al., 2011). Another study has shown that specific brain regions such as the primary motor, the parietal, and frontal cortices exhibit
distinct time-frequency patterns that are closely linked to the overall movement kinematics of the gait cycle (J. Gwin et al., 2011). Similarly, it was shown that task-dependent EEG can be extracted during slow to moderate walking speeds (De Sanctis, Butler, Green, Snyder, & Foxe, 2012) and that cortical modulations seen in EEG differ between active and passive walking conditions (Wagner et al., 2012). More recently, Wagner and colleagues showed that providing interactive feedback during walking enhances premotor and parietal areas in the brain that are thought to play an important role for motor planning and intention (Wagner et al., 2014). These studies demonstrate that cortical dynamics respond to changes in task parameters indicating that EEG can be used to study neural control during human locomotor tasks. The typical frequency bands that are investigated in movement related tasks are theta ($\theta$: 4 – 8 Hz), alpha ($\alpha$: 8 – 12 Hz), beta ($\beta$: 12 – 30 Hz) and low gamma ($\gamma$: 30 – 50 Hz) frequency bands as they are believed to reflect different aspects with respect to motor planning, execution and control (Pfurtscheller, Neuper, & Krausz, 2000; Taniguchi et al., 2000; Jurkiewicz, Gaetz, Bostan, & Cheyne, 2006; Waldert et al., 2008; J. Gwin et al., 2011). This was supported by a recent study that found sustained suppression of cortical oscillations in the $\alpha$ and $\beta$ band while cortical activity in the low $\gamma$ band seemed to be modulated during the gait cycle phases (Seeber et al., 2014) suggesting that these responses characterize different elements of human walking. A follow up study found that low and high $\gamma$ amplitudes are modulated throughout the gait cycle, however, their amplitude envelopes were negatively correlated throughout the movement (Seeber et al., 2015). The majority of the mentioned studies have been conducted during human walking at low intensities. The aim of this study was to investigate cortical activity patterns using EEG during high effort locomotor tasks. Cycling avoids the high impact forces that are typically observed during high effort running and has often been used in studies investigating neuromuscular strategies due to
the well-controlled movement and repeatability of the task (Enders et al., 2013). In fact, it has previously been used for EEG measurements during high intensity cycling and evidence was provided for increased communication between mid/anterior insular and motor cortex (Hilty, Langer, Pascual-Marqui, Boutellier, & Lutz, 2011). This increased communication between cortical areas was found at the end of the cycling exercise and returned to baseline after a rest period suggesting that (muscle) fatigue alters interaction between cortical structures. Expanding upon these findings, the purpose of this study was to localize electrical brain activity using EEG during cycling at a constant workload and quantify changes in temporal brain activation throughout an exhaustive bout of exercise. Based on previous observations in cycling (Schneider, Brümmer, Abel, Askew, & Strüder, 2009; Brümmer et al., 2011), we hypothesized that electrocortical sources will be located in the motor areas, the frontal cortex and the parietal cortex. Furthermore, it was hypothesized that EEG activity within motor areas will demonstrate an oscillating pattern of increased and decreased activation throughout the pedaling cycle. We further hypothesized that overall EEG activity would increase as fatigue develops throughout the exercise duration.

5.2 Materials and methods

5.2.1 Subjects and ethics approval

Ten healthy, experienced male cyclists (Table 5.1) with no history of lower limb injury within the past two years and no known neurological or muscular deficits volunteered for this study. All subjects provided written informed consent prior to testing. All procedures complied with the standards of the Declaration of Helsinki and were reviewed and approved by the University of Calgary research ethics review board.
Table 5.1 Subjects’ characteristics including lactate thresholds (LT 1 and LT2) and 85% of maximum aerobic power (MAP) that was used for the time-to-exhaustion trial.

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5.2.2 Experimental protocol

Each subject performed testing on three different days. All experimental protocols were supervised by a Canadian Society of Exercise Physiology Certified Exercise Physiologist (CSEP-CEP) and participants were cleared for exercise using a Physical Activity Readiness Questionnaire (Par-Q+). Resting blood pressure and heart rate were measured prior to daily testing and standardized ceiling levels according to the Canadian Society of Exercise Physiology were adhered to. All testing was completed using a Velotron Dynafit Pro cycle ergometer (RacerMate Inc., Seattle, WA) that was calibrated for each testing session (Figure 5.1). All participants used their own pedals (clipless) and corresponding footwear that locked into the pedals to accommodate their usual bike racing equipment. The first testing day was used to establish the maximum aerobic power (MAP) capacity of each subject based on an incremental test. Testing on the second day consisted of a time-to-exhaustion (TTE) test at 85% of the
individual’s MAP and was used for familiarization with the protocol and equipment. The third day was a repeat of the second day and was used for the data analysis. The three testing sessions for each subject were separated by 48 ± 1 hours. To increase repeatability of the results, caffeine intake was restricted to two hours prior to testing and the subject was asked to maintain a normal diet and refrain from any resistance training for the duration of the study.

5.2.3 Maximum aerobic power (MAP)

On the first day of testing an incremental cycling exercise test was used to establish blood lactate thresholds LT1 and LT2 for each subject according to the double breakaway model (Kindermann, Simon, & Keul, 1979; Anderson & Rhodes, 1989). Subjects were given twenty minutes of rest after the incremental test prior to starting the MAP protocol. The MAP test was started at a workload slightly below the LT1 and the workload increased every minute by 25W. The test was terminated when the cadence dropped by more than 15 revolutions per minute (RPM) or below 70 RPM (Figure 5.1). Subjects were included in the study if they reached an MAP of at least 4.5W/kg.
Figure 5.1 The top panel (A) shows a schematic drawing of the experimental setup. Participants were equipped with a tight fitting 64 channel EEG system and several electrodes to record lower limb electromyography (not used in this study). Cables were securely attached to the subjects back to avoid artifacts due to cable movement. The middle panel (B) shows the cadence of a representative subject for a complete time-to-exhaustion trial (gray line). The black line shows the cadence when applying a moving average with a window size of 50 pedal revolution. The dashed black line shows the cadence that the participant voluntarily chose to start the trial. The dotted line shows the corresponding cut off cadence to define task failure. The areas with the horizontal lines depict the time frame corresponding to the fresh and fatigue condition used for the analysis. The shaded gray area corresponds to the last 5% of the trial ultimately prior to task failure. The bottom panel (C) shows the average cadence across all subjects for the fresh and fatigue phase as well as immediately before task failure. * denotes a significant difference compared to the fresh condition (P < 0.01). † denotes a significant difference compared to the fresh and fatigue condition (P < 0.01).

5.2.4 Time-to-exhaustion (TTE) trial

Prior to the TTE trial, each subject performed a standardized warm-up protocol based on three five-minute stages corresponding to resistance values below, at, and above the measured LT1. After the warm-up, the TTE trial was performed at a constant workload of 85% of the MAP with the same seat and handlebar settings of the ergometer that were used to perform the MAP test. On both days subjects were unaware of the workload and the elapsed time of the TTE trial to ensure consistency between days. The preferred cadence was freely chosen by the cyclists (typically between 90 and 100 RPM) and the test was terminated if the cadence dropped by 15 RPM or below 70 RPM. Verbal encouragement was provided throughout the test on both days to ensure maximum performance.

5.2.5 EEG Data collection

Subjects cycled at constant intensity using the ergometer described above. A magnetic switch was used to synchronize the data streams and identify the pedaling cycle. The switch sent a square wave pulse that was recorded in synchrony with the EEG data in order to identify individual pedaling revolutions. EEG was recorded using an active electrode 64-channel (10-20
positioning) BrainVision actiCHamp system (Brain Products GmbH, Germany). Subjects wore a tight fitting electrode cap corresponding to the measured head circumference using a chinstrap to reduce movement of the cap (Figure 5.1). For each subject nasion, inion and preauricular points were used as anatomical landmarks to position the electrode cap. Prior to data collection, SuperVisc electrode gel (EasyCap GmbH, Germany) was used to ensure that the impedance was less than 20 kΩ for each channel. During acquisition, all EEG channels were referenced to the parietal midline (Pz) electrode and a frontal midline (AFz) electrode was used as ground. EEG signals were recorded with a sampling frequency of 500 Hz per channel and stored on a computer for offline processing. All data processing was performed in Matlab (The Mathworks, Natick, MA) using custom written software in combination with scripts based on EEGLab 13.2.2b, an open source toolbox for the analysis of electrophysiological data sets (Delorme & Makeig, 2004).

5.2.6 EEG Data analysis

Analysis of continuous EEG signals was carried out according to previously used methodologies (J. Gwin et al., 2011; Wagner et al., 2012, 2014; Kline, Poggensee, & Ferris, 2014). Briefly, EEG signals were band pass filtered (1-50 Hz) in order to remove signal drifts as well as line noise and were re-referenced to a common average reference. Channels were removed if one of the following criteria were true: (1) channels with standard deviation (SD) larger than 1000 μV, (2) channels whose kurtosis was more than 5 SD from the mean and (3) channels that were uncorrelated with neighboring channels (r < 0.4) for more than 0.1% of the time. On average 51.6 channels were used for further analysis (SD: 1.96, range 49 – 54). Independent component analysis (ICA) was used to decompose the signal into maximally independent components (IC) (Makeig, Bell, Jung, & Sejnowski, 1996). ICA was applied to the
data set of individual subjects. EEG data corresponding to the entire time-to-exhaustion trial (approximately seven minutes) was used for the ICA decomposition. ICs representing line noise, movement artifacts and eye activity were rejected prior to further analysis (Jung et al., 2000). In order to locate the neural sources in brain space, an equivalent current dipole model was computed for individual component scalp maps using the DIPFIT plugin within EEGLab (Oostenveld & Oostendorp, 2002). Each IC was modeled as a single dipole. We used a boundary element head model based on the Montreal Neurological Institute template that utilizes the average of 152 MRI scans from healthy, young adult individuals. No specific spatial constraints were enforced as spatial accuracy is limited without the individual anatomy of subjects. ICs were excluded from further analysis if the projection of the dipole to the scalp accounted for less than 80% of the scalp map variance. All remaining ICs of all individual subjects (approximately 100 in total) were clustered across all subjects using k-means clustering algorithms implemented in EEGLab. The algorithm used the dipole location in brain space and the power spectra of each individual IC for clustering purposes and was reduced to the first ten principal dimensions (as in Gwin et al., 2011). Clusters and dipoles indicating eye movement artifacts were not considered for further analysis. Additionally, any components that were located near the lower back part of the head were not considered for further analysis as they typically represent EMG activity from neck muscle that is characterized by an increase in spectral power above 30 Hz. Lastly, any clusters that were located in deeper brain structures near the cerebellum were not considered for analysis as EEG is not able to reliably localize neural activity in these areas.

5.2.7 Spectral analysis of EEG data

For all individual components in the identified electrocortical clusters we calculated power spectra using Welch’s method. The average power spectra for each cluster were compared
for different stages of the exercise corresponding to the first, middle and last 20% of all pedal revolutions corresponding to the fresh, middle and fatigue condition during the time-to-exhaustion trial. An analysis of variance (ANOVA) with 3 conditions (fresh, middle, fatigue) was computed within the EEGLab toolbox in order to compare power spectra between conditions controlling for false discovery rate (Benjamini & Hochberg, 1995) in case of multiple comparisons (P < 0.05).

5.2.8 Time-frequency analysis

Specifically for electrocortical clusters in the motor areas, we calculated spectrograms for each pedal revolution as a function of crank angle. Spectrograms were calculated based on a set of sinusoidal wavelets (Delorme & Makeig, 2004). The number of cycles increased slowly with increasing center frequency which allows for a better frequency resolution at higher frequencies compared to a traditional wavelet approach using constant cycle length. The time-frequency spectrograms were time-locked to the start of the pedal revolution and then linearly time warped so that the onset and offset of each pedal revolution occurred at the same latencies (J. Gwin et al., 2011; J. Gwin & Ferris, 2012; Castermans, Duvinage, Cheron, & Dutoit, 2014; Seeber et al., 2015). The time warping procedure uses event latencies of each individual pedal revolution onset and offset and warps these latencies to the average onset and offset latency, thereby, time normalizing each pedal revolution. In order to display electrocortical fluctuations within a pedal revolution we expressed the time-frequency transformed data relative to the average spectrogram (averaged across the time domain of the pedal revolution) similar to previous studies (J. Gwin et al., 2011; Wagner et al., 2012, 2014; Kline et al., 2014).
This was done based on the following equation:

\[ Y_{dB} = 10 \cdot \log_{10} \frac{Y_t}{Y_0} \]  \hspace{1cm} \text{Equation 5.2.1}

Where \( Y_t \) is the power at time \( t \) and \( Y_0 \) is the average power over the pedaling cycle.

These fluctuations from baseline are typically referred to as event-related spectral perturbations (ERSP). We calculated ERSPs for each component within the motor area cluster. A grand average ERSP was obtained by averaging the individual ERSPs. Significant pedaling ERSPs were identified using bootstrapping methods available within EEGLab (200 iterations). Bootstrapping is based on surrogate data distributions by randomly resampling the observed data, re-computing the outcome variable and comparing the experimental data to the generated surrogate data distribution. Multiple comparisons were controlled using the false discovery rate with a significance level set at 0.05. All non-significant fluctuations from baseline in the ERSP plots were masked for visualization in this manuscript. In order to reveal the relative timing of brain activity we calculated waveforms representing spectral power fluctuations in the \( \alpha \) (8-12 Hz), \( \beta \) (12-30 Hz) and low \( \gamma \) (30-50 Hz) band. ERSPs and waveforms were visualized for the first 20% of the exercise (fresh) and the last 20% of the exercise (fatigue). These timeframes correspond to approximately 120 – 135 pedal revolutions. Comparisons between the ERSP conditions was made within EEGLab using the bootstrapping procedure outlined above using the false discovery rate to correct for multiple comparisons.

5.2.9 EMG data collection and analysis

While the analysis of muscle activity was not the primary focus of this manuscript, surface electromyography (EMG) data were collected to ensure if potential cortical changes were
associated with altered muscular activation patterns. Details of the data collection and analysis techniques are provided in a previously published manuscript that utilized the same techniques (Enders, von Tscharner, & Nigg, 2015). Briefly, muscle activity was collected from muscles spanning the ankle, knee and hip joints with a sampling rate of 2000 Hz. Raw EMG signals were separated into individual pedal revolutions according to a magnetic pedal switch. In order to obtain temporal waveforms, the EMG activity was wavelet transformed (Vinzenz von Tscharner, 2000). The output of the wavelet transform is an intensity pattern indicating the EMG activity at each time point for specific center frequencies. Summing up the activity across all frequency bands results in the total intensity for each time point. These temporal waveforms were normalized to the pedaling cycle with a time resolution corresponding to 0.5° of the crank cycle. Grand average waveforms were obtained by averaging the trials of each subject corresponding to the first and last 20% of the time-to-exhaustion trial.

5.3 Results

5.3.1 Time-to-exhaustion

On average, participants were able to produce 85% of their maximum aerobic power for 7:04 minutes (range: 6:01 – 8:58 minutes). Participants started the trial at a cadence of approximately 97 RPM. The cadence significantly dropped to 90 RPM during the last 20% of the TTE trial. As per our definition of task failure, a drop in cadence of 15 RPM or below an absolute number of 70 RPM, the average cadence for the last 5% of the pedal revolution decreased to 86 RPM (Figure 5.1).

5.3.2 Location of clusters in brain space

Across all subjects, we identified four electrocortical clusters that contained components from more than half of our subjects. The corresponding Talairach coordinates (Lancaster et al.,
and Brodmann areas (BA) are illustrated in Table 5.2. Two clusters (left and right hemisphere) were identified in the parietal cortex with corresponding BA 39 and 7. One cluster was identified in the superior frontal gyrus of the frontal cortex corresponding to BA 8. Lastly, we identified one cluster in the supplementary motor area (SMA) of the brain in the precentral gyrus of the frontal cortex corresponding to BA 6. Additionally, two more clusters were identified corresponding to the right frontal and right premotor areas, however, only four and five subjects, respectively, contributed to these clusters. According to our inclusion criteria if a cluster did not contain dipoles of at least more than half of the tested subjects, it was not included in any further analysis.

Table 5.2 Talairach coordinates for identified clusters (geometric mean)

<table>
<thead>
<tr>
<th>Cluster</th>
<th>Nearest Gray Matter Brodmann Area&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Talairach coordinates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal cortex, superior frontal gyrus</td>
<td>BA 8</td>
<td>(-21, 48, 52)</td>
</tr>
<tr>
<td>Frontal cortex, precentral gyrus</td>
<td>BA 6</td>
<td>(-23, -19, 70)</td>
</tr>
<tr>
<td>Parietal cortex, superior parietal lobule</td>
<td>BA 7</td>
<td>(38, -60, 60)</td>
</tr>
<tr>
<td>Parietal cortex, inferior parietal lobule</td>
<td>BA 39</td>
<td>(-48, -65, 46)</td>
</tr>
</tbody>
</table>

<sup>1</sup> Determined using the Talairach client ([www.talairach.org](http://www.talairach.org)) (Lancaster et al., 2000)
5.3.3 Changes with exercise duration

All clusters of cortical activity showed a significant increase in EEG power (P < 0.05). No differences were found between the fresh and middle portion of the TTE trial and, therefore, the results are focused on the fresh and fatigued states. The left frontal cortex showed an increase in α-, β- and γ-band while the clusters in the supplementary motor area and left parietal cortex only showed a significant increase in the α- and β-band and the right parietal cortex only for the α-band (Figure 5.2). The strongest increase in EEG power was observed in BA 8, followed by increases of smaller magnitude in the SMA (BA 6) and the parietal cortex.
Figure 5.2 Scalp map projections from the dipole clusters and power spectra for electrocortical sources corresponding to frontal cortex (BA 8, top left), SMA (BA 6, bottom left), right parietal cortex (BA 7, top right), and left parietal cortex (BA 39, bottom right). The color scale indicates the strength of the cluster average scalp projection to each electrode. The traces indicate the fresh (black) and fatigue (gray) conditions with shaded gray areas indicating the 95% confidence intervals. The MRI images show the dipole clusters in the sagittal and coronal planes.

5.3.4 Spectral fluctuations within motor area

The ERSP pattern for BA 6 (SMA) is visualized with warm colors, indicating increased brain activity, and cool colors indicating decreased brain activity, with respect to the average spectrogram that was considered as baseline (Figure 5.3). All non-significant modulations of spectral power were masked (green) for better visualization. All frequency bands showed an oscillating pattern of increasing and decreasing activity throughout the pedaling cycle in both
conditions. In the fresh condition, significant modulations in $\alpha$, $\beta$- and $\gamma$-band power are characterized by two local minima representing event-related desynchronization (ERD), which occur before the onset of right and left down stroke, respectively. Modulations of $\gamma$-band power remain similar in the fatigue condition, with the second negative peak occurring slightly later compared to the fresh condition. On the contrary, modulations of $\alpha$- and $\beta$-band power show an altered pattern in the fatigue condition with a pronounced ERD occurring prior to the onset of the right down stroke, followed by a phase of event-related synchronization (ERS) prior to the left down stroke. Overall, there was a larger amplitude modulation in the $\alpha$- and $\beta$-band in the fatigue condition.
**Figure 5.3** ERSP plot (A) of BA 6 showing modulations in EEG spectral power throughout the pedaling cycle (x-axis) as a function of frequency (y-axis, log scaled) with warm and cool colors indicating increased and decreased activity with respect to the average spectrogram, respectively. The left column shows data for the fresh condition (first 20%) and the middle column for the fatigue condition (last 20%). The right column shows the difference (fresh minus fatigue) between the two conditions with any non-significant differences set to zero. The plots below (B)
show the time-dependent brain activation across the pedaling cycle in the $\alpha$, $\beta$ and low $\gamma$ frequency bands for the fresh (left) and the fatigue condition (right). The shaded pink and white areas indicate the down stroke (power production phase) of the right and left leg, respectively. The onset of right down stroke (RDS) and left down stroke (LDS) corresponds to the right and left leg passing the top dead center and is indicated by the arrows below the x-axis.

5.3.5 Muscle activation patterns

Grand average temporal waveforms of EMG activity were visualized for both conditions (Figure 5.4). The waveforms are in general agreement with previous results investigating muscle activity during cycling (Ryan & Gregor, 1992; Baum & Li, 2003; Enders, von Tscharner, et al., 2015). Most muscles showed a trend towards increased muscle activity, however, across all subjects the differences were not statistically different. The overall temporal pattern of muscle recruitment, however, seemed very robust despite the development of significant fatigue.

**Figure 5.4** Grand average EMG waveforms in the fresh (black) and fatigue (gray) condition for six lower limb muscles. The x-axis shows the crank cycle with zero referring to the top dead center (TDC). The y-axis shows the EMG activity normalized to the mean activity of each muscle across the pedaling cycle in the fresh condition.
5.4 Discussion

5.4.1 Modulation of cortical activity during cycling

This is the first study to quantify changes in the temporal pattern of electrocortical activity during high intensity cycling in a time-to-exhaustion trial. This expands on previous work investigating intra-cortical communication during a cycling time-to-exhaustion trial where communication between mid/anterior insular and motor cortex significantly increased with the development of fatigue (Hilty et al., 2011). Similar to previous studies on gait, the results of our study highlight temporal patterns of human brain activity that are spatially localized to the motor area within the frontal lobe (BA 6) (J. Gwin et al., 2011; Wagner et al., 2012). Significant modulations from baseline were observed in EEG power for an electrocortical cluster that was localized in BA 6 representing the SMA. Significant ERD in EEG power were observed across the $\alpha$, $\beta$ and $\gamma$ frequency range for the SMA during the transition from the recovery phase to the power production phase for both legs indicating activation and increased neuron excitability for these brain areas at these specific latencies (Pfurtscheller & Lopes da Silva, 1999; Neuper & Pfurtscheller, 2001). Thus, neural activation within the SMA is greatest when muscles are recruited that are critical in transitioning the lower limb from a flexed to an extended position. This result is in agreement with previously described cortical activation patterns during cycling (Jain et al., 2013). Interestingly, a study quantifying cortical dynamics during walking supports the notion that modulation of activity in the BA 6 is related to movement with specific phases of repetitive locomotor activity (Wagner et al., 2012). They also found a trend for increased neural activation in the gamma frequency band in active compared to passive walking. Our results during active cycling also show modulation of gamma activity in the SMA supporting the
suggestion by Wagner and colleagues (2012), that it might be an important contributor to motor planning and sensorimotor processing.

The role of the motor areas in the cycling task used in this experimental protocol can be explored in more detail when interpreting the alternating pattern of desynchronization and synchronization of EEG power (Figure 5.3). Desynchronization refers to clusters of neurons that are not firing in synchrony and reflect activity distributed across various brain areas. Neural desynchronization is often interpreted as active information processing (Pfurtscheller & Berghold, 1989; Jurkiewicz et al., 2006). An increase in desynchronization can be indicative of an increase in task complexity with a higher demand for information processing (Pfurtscheller & Lopes da Silva, 1999). The opposite phenomenon, an increase in EEG power at a given frequency, is typically observed due to a synchronized firing of neurons. Although it is generally believed that ERS in the alpha and beta band reflects coherent activity and a deactivated communication between neural networks (Pfurtscheller & Lopes da Silva, 1999), in the context of movement tasks it is often interpreted as movement-related sensory processing (Cassim et al., 2001). In summary, ERD reflects active information processing with activity distributed across neural networks while ERS reflects a more focal activation pattern indicating a neural cell assembly responding in the same way. The results in this study show different responses for the alpha and beta compared to the gamma frequency band and will, therefore, be discussed separately.

In the alpha and beta band, during the fresh condition, we see a small ERD that occurs during the phases of the right and left down stroke followed by ERS towards the end of the crank cycle that is stronger in the beta compared to the alpha band. In both frequency bands this pattern is changed during the fatigue condition and pronounced in amplitude. A clear phase of ERD
during the down stroke of the right leg is followed by a phase of ERS in the second half of the cycle. The magnitude of ERD and ERS are increased in both alpha and beta frequency band. Specifically, during the fresh condition the phases of ERD, representing an active information processing behavior, correspond to the phases when the leg prepares for force production and transitions from a flexed to an extended position (Figure 5.3).

The gamma frequency band shows similar behavior to the alpha and beta frequency bands during the fresh condition with oscillations of ERD and ERS throughout the pedaling cycle. Again, phases of ERD, interpreted as active information processing, correlate well with the timing of leg force production. While the temporal pattern seemed to be altered in the alpha and beta band, the oscillations in the gamma band remained similar. In both conditions, the gamma band shows a pattern of two local minima corresponding to the initiation of power production and preparation for the extension phase of the right and left leg.

The oscillating pattern of ERD and ERS could be interpreted as an alternating behavior in the motor areas reflecting a distributed activity and active information processing in preparation for leg extension (ERD) followed by a focal activation behavior (ERS) during the main phase of force production. This pattern was most pronounced in the gamma frequency band. This observation was made in a cluster slightly localized in the left SMA. One may expect a mirror effect in the other hemisphere or a cluster that is located over the central midline. Our identified cluster contained dipoles located in both the left hemisphere as well as in the midline of BA 6. While we did find a cluster in the right part of the premotor cortex, this cluster did not contain ICs from more than half of our subjects.

Overall, we speculate that differences in EEG power modulation between the fresh and fatigued state are due to an increased effort and task difficulty that participants need to cope
with. An alternative option would be a substantial change in neuromuscular strategies of the leg muscles to keep up with the cycling task. However, preliminary analysis of EMG data that was collected in synchrony with the EEG data does not support the hypothesis of altered lower limb neuromuscular strategies as the overall EMG pattern remained similar (Figure 5.4).

5.4.2 Spectral power increase in EEG with fatigue

Our study observed a broadband increase in EEG power, even though for most identified clusters this was only true in the $\alpha$- and $\beta$-band. This increase across a broader frequency band is in contrast to studies that have investigated different walking conditions and found changes limited to the $\alpha$- and $\beta$-band (Wagner et al., 2012, 2014). It is unclear, however, if our fatigue protocol directly relates to comparisons of active and passive walking (Wagner et al., 2012) or different visual feedback conditions (Wagner et al., 2014). Typically, active movement is associated with desynchronization in the $\alpha$- and $\beta$-band and, therefore, it is not surprising to find such differences between active and passive movement. Instead our comparison was between two conditions that were both based on intense movements. Interestingly, a study that has investigated fatigue on a recumbent bicycle ergometer shows results that are very similar to this study. They showed that as participants fatigued during the cycling exercise there was a broadband increase in spectral power that was significant in the $\theta$ (4.5 – 7.99 Hz), low $\alpha$ (8 – 10.49 Hz), high $\alpha$ (10.5 – 12.99 Hz), low $\beta$ 1 (13 – 17.99 Hz) and high $\beta$ (18 – 30 Hz) frequency bands (Bailey, Hall, Folger, & Miller, 2008). Another possibility is noise in the acquired EEG that was not removed by our data analysis. While this may partially contribute to our observation, the changes in modulation of ERD and ERS also suggest a response in cortical involvement during the exercise. Limitations with respect to noise and motion artifacts are further discussed at the end of this section.
5.4.3 Interaction of electrocortical clusters

The four identified clusters of electrical activity in specific cortical domains (prefrontal, premotor and posterior parietal cortices) were consistently active in the majority of subjects in this study. Common activation between these areas indicate a sequence of cognitive processing that includes executive control, motor planning and execution as well as sensorimotor integration. Indeed, previous research suggests that activation in the prefrontal cortex area relates to the executive behavioural control function (Jun Tanji & Hoshi, 2008) and motor planning (Wise, Boussaoud, Johnson, & Caminiti, 1997; J Tanji, 2001; Rizzolatti & Luppino, 2001). Information about motor planning may be passed on to the SMA and premotor cortex as it is well documented that these areas have strong connections to the prefrontal cortex (Rizzolatti & Luppino, 2001; Chouinard & Paus, 2006), specifically the dorsolateral prefrontal cortex (Lu, Preston, & Strick, 1994). Thus, the output of the prefrontal cortex likely targets specific premotor areas. It has been proposed that the prefrontal dependent motor areas (anterior parts of the premotor cortex and SMA) receive higher order cognitive information regarding motor plans and motivation (Rizzolatti & Luppino, 2001) which supports the executive control function of the frontal areas. Interestingly, the largest response in neural activity accompanying fatigue is seen in the frontal areas. We speculate that this is consistent with an increase in executive control to keep up with the challenging task demand. However, this speculation needs careful evaluation in a future study.

In our analysis no cluster was directly associated to activity in the primary motor cortex. Several technical as well as functional explanations may describe this observation. It has to be noted that EEG has a limited spatial resolution limiting the exact location of activity within the motor areas. Further, individual anatomy varies across participants and this study did not utilize
individual MRI head models which would improve source localization. However, it is well
known that strong interconnections between premotor and primary motor areas exist. It suggests
that information that is processed and passed on to the premotor cortex is directed further to the
primary motor cortex (Künzle, 1978; Chouinard & Paus, 2006) and the spinal cord (Dum &
Strick, 1991; Münchau, Bloem, Irlbacher, Trimble, & Rothwell, 2002). In fact, the majority of
cortico-cortical connections of the primary motor cortex are with BA 6 (Leichnetz, 1986;
Stepniewska, Preuss, & Kaas, 1993) implying that reciprocal information processing between
premotor and primary areas plays a crucial role in motor execution. It is further known that both
premotor and primary motor areas have strong connections to the spinal cord through
corticospinal neurons that are activated during movement (Dum & Strick, 1991; Quallo,
Kraskov, & Lemon, 2012).

Lastly, the connectivity between parietal areas and motor areas (specifically the SMA and
premotor cortex) has been demonstrated in many different scenarios. For a detailed review of
this network the reader is referred to more in depth literature (Desmurget & Sirigu, 2009).
Studies link activity in the parietal cortex to motor awareness and movement intention prior to
movement (Desmurget et al., 2009), coordinative aspects of movement, and functioning as an
interface between sensorimotor and visually guided aspects of movements (Taira, Mine,
Georgopoulos, Murata, & Sakata, 1990; Buneo & Andersen, 2006). The fact that the posterior
parietal cortex plays a role in sensory and motor function led to the proposal that it is heavily
involved in sensory-motor interaction. Interestingly, the parietal cortex has typically been
identified in studies focusing on real-time EEG recordings during repetitive locomotor tasks (J.
Gwin et al., 2011; Wagner et al., 2014). Specifically, a premotor-parietal network has been
identified during rhythmic walking which is believed to represent motor planning and intention
and has been shown to increase activity in the presence of task feedback (Wagner et al., 2014). In summary, connectivity between parietal and premotor areas seems to be crucial for motor planning as well as sensory motor integration. Increased EEG power was observed in this area which might suggest the importance of motor planning and the integration of sensory input towards the end of an intense exercise.

5.4.4 Limitations: Muscle drive vs. sensory afferent integration

The spectral analysis performed in this study adds to the emerging understanding that the cortex may play a more important role during rhythmic movement activity than previously thought. It confirms similar findings of alternating latencies of event-related desynchronization and synchronization within a movement cycle (J. Gwin et al., 2011; Wagner et al., 2012, 2014; Jain et al., 2013). However, solely based on the spectral analysis it remains unknown if the observed cortical activation patterns are directly involved in the transmission of motor commands to facilitate muscle activation. Another possibility, a hypothesis that was previously discussed (J. Gwin et al., 2011), is the integration of sensory afferent signals that are used to modulate efferent corticospinal transmission. Most likely, the observed activity reflects involvement in both descending efferent pathways as well as sensory information processing. In order to investigate this proposal in more detail, a coherence analysis should be used in order to address the idea of an anatomical coupling between cortical and muscular signals during movement (Petersen et al., 2012).

5.4.5 Limitations: Movement-related artifacts

Movement-related and specifically gait-related artifacts have been a central issue to the debate about the interpretation of EEG data recorded during locomotor activities. Following the recommendation of previous reports, we excluded any components that were clearly indicative
of electromyographic artifacts (neck, jaw, facial). Additionally, we recorded the data in an electrically shielded chamber to minimize electromagnetic interference from power lines and devices. Due to the nature of the experimental protocol, we had to address the issue of perspiration. Sweating typically results in very slow drifts of the EEG signal. We found these drifts to be well below 1 Hz and, thus, we were able to remove these drifts using the applied filters. Additionally, sweating was relatively constant throughout the exercise as subjects started to sweat during the warm up period. Therefore, electrode impedance did not change significantly throughout the TTE trial. Participants were not allowed to stand up from the saddle to minimize head and upper body movement as much as possible. However, some movement still occurs during an intense cycling trial and while we have addressed common noise issues from an experimental and computational side, there is a remaining issue as artifact sources were shown to greatly vary across subjects and efforts (Kline, Huang, Snyder, & Ferris, 2015) making it difficult to reject artifacts based on templates and models. Therefore, most likely, many reports of EEG during locomotion contain a mixture of true electrocortical and artifact signals which should be kept in mind by the reader.
Chapter Six: CORTICOMUSCULAR COHERENCE OF THE PRIMARY MOTOR CORTEX AND LOWER LIMB MUSCLES DURING A RHYTHMIC PEDALING TASK

6.1 Introduction

To move limbs in a skillful manner requires volitional supraspinal commands (Armstrong, 1988; Schaal et al., 2004; J. F. Yang & Gorassini, 2006), spinal neural networks (S Grillner & Zangger, 1979; Dimitrijevic et al., 1998; Duysens & Van de Crommert, 1998), as well as the integration of sensory afferent feedback (Pearson, 2004; Zehr & Duysens, 2004; Akay, Tourtellotte, Arber, & Jessell, 2014; Fink et al., 2014). Rhythmic movement, during activities such as walking, running or cycling, has primarily been associated with spinal circuits of interneurons that are responsible for generating rhythmic, bilateral motor patterns (Butt & Kiehn, 2003; Lanuza, Gosgnach, Pierani, Jessell, & Goulding, 2004). It is often stated that the output of such pattern generators is modulated by sensory feedback from the moving limbs (Pearson, 2004), and only to a lesser degree by supraspinal inputs from the cortex. Contrary to rhythmic movement, research focusing on discrete voluntary movements has largely investigated the cortical contribution to movement generation and muscle activation (Marsden et al., 2000; Jurkiewicz et al., 2006; Baker, 2007). While researchers agree on the importance of cortical involvement for such discrete tasks, the role of cortical contributions to rhythmic movement generation are not well understood since minimal research has focused on this topic in humans because the cortical contribution to rhythmic movements was considered to be minor compared to the spinal neural networks. Furthermore, it is challenging to obtain non-invasive electrophysiological recordings, such as electroencephalography (EEG), during whole body movements in humans. Both of these issues have been addressed and challenged in recent years as new developments in hardware and software have made EEG recordings during human
movement possible. As a result, there has been emerging evidence that cortical areas may play a more important role in human rhythmic movements than previously thought. For example, researchers have used EEG recordings during active and passive walking and cycling tasks, and have found increased neural activity when humans actively performed a movement compared to a passive condition (Wagner et al., 2012; Jain et al., 2013). Studies focusing on gait have shown that the cortical contribution of a variety of brain areas was related to the gait cycle (J. Gwin et al., 2011; Wagner et al., 2014), and that EEG amplitudes were modulated during specific gait phases (Seeber et al., 2014, 2015). In an experiment using a recumbent cycling ergometer, researchers were able to show that amplitude modulations of an electrode overlaying the primary motor cortex were correlated with electromyography (EMG) signals acquired from leg muscles used for pedaling (Jain et al., 2013). Even stronger evidence for a direct cortical contribution to muscle activation was shown during treadmill walking, when researchers showed significant corticomuscular coherence between the primary motor cortex and the tibialis anterior muscle (Petersen et al., 2012). The timing of significant coherence coincided with the timing of peak muscle activation of the tibialis anterior during the terminal swing phase of the gait cycle, suggesting a cortical contribution to the observed muscle activation pattern. Most other studies have quantified coherence during quasi-static isolated contractions of upper limb muscles, thereby providing little insight into whole body movements.

Corticomuscular coherence measures the degree to which electrical signals recorded from cortical areas (typically the primary motor areas) and electrical signals from muscles share a common input and display a frequency specific correlation. It is commonly interpreted as a physiological descending drive of corticospinal input to motor neurons. However, other sources of common input to motor neurons may contribute to the estimate of corticomuscular coherence
as well. For example, a common sensory afferent input to a pool of motor neurons may lead to a correlation between two electrical signals (Farina et al., 2014). Therefore, it is of great interest to investigate the direction of information flow between EEG and EMG. This will allow researchers to quantify whether corticomuscular coherence is primarily due to a descending cortical drive, or rather a common afferent input signal. This analysis can be accomplished using partial directed coherence (PDC), an approach to describe a directed, frequency-dependent relationship between time series (Baccalá & Sameshima, 2001).

In summary, few studies have utilized measures of coherence during dynamic rhythmic whole body movements such as walking, running or cycling. The only study that quantified corticomuscular coherence during walking suggested that the observed result was based on a descending cortical drive, based on a phase analysis that was performed (Petersen et al., 2012). This walking study was completed at a very low intensity; other studies have also tried to quantify the influence of high intensity contractions leading to fatigue on coherence. All these studies, however, used isometric contractions to elicit fatigue, which is uncommon in daily life. Furthermore, the results of these studies were mixed, with some studies finding increased coherence post fatigue (Tecchio et al., 2006; Ushiyama et al., 2011) and other showing a decrease in corticomuscular coherence (Tuncel, Dizibuyuk, & Kiymik, 2008; Q. Yang et al., 2009; Siemionow, Sahgal, & Yue, 2010). Studies utilizing transcranial magnetic stimulation have shown that motor output is suboptimal during a fatigued state and contributes to a decline in force production (Gandevia, Allen, Butler, & Taylor, 1996). It can be speculated that this suboptimal motor output may lead to a decrease in the corticospinal coupling, and may manifest as a reduction in corticomuscular coherence. Thus far, however, nobody has utilized PDC to quantify the direction of information flow between EEG recorded over the motor cortex and
multiple lower limb muscles during a whole body exercise task that is both dynamic and physically demanding in order to induce fatigue. Therefore, the purpose of this study was to record EEG and EMG signals while participants were cycling at a high intensity, and to quantify PDC for an early phase of the exercise and a late phase of the exercise after the onset of fatigue. It was hypothesized that (1) a significant coherence would be observed between EEG and EMG signals, (2) fatigue would lead to a decrease in corticomuscular coherence and (3) the observed coherence would primarily be a result of a descending cortical drive to the muscles.

6.2 Materials and methods

6.2.1 Subjects and ethics approval

Ten male cyclists (age: 27.5 (5.6) years, mass: 71.8 (6.1) kg, maximum aerobic power output: 5.8 (0.7) W/kg, cycling experience: 4.9 (3.6) years) were recruited for this study. All participants were free from lower limb injury within the past two years and had no known neurological or muscular deficits that would interfere with the study. All subjects were informed about the nature of the study and provided written informed consent prior to the first testing session. All procedures complied with the standards of the Declaration of Helsinki and were reviewed and approved by the University of Calgary research ethics review board.

6.2.2 Experimental protocol

A detailed description of the experimental procedures has been published previously (Enders, Cortese, et al., 2015). Briefly, for each subject testing was performed over three sessions that were separated by a time window of approximately 48 hours. On all three testing days, a Velotron Dynafit Pro cycle ergometer (RacerMate Inc., Seattle, WA) was used in combination with the participant’s personal clipless pedals. On the first day of testing, the maximum aerobic power output (MAP) was determined for each participant. The second and
third testing days consisted of a time-to-exhaustion (TTE) trial at 85% of the MAP value. The second day was treated as a familiarization with the protocol and data was analyzed for the third testing day. Caffeine intake was restricted at two hours prior to testing, and the subjects were asked to maintain a normal diet and refrain from any resistance training for the duration of the study. Participants were allowed to freely choose their cadence for both the MAP and the TTE portion of the study. Both the MAP and the TTE trial were ended as soon as the cadence dropped by more than 15 revolutions per minute or below an absolute cadence of 70 revolutions per minute. In order to be included for the TTE trial, participants had to reach a minimum MAP value of 4.5 W/kg.

6.2.3 EMG Data collection

Bipolar Ag/AgCl electrodes (10 mm diameter, 22 mm inter-electrode distance) were used to record surface EMG signals from the tibialis anterior (TA), soleus (SOL), gastrocnemius medialis (GM), biceps femoris (BF), rectus femoris (RF), vastus lateralis (VL) and vastus medialis (VM). Surface electrodes were placed on the skin according to published guidelines (Hermens et al., 2000) after hair was removed and the skin was cleaned using isopropyl wipes. The ground electrode was placed on the tibial tuberosity. Amplifiers and cables were taped to the leg to reduce the influence of movement artifacts. EMG signals were amplified (Biovision, Wehrheim, Germany) with an amplification factor of 2500, band pass filtered (10 – 500 Hz) and recorded with a sampling frequency of 2000 Hz (Biovision, Wehrheim, Germany) using a 12-bit A/D converter and stored on a computer for offline processing.

6.2.4 EEG Data collection

Each participant was equipped with a tight fitting electrode cap based on each individuals head circumference. The position of the cap was based on the anatomical landmarks of the
nasion, inion and preauricular points, and the electrode cap was secured with a chin strap. EEG was recorded using an active electrode 64-channel (10-20 positioning) BrainVision actiCHamp system (Brain Products GmbH, Germany). SuperVisc electrode gel (EasyCap GmbH, Germany) was used to reduce the impedance of all EEG channels below 20 kΩ. During the data collection, the parietal midline (Pz) and the frontal midline (AFz) electrodes were used as the reference and ground electrodes, respectively. EEG signals were recorded with a sampling frequency of 500 Hz per channel. Additionally, a magnetic pedal switch was used to synchronize the EMG and EEG data streams and identify individual pedaling cycles. All data analysis was performed in Matlab (The Mathworks, Natick, MA). Data cleaning and artifact rejection was done using the open source toolbox EEGLab 13.2.2b (Delorme & Makeig, 2004). Corticomuscular coherence was calculated using a combination of custom written Matlab scripts and a publicly available toolbox based on previously published results (Omidvarnia, Mesbah, O’Toole, Colditz, & Boashash, 2011).

6.2.5 Data preprocessing

Continuous EEG signals were analyzed similarly to previous studies dealing with dynamic EEG recordings. (J. Gwin et al., 2011; Wagner et al., 2012, 2014; Kline et al., 2014). EEG signals were band pass filtered (10-40 Hz) in order to focus the analysis on alpha, beta and gamma frequency bands, where corticomuscular interactions have typically been found. Individual channels were removed if their standard deviation (SD) was larger than 1000 μV, or if the channel’s kurtosis was more than 5 SD from the mean. Independent component analysis (ICA) was used to decompose the signal into maximally independent components (IC) (Makeig et al., 1996). ICA was applied to the data set of individual subjects. ICs representing line noise, movement artifacts, eye activity and muscle artifacts were rejected prior to further analysis (Jung
et al., 2000). Raw EMG data was initially bandpass filtered between 5 – 400 Hz and subsequently resampled to 500 Hz to match the EEG sampling frequency. The square wave signal of the pedal switch was then used to identify individual pedal revolutions in the continuous EEG and EMG signals.

6.2.6 Partial Directed Coherence

In order to analyze the coupling and the direction of information flow between cortical and muscular signals, PDC was calculated. These PDC calculations were based on publicly available Matlab scripts (Omidvarnia et al., 2011) using a multivariate autoregressive model. Such models have been previously used to assess PDC between EEG and EMG signals (Budini et al., 2014). The PDC represents a time-frequency representation of the directional information flow between different time series (e.g. cortical and muscular recordings), and is based on the concept of Granger causality (Granger, 1969). To reveal significant values of coherence, 20 surrogate PDC patterns were calculated for each pedal revolution. PDC values of each individual pedal revolution were then compared to the surrogate distribution with a significance level set at 0.01 yielding a threshold statistic. All time-frequency values of the real data that did not exceed the threshold were set to zero and deemed insignificant. The PDC calculations were completed for both directions of information flow (i.e. EEG to EMG and EMG to EEG) between the central midline Cz electrode and each of the seven muscles.

The outlined PDC calculations were completed for two conditions corresponding to the early and late phases in the TTE. The early phase was defined as the first 50 pedal revolutions corresponding approximately to the first 30 to 40 seconds of the TTE. The fatigue condition was defined as the last 50 pedal revolutions prior to task failure. Maximum coherence between 10 – 40 Hz, spanning the alpha, beta and low gamma bands, was calculated for both conditions and
muscles and compared between the early and the fatigue conditions. Similarly, the frequency at which maximum coherence occurred was compared between the early and the fatigue conditions.

6.2.7 Statistics
A repeated measures 2 x 7 ANOVA with factors condition (early and fatigue) and muscle was computed for the maximum coherence values and the frequency of maximum coherence. Multiple comparisons were done where appropriate and inflation of type I error was addressed using a Bonferroni correction. Statistical tests were considered significant using $\alpha = 0.05$. All data are presented as means and 95% confidence intervals.

6.3 Results
6.3.1 Information flow from cortex to muscles

When evaluating the information flow from the cortex to the muscles (EEG to EMG), the PDC results indicated phases with significant coherence between the EEG and the EMG signals, with the maximum coherence values coinciding with phases of strong muscle activation (Figure 6.1). While the timing of coherence was unaltered between the early and the fatigue conditions, there was a significant main effect for condition (early vs. fatigue, $P = 0.005$) seen as a reduction in the absolute coherence value.
Figure 6.1: Time-frequency patterns of partial directed coherence for the tibialis anterior muscle for the early (A) and fatigue (B) conditions (top) and the corresponding temporal waveform of coherence in the range of 10 – 40 Hz (blue line) and the corresponding EMG activity of the tibialis anterior for 5 pedal revolutions (red line) for the early (C) and fatigue (D) conditions (bottom).

The time-frequency differences for all muscles between the early and the fatigue condition (Figure 6.2) showed a significant decrease in the fatigue condition for all muscles except for the biceps femoris (Figure 6.3). Results were similar between the beta and low gamma frequency bands. The frequency at which the maximum coherence occurs was not significantly different between both conditions.
Figure 6.2: Time-frequency patterns of partial directed coherence for all seven muscles for the early (left) and fatigue (middle) condition. Differences between the two conditions are shown on the right side. Time-frequency points that did not show a significant difference between both conditions were masked and set to zero (white color).
Figure 6.3: Frequency specific differences in maximum coherence values between the early and the fatigued conditions for information flow directed from the cortex to the muscle (EEG to EMG). Results are shown for the beta band (top) and the low gamma band (bottom) for all seven muscles. Bars represent the grand average mean value across all subjects. Positive values indicate a stronger coherence in the early compared to the fatigue condition. Significant differences (P < 0.05) are masked with an asterisk.

6.3.2 Information flow from muscles to cortex

When evaluating the information flow in the opposite direction (EMG to EEG), the maximum coherence values were lower compared to the direction EEG to EMG. Comparing the differences in coherence between the early and fatigue conditions for the EMG to EEG direction shows an overall increase in coherence and, therefore, the opposite behavior compared to EEG to
EMG (Figure 6.4). For the beta band, changes were seen in all muscles except the vastus lateralis. In the low gamma band, only the gastrocnemius medialis, biceps femoris and vastus medialis reached the level of significance.

![Beta-band (12-30 Hz) and Gamma-band (30-45 Hz) coherence differences](image)

**Figure 6.4**: Differences in maximum coherence values for the beta (top) and low gamma (bottom) bands between the early and the fatigue conditions when the direction of information flow was from the muscle to the cortex (EMG to EEG). Bars represent the grand average mean value across all subjects. Negative values indicate an increased coherence when participants were fatigued compared to the early condition. Significant differences ($P < 0.05$) are masked with an asterisk.
6.4 Discussion

This study aimed to quantify the strength and direction of corticomuscular coherence between the motor cortex and multiple lower limb muscles during a high intensity cycling exercise that resulted in the onset of fatigue and subsequent task failure. The three main observations of this study were (1) a significant level of corticomuscular coherence between the EEG and the EMG for all measured muscles, (2) a drop in corticomuscular coherence from EEG to EMG in the fatigue condition and (3) an increase in the measured coherence during the fatigue condition from the EMG signal to the EEG signal.

6.4.1 Corticomuscular coherence from EEG to EMG during a cycling task

All seven muscles in this study exhibited a substantial level of corticomuscular coherence with the central EEG electrode Cz. The results showed that peak coherence occurred predominantly during phases when muscle activation was largest within the pedal cycle. This suggests that corticomuscular coherence is related to the temporal activation pattern of muscles. The current results confirm previous results obtained for the tibialis anterior during walking (Petersen et al., 2012), where the authors reported maximum coherence during the terminal swing phase when the tibialis anterior muscle is primarily used for ankle dorsiflexion in preparation for initial contact (heel strike). In our study, maximum coherence for the tibialis anterior was found prior to the top dead center when cyclist ‘pulled’ the crank, and subsequently when passing the top dead center, stabilizing the ankle joint to transfer the power to the crank during the following down stroke. Similarly, maximum coherence for the knee extensors occurred during the down stroke phase when these muscles were maximally activated in order to produce the majority of the power during the pedaling cycle. This suggests that a descending
cortical drive to the motor neurons controlling the lower limb muscles is strongest during phases of strong muscle activation.

6.4.2 Reduced corticomuscular coherence from cortex to muscle with fatigue

For the first time, this study quantifies the effect of fatigue on corticomuscular coherence during a dynamic whole body exercise at a near maximum intensity. When evaluating the information flow from the cortex to the muscles, there was a clear result of decreased corticomuscular coherence with increasing fatigue (Figure 6.2 and Figure 6.3). Previous studies have reported inconsistent results regarding an increase or decrease of coherence in response to fatigue (Tecchio et al., 2006; Tuncel et al., 2008; Q. Yang et al., 2009; Siemionow et al., 2010; Ushiyama et al., 2011). Several possible mechanisms might explain why corticomuscular coherence decreased with fatigue. A key factor for reduced coherence from cortex to the muscles might be a suboptimal or reduced output from the primary motor cortex to the motor neuron pool. This is supported by several studies using transcranial magnetic stimulation that have shown that cortical output is reduced during sustained contractions and the development of fatigue in upper (Gandevia et al., 1996; Søgaard, Gandevia, Todd, Petersen, & Taylor, 2006) and lower limb muscles (Gruet et al., 2014; Temesi et al., 2014). Typically, these studies conclude that the suboptimal output from the primary motor cortex results in a failure to drive the muscle maximally, which may in turn explain changes in corticomuscular coherence seen in the current study.

The decrease in corticomuscular coherence might also be related to inhibition between different cortical areas projecting to the motor cortex. For example, motor output is significantly reduced to upper limb muscles when nerve stimulation is delivered around 20 ms prior to cortical activation (Tokimura et al., 2000). Arguably, this time delay may be slightly longer for lower
limb muscles; however, the time delay of 30 ms in the current study might be reasonable for inhibition to occur in the more proximal lower limb muscles. As the cycling exercise progresses, the effect of short latency inhibition might be altered as sensory afferent feedback to the cortex changes with fatigue (Macefield, Hagbarth, Gorman, Gandevia, & Burke, 1991; Darques & Jammes, 1997; Darques, Decherchi, & Jammes, 1998). This inhibitory effect could be a potential reason for a reduced motor output, which may lead to decreased corticomuscular coherence. Support for this speculation is based on cycling exercises, which suggests that fatigue-related inhibitory neural feedback to the cortex limits motor output and exercise performance (Amann & Dempsey, 2008). In summary, the decreased corticomuscular coherence with fatigue is speculated to be a result of a reduced motor output, which might be related to inhibition from somatosensory inputs. It is further speculated that the spinal contribution for the control of muscle activation might increase with fatigue and the cortical contribution decreases. Support for this speculation is based on studies that showed increases in H-reflex with fatigue (Leonard et al., 1994), as well as increased stretch reflexes (Zhang & Rymer, 2001; Biro, Griffin, & Cafarelli, 2007). Both studies speculated that these are mechanisms by the human body to compensate for a reduced central drive during fatigue in order to preserve force output.

6.4.3 Increased corticomuscular coherence from muscle to cortex with fatigue

Contrary to the information flow from the cortex to the muscles, the coherence from the EMG signals of the muscles to the EEG signal of the cortex showed a significant increase with fatigue. This indicates an increased common input that might be driven by increased afferent signals from the muscles in the state of fatigue. Indeed, peripheral muscle fatigue has been shown to significantly alter and increase sensory feedback (Darques & Jammes, 1997; Amann & Dempsey, 2008). This sensory afferent feedback will reach the somatosensory cortex, which is
known to have substantial connections with the primary motor cortex. In fact, it was shown that somatosensory activity in the cortex can modulate output from the motor cortex. In a study using transcranial magnetic stimulation, motor evoked potentials decreased as fatigue developed, however, in the presence of sensory stimuli, the motor evoked potential did not change despite significant fatigue (Rollnik, Schubert, Albrecht, Wohlfarth, & Dengler, 2000). This demonstrates the potential of sensory information to mediate motor output and potentially attenuate suboptimal motor output as fatigue develops in an attempt to allow for maximum performance in the later stages of a high performance task. Therefore, it could be speculated that increased sensory feedback in the presence of fatigue might be a mechanism to maintain motor output from the primary motor cortex at a high level throughout a strenuous task. Contrary to the previous speculation, it has also been shown that sensory afferent feedback inhibits motor output, and might actually compromise endurance exercise performance (Amann et al., 2013). Utilizing transcranial magnetic stimulation in conjunction with sensory stimulation during a fatiguing exercise might contribute to our understanding of whether sensory feedback inhibits or facilitates output from the motor cortex. Similar studies have been done in upper limb muscles demonstrating that both inhibition and facilitation of motor cortex output is possible (Tokimura et al., 2000; Devanne et al., 2009). Independent of an inhibitory or excitatory effect of the sensory feedback, the current results suggest that there is an increased common afferent input as fatigue develops, as demonstrated by increased coherence from the muscles to the cortex. The opposite behavior when comparing the two directions of information flow might partially explain why previous studies, which did not account for the direction of coherence, found mixed results (Tecchio et al., 2006; Tuncel et al., 2008; Q. Yang et al., 2009; Siemionow et al., 2010; Ushiyama et al., 2011). Therefore, it can be concluded that when comparing coherence between
different conditions, it seems to be of great importance to evaluate not only the possibility of common input due to a central drive but also due to a common sensory input.

6.5 Summary

High intensity cycling shows a significant coherence between the motor cortex and lower limb muscles that is related to phases of muscular activation to perform the movement. The strength of coherence from the cortex to the muscles (EEG to EMG) is weakened with the development of fatigue throughout the exercise. Contrary, the coherence between the EMG and the EEG signal is enhanced in the fatigued athletes.
Chapter Seven: SUMMARY AND CONCLUSIONS

This thesis aimed to quantify muscular and cortical contribution to the execution and control of rhythmic locomotor type movement in humans as well as the connectivity between EMG and EEG signals. The specific aims were (1) to evaluate the spatial and temporal variability of surface EMG signals under different load conditions as a measure of the control of muscle activation patterns, (2) to identify sources of neural activity within the cerebral cortex and to quantify temporal activation patterns of motor areas during a rhythmic pedaling movement and (3) to link electrical muscle and cortical signals by means of a directed coherence analysis in order to identify the direction of information flow and the degree of a common shared input in both signals. All experimental protocols were completed using a cycling ergometer. In order to answer the first specific aim, participants were equipped with surface electrodes and muscle activity was measured from seven leg muscles while participants were cycling at 150 W and 300 W. For the second specific aim, a 64-channel EEG cap was used to record cortical activity while participants completed a time-to-exhaustion trial at 85% of their maximum aerobic power output. Lastly, in order to answer the third specific aim, we combined the recording and analysis of EMG and EEG in order to quantify the strength and direction of information flow between the cortex and lower limb muscles during the time-to-exhaustion trial. The following subsections will review the main conclusions for all three specific aims, critically evaluate the limitations associated with each result and provide an outlook for future research questions.

7.1 Variability of muscle activation patterns

Similar results were obtained from the analysis of the spatial and temporal variability of muscle activation patterns implying several conclusions. As the load increased during the pedaling task, the number of different solutions (i.e. correlated activation of muscles) used to
complete the task decreased. This finding suggests that, as the task becomes more difficult, the possible solutions for the successful execution of the task become more constrained to only a few basic muscle coordination patterns. This can be viewed as a decrease in the solution space of the pedaling task. Secondly, our results showed that for any of the given muscle coordination patterns (e.g. synergistic activation of knee extensor muscles), the variability of the time dependent waveform decreases with increasing task difficulty. This suggests that while the number of solutions decreased with a higher load, the precise execution of the selected strategies or solutions becomes more critical as the task becomes more difficult. The observation of more precisely executed muscle coordination patterns was visible in both the amplitude variability of the coordinated muscle activation patterns as well as the temporal structure in these patterns. The changes in variability observed in both studies might suggest that the reliable execution of a few critical coordinated muscle activation patterns is crucial for high power output. Two issues about these results need to be considered. First, the narrowing of the solution space is an observation across all individuals tested and, therefore, suggests a general increase in task difficulty that was experienced by all participants. Second, the more precise execution of an individual muscle coordination pattern, however, is a result that is based on the analysis of different pedal revolutions within the same individual, rather than across different participants.

A third observation was the fact that certain muscles seemed to play a more dominant role as the load was increased. This was particularly true for the coordinated activation of knee extensor muscles, which are some of the critical power producing muscles in cycling. This result suggests that, as the task increases in difficulty, participants seem to select coordination patterns that are efficient for producing a high power output and secondly, reduce the variability in the
execution of these critical coordination patterns. It is speculated that it could be a mechanisms to focus neuromuscular control on the most critical task components. For a pedaling task this might be the predominant power production that occurs in the crank cycle between the top dead center and the following 90 - 120°.

However, there are certain limitations that should be kept in mind. One methodological aspect that is important to the correct interpretation of the data is the use of a PCA that is applied individually to each experimental condition. It follows that the base vectors that span the solution space are not equivalent between the two experimental conditions. While this has the advantage to quantify changes in the correlated activation patterns between muscles in response to an altered load, it does not allow to make direct comparisons between the temporal waveforms of any principal component between the conditions.

It should also be noted the subject pool used for these studies was not limited to cyclists. This brings up two points to consider when interpreting the results. First, given the heterogeneity of the participant sample, it is very likely that there are differences in their muscular architecture, and potentially even in their individual force-length and force-velocity relationships. For example, it was shown that cyclists have a different moment-length relationship compared to runners for the rectus femoris muscle (Herzog, Guimaraes, Anton, & Carter-Erdman, 1991). During cycling the hip joint is typically in a strongly flexed position while during running it is in a rather extended position. As a result, cyclists were stronger at short compared to long rectus femoris lengths while the opposite was true for runners. We did not quantify force-length properties in any of our studies and, therefore, are unable to evaluate if such differences might have contributed to the observed results. However, the comparisons made in both studies are within a subject and not between subjects. Therefore, we speculate that differences between
subjects are most strongly manifested in the number of principal components needed to explain
the whole data set. This speculation was confirmed by the fact that the number of principal
components was slightly larger when performing a group analysis combining all subjects (21
components for 150 W, 10 components for 300 W) compared to performing a PCA on each
individual subject (~ 18 components for 150 W, 8 components for 300 W).

Based on the findings and limitations of the presented data, there are some possibilities
how to advance this research question in the future. The majority of studies investigating the
structure of variability in a movement task are performed during discrete upper limb reaching
tasks. The advantage of such tasks is a clearly defined task goal and in the most simplistic case a
binary task outcome (target reached or target missed). This allows studies to directly link
variability to a task outcome. This becomes much more difficult during rhythmic movement as it
is more challenging to define the task goal based on a few characteristics. Nevertheless, being
able to link muscle activation patterns during cycling to a task specific goal would increase the
implications that can be drawn from the structure that was found in the EMG signals. A first
approach would be to measure the forces applied to both pedals in real time. This could be used
to quantify the effective force applied to the pedals as a function of the crank cycle. It would
allow researchers to connect the variance structure of muscle activation patterns found in the
EMG signals to the temporal force characteristics of the pedaling movement. It can be speculated
that variance in the muscle activation patterns becomes small during phases when force applied
to the pedals is highly critical for the pedaling movement.

A second line of research that naturally follows from this thesis is to analyze the variance
structure in the EMG signal and in EEG signals that have been acquired simultaneously during a
rhythmic motor task. While this was beyond the scope of this thesis, it would allow researchers
to investigate whether or not brain signal variability is linked to motor and task variability during rhythmic movements. Similar analyses have been performed to establish a relationship between brain signal variability and healthy aging (McIntosh, Kovacevic, & Itier, 2008; McIntosh et al., 2013; Misić, Mills, Taylor, & McIntosh, 2010). The results show that brain signal variability becomes more variable across the whole brain with maturation and decreases again with older age. Interestingly, as children develop to young adults and brain signal variability increases their reaction to an auditory or visual stimulus becomes faster (McIntosh et al., 2008). During healthy aging, brain signal variability decreases and a slowing of the reaction time is typically seen in this age group (McIntosh et al., 2013). The authors of the studies suggest brain signal variability as a measure of information processing and it might potentially relate to task performance. This concept could be used to study the relationship between brain signal variability of the central nervous system and link it to muscle activation pattern variability of the musculoskeletal system. I would speculate that increases in brain signal variability might be accompanied by maturation of gait dynamics and more stable muscle activation patterns. However, this hypothesis needs careful investigation and remains speculative at this point.

### 7.2 Cortical contribution to rhythmic movement

The analysis of the EEG signals acquired during the pedaling task yielded results with respect to spatial and temporal activity of the cerebral cortex. The task in this study was focused on movement and results showed that neural activity that was located within frontal, parietal and motor areas. It shows that cortical contribution to movement is not exclusively limited and observed in primary and secondary motor areas but also in other parts of the cortex that are relevant for executive control, motivation and association between different inputs of information.
The time-dependent neural activity was quantified with respect to the repeating movement cycle and the results showed that the neural signals were linked to the phases of the pedaling movement. Specifically, the results indicated that strong neural activation was related to phases of the pedaling cycle when muscular contraction was critical to produce the power required to maintain the task. This result, however, was frequency dependent. While activity in the alpha and beta band responded with an increase in amplitude as the time-to-exhaustion trial progressed, activity in the low gamma band was not altered throughout the movement task. In addition to a time-dependent analysis of neural activity in the motor areas, we also quantified the overall response in EEG signal power throughout the entire movement task. For all identified cortical areas, the EEG power during the pedaling movement increased over time as participants became more exhausted towards the end of the time-to-exhaustion trial. This indicates a cortical response related to the increase in difficulty to keep up with the task demand. Interestingly, this result was most strongly observed in the frontal area of the cortex, a brain region that has been associated with executive control and motivation. This suggests that cortical involvement in this task is not limited to motor processing but includes also a motivational component that seems to become stronger towards the end of the task. In summary, the results showed that cortical involvement, including but not limited to motor areas, during a rhythmic whole body movement task can be observed in the majority of participants tested in this study. EEG activity in the motor areas suggest that neural activity is to a certain extent related to the movement cycle phases and, most likely, the associated muscular requirements.

Analyzing EEG signals during a rhythmic whole body movement is a field in neuromechanics with increasing interest in the scientific community over the last ten years. Acquiring an EEG signal during whole body movements has been deemed a significant
challenge in the past decades and, despite recent successful recordings (J. Gwin et al., 2011; Wagner et al., 2012; Jain et al., 2013), is still a controversial topic of debate (Castermans et al., 2014) and, therefore, specific limitations should be kept in mind. The biggest challenge is the contamination of the cortical signal with mechanical, environmental and physiological artifacts. Typically, noise can be significantly attenuated by averaging a large number of trials. As noise is often random in nature, an averaging process typically increases the signal to noise ratio as a random process will result in an average close to zero over a large enough number of trials. However, some of the typical artifacts during an EEG data collection are not random. Specifically, during rhythmic movement it is possible that an artifact occurs at the same time in the movement cycle in case it is caused by the movement itself. Such artifacts are typically referred to as time-locked, meaning that they do not occur at random times but are fixed in time with respect to a certain event. The most typical example in EEG recordings has been initial foot contact with the ground during walking or running, however, similar phenomena may occur during other rhythmic movements. There is an inherent difficulty associated with removing time-locked noise and artifacts. Averaging trials with such time-locked artifacts will not result in an attenuation in the noise as the timing of the artifact remains similar within the movement cycle. In fact, averaging these trials might manifest the artifact within the temporal waveform. For this thesis, cycling was chosen as it was a repeatable movement pattern resembling a rhythmic activation of muscles and limbs without the large artifact caused by initial ground contact known from studies utilizing walking or running as rhythmic movements. Attempts to minimize obvious time-locked artifacts arising from movement include restricting the cyclists from standing during the cycling trial. Other sources of noise such as facial or neck EMG contributions which are unlikely to be time-locked to the movement cycle were removed or minimized using ICA.
Nevertheless, a recent study showed that noise varied significantly across electrode location but also between different subjects (Kline et al., 2015). While this may attenuate the amplification of patterned noise, it also poses a difficult challenge for decomposition algorithms such as ICA.

An improvement to the experimental setup that could be used in this thesis would be an electrode position scanning system. It allows for the identification of the 3D coordinates of all electrodes on the participant’s head. Knowing the spatial coordinates for each participant significantly improves the localization of neural sources in brain space as it accounts for slight variations in cap placement and more importantly different head sizes and shapes across subjects.

Lastly, an improvement that could be made is the use of a larger electrode system. This would have two effects. First, it would improve the localization of neural sources as more electrodes would be available for the approximation algorithm. Secondly, it would give researchers more opportunities to reject noisy channels while maintaining equal spatial coverage of the entire head with the remaining electrodes. It was shown that 32 electrodes are sufficient to detect the major neural sources of activity (Lau, Gwin, & Ferris, 2012) and some researchers use a lot less electrodes to detect EEG dynamics (Presacco et al., 2011). While the 64 channel setup used in this study is deemed sufficient to record cortical dynamics, it could have potentially been improved by using the full 128 channel cap.

As mobile EEG recordings are fairly novel and only a few studies have been carried out so far, there is ample room for improvement and progress with respect to hardware, software and experimental setups. The most substantial improvement for future EEG collections is to isolate movement-related artifacts. A new technique has recently been tested and has been shown to successfully isolate movement-related artifacts (Kline et al., 2015). In the future, this technique
could be used in a dual cap setup to differentiate between cortical signals and artifacts. The concept would be based on two EEG recording systems. The first EEG cap is prepared as usual and fixed to the subjects head. It will record a mixture of cortical and artefactual signals. Above the first EEG cap, a non-conductive layer such as a swim cap is used to shield any electrical signals from within the scalp. Above the nonconductive layer, a second EEG cap is used. The electrodes on this cap will exclusively measure motion artifacts and, thereby, isolate the artefactual component of the first EEG cap. This artefactual component could be subtracted from the mixture of cortical and noise signals measured by the first EEG cap. While this seems to be a promising approach to advance the field of dynamic EEG recordings, the method has yet to be used for disentangling cortical and artefactual signals.

A second avenue of future research is the dissociation between sensory and motor cortical signals in movement-related recordings. Due to the volume conduction and the limited spatial resolution of available EEG systems, it has been a major challenge to attribute cortical signals decisively to sensory or motor areas in the brain. Nonetheless, this is arguably a very important question when investigating the cortical contribution to the control of human locomotion. One possibility would be compare active and passive movements (Wagner et al., 2012; Jain et al., 2013). Active movements require muscle activation and force production by the participant while in a passive condition the subject is passively moved through the movement cycle. This could be an interesting initial approach, however, it might not eliminate motor components completely as it is known that simply imagining movement elicits a cortical response in motor areas (Pfurtscheller & Neuper, 1997; Pfurtscheller, Brunner, Schlögl, & Lopes da Silva, 2006), a phenomenon that is often used for brain-machine interfaces.
7.3 Corticomuscular coupling during human movement

The last chapter of this thesis attempts to interpret simultaneous recordings of EEG and EMG signals during rhythmic movement. Partial directed coherence was used in order to assess (a) the strength of coupling between the EEG and EMG signals and (b) to evaluate the direction of information flow between both signals. The results from our recordings show that there is a significant, direction-dependent coherence between the two signals. First, the information flow between the cortex and the muscles is stronger compared to the opposite direction. Second, coherence between cortex and muscle is significantly reduced as participants fatigue during the pedaling task. This suggests a reduced drive from the cortex to the muscles with the development of fatigue. Two results were found when evaluating the coherence between the muscles and the cortex. The magnitude of coherence is lower and, opposite to the other direction of information flow, there is an increase in the magnitude of coherence with the development of fatigue. This might be a result of increased afferent feedback that is received and processed in the cortex. Overall, it shows that corticomuscular coherence should be evaluated in a direction-dependent fashion as the different directions might be affected differently with exercise. While this study provided some interesting results about the control of human movement, the conclusions are limited to supraspinal contributions based on EEG and the measurement of muscle activity using EMG. The lack of data regarding the contribution of spinal networks is a limitation in this dissertation. Corticomuscular coherence is typically used to assess the degree of common input to motor neurons and is most often interpreted as a measure of the strength of supraspinal contribution to muscle activity. However, it should be kept in mind that coherence can be influenced by other sources of common input. Sensory afferent feedback is often mentioned as another possible source of common input to motor neurons and we have accounted for this
possibility through the direction-dependent analysis. Nevertheless, it has been suggested previously that a rhythm generator in a subcortical structure could modulate descending motor commands as well as sensory afferent feedback (Mima et al., 2000). The experimental setup used in this study had no means to test the hypothesis of a subcortical structure that provides common input to supraspinal centers and motor neurons.

Another limitation arises from the limited spatial resolution of EEG. Volume conduction results in a smearing of the EEG signal at the electrode level making it difficult to establish a somatotopical representation of the different leg muscles involved in cycling. Therefore, we were unable to investigate spatial differences in corticomuscular coherence for the measured EMG signals of the seven leg muscles. This limitation could potentially be addressed by combining EEG with measurements of functional magnetic resonance imaging to get a spatial representation of cortical activity. Another possibility would be to use magnetoencephalography instead of EEG. However, both of these techniques cannot be used for whole body movement such as cycling.

The last chapter of this thesis is one of a few studies within the last decade that has addressed corticomuscular interaction during a rhythmic whole body movement task. Historically, research has focused on the cortical contribution to discrete upper limb movements while the central pattern generator has been a paradigm of interest for neurophysiologists and biomechanists alike. Our results indicate that the cortex contributes to movement and muscle activity during rhythmic movement as well. As a next step, it would be interesting to compare corticomuscular coherence between a rhythmic locomotor task and a discrete locomotor task. It could be hypothesized that the cortical contribution is increased for discrete movements during the initiation and termination of the movement while it is less important during the maintenance
of a rhythmic pattern. One study investigated a similar question using transcranial magnetic stimulation comparing rhythmic arm cycling and a tonic contraction and showed that cortical excitability was significantly lower during rhythmic arm movement (Carroll, Baldwin, Collins, & Zehr, 2006). This suggests a decreased motor drive from the motor cortex during rhythmic movements compared to sustained muscular contractions.

A second possible extension of the research in this thesis could be the systematic investigation on the sensory afferent input on corticomuscular coherence. Multiple scenarios could be possible to address this question. One possibility is to elicit fatigue in just one leg and evaluate corticomuscular coherence during exercise in the other leg. Another possibility would be a combination of EEG and peripheral nerve stimulation. This technique would allow researchers to reliably elicit sensory processing on spinal and cortical levels and evaluate its effects on corticomuscular coherence. Due to the direction-dependent response of corticomuscular coherence observed in our study, it is suggested that the investigation into common sensory and motor inputs during rhythmic movement might be the logical next step.
7.4 Conclusions

This dissertation investigated muscular and cortical contributions to a rhythmic pedaling movement in humans. The presented data yields a number of conclusions that can be drawn.

1. The solution space for the pedaling movement decreases with increasing load of the movement task. Additionally, the coordinated activation of muscles is executed with less variability as the load of the pedaling task increases.

2. EEG recordings during a rhythmic pedaling movement show a cortical involvement that is distributed across frontal, parietal and motor areas. Changes in EEG power in motor areas is coupled to specific phases of the pedaling movement.

3. There is a significant coherence between EEG and EMG recordings during a rhythmic pedalling task.

4. As fatigue develops during the pedaling task, corticomuscular coherence between the cortex and lower limb muscles is altered in a direction-dependent fashion.
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