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TITLE OF THE DOCTORAL THESIS

Postural monitoring and neuromuscular synergies related to damages due to a sedentary lifestyle.

S.S.D. M-EDF/01

Coordinator: Prof.ssa Michela Rimondini

Signature Michela Rimondini

Tutor: Prof.ssa Paola Cesari

Signature Paola Cesari

Doctoral Student: Dott.ssa Anna Benamati

Signature Anna Benamati

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ABSTRACT

Each year, there is a growing prevalence of sedentary behaviors and an increment of pathologies linked to bad lifestyle habits and physical inactivity. If we consider the typical day of a person who works in an office sitting for several hours in front of the computer, we understand how he or she may be susceptible to developing neuromuscular pathologies both at the trunk and upper limb level. At the level of the trunk, low back pain (LBP) is certainly the most present, while at the level of the upper limbs, the hand is the most exposed, and the scribe's cramp is an example of this.

The great challenge today in preventing and treating these pathologies lies in the difficulty in performing a clear diagnosis due to the lack of understanding of the main causes, as they often stem from a complex interplay among biomechanical, behavioural, neurophysiological, and environmental factors. This complexity makes it difficult to identify targeted and comprehensive intervention strategies.

A possible approach to addressing these issues is to study the behavior resulting from the pathology by applying the motor control perspective, which enables the analysis of how the neuromuscular system, through the muscle synergies, anticipates, adapts, and compensates in the face of perturbations. In this context, two complementary studies were conducted: the first focused on analyzing postural and compensatory strategies in individuals with chronic and latent LBP, and the second explored the postural control of a hand in the act of producing force in multi-finger tasks by analysing the muscular synergies and the fine motor control mechanisms.

The first study aimed to test the motor anticipation and adaptation patterns in subjects who were affected by low back pain (LBP) but in the absence of pain for more than 10 days. The task was to maintain an upright posture while self-inducing perturbations through the release of a weight positioned either in front of or behind the body. Muscle activity was registered with a system made of 14 sensors of electromyography (EMG). When compared with healthy subjects, the analysis revealed that individuals affected by LBP pre-programmed a more conservative control of action by increasing the amount of muscle co-contraction. These findings underline the presence of differences between healthy and LBP individuals, even if the latter were tested in the absence of pain. It is worth mentioning that differences were particularly present for the synergies applied in preparation for the action.

The second study focused on understanding how hand muscle synergies contribute to force stabilization during a task. The experiment analyzed force exertion on customized cells designed to measure the force produced by the index, middle, ring, and little fingers, along with sensors to monitor motor unit (MU) activity in two key agonist-antagonist muscles controlling these fingers. Through the application of motor control theories and techniques, it was possible to identify stabilizing synergies at different levels of control: at the level of force production, at the level of individual agonist and antagonist muscles considered separately, and at the level of the interaction between these muscles analyzed as a single functional entity.

These studies highlight the value of testing the control of movements for a better understanding of muscle synergies developed during action preparation and action performance. The findings might provide a foundation for developing more effective prevention and rehabilitation strategies, focused on personalized and innovative approaches. Finally, this work emphasizes the importance of integrating motor control knowledge into clinical and therapeutic programs, with the goal of improving quality of life and reducing the risk of recurrence.

Contents

1 PREFACE

1.1 Aim of the dissertation

This PON PhD of the 37th Cycle - PNRR included as a constrained topic the “Optimisation of postural monitoring tools and aids through statistical and biomechanical models with the purpose of limiting the damages due to sedentariness and western lifestyle, promoting the knowledge of physical activity ergonomics, medicine of wellness.” The description was: “To develop a new alliance with nature, humans need to abandon their inadequate lifestyles: they are born to walk and to run but instead spend the majority of their time sitting. As humans, to remain aligned with our evolution and to maintain a good state of well-being, performing daily physical activity is not sufficient. Therefore, it becomes fundamental to search for a deep understanding of the roots that underline the need to move, for then appreciate the relevance of actions, and the rules that govern them and increase the awareness about their importance in our everyday life and along our life span. Considering the workplace, the way it is structured and logistically organized represents a great opportunity for increasing such awareness which is necessary for obtaining an efficient promotion for spreading the culture of movement. The main idea is to develop a specific approach to be applied to a specific working environment where the worker is considered as the main actor able to recognize the negative effects of sedentarism and to know the minimum amount of daily physical activity necessary for maintaining a sufficient state of efficiency. In order to reach this aim, the study will consider the optimization of tools and aids specific to a particular working environment where, through the elaborations of statistical and biomechanical models, it will be possible to develop specific applications and strategies. The daily use of specific tools and apparatus will increase awareness about the positive aspect of action performance and will convince individuals to be active and so be better predisposed to live a sustainable and healthier life producing a social impact in line with the main aim of the “Agenda 2030”. A more sustainable city with a reduced volume of traffic due to the presence of a more efficient and ecological way to travel will better preserve the environment. The planet's health and the health of individuals are strongly tight. The present project will involve experts from the Neuroscience Biomedicine and Movement Department (particularly from the Movement Science area) in collaboration with experts from the informatic department (particularly from the robotic area) along with physiatry and physiotherapists from LabofMove (specialized in movements and proprioceptive and automatisms: postural respiratory, cardiovascular and metabolic).”

Following the doctoral aim as explained above, and considering the opportunity given by the collaborations and internships related to the project, we decided to focus our attention on issues related to the control of postures and, in particular, on the development of negative postures, as the one present in a typical office environment. We were thinking that through this approach we will add relevant knowledge about ad hoc prevention and treatment by providing insight for innovative strategies in motor rehabilitation and optimization of physical performance. An additional strength of this thesis lies in integrating different movement analysis techniques applied to dynamic signals, registered from muscle activity via electromyography (EMG) and body stability via force sensors (force platforms).

2 INTRODUCTION

2.1 Definition of sedentary behavior

Although in common language, the term sedentariness is often associated with concepts such as inactivity, unhealthy behavior, or a passive lifestyle, in the scientific field the quest for a universally accepted and unambiguous definition represents a complex challenge. With the growing interest in sedentary behaviors, the urgency of standardized definitions applicable across various disciplines has emerged. This necessity is further driven by the increase in physical inactivity and the correlation between sedentary behaviors and negative health indicators, such as cardiovascular morbidity and other chronic conditions. The lack of terminological clarity has led to confusion, with diverse methodological and conceptual approaches to defining and measuring sedentary behavior. For example, in motor sciences, the term "sedentary" can be referenced in different ways:

- As a *metabolic parameter*, defined as energy expenditure below 1.5 METs. However, this value may not be adequate for all age groups, as metabolic thresholds vary between children, adults, and the elderly (Mansoubi et al. 2015);

- In *relation to posture*, is considered as the time spent in a seated or reclined position. This approach, however, risks underestimating the energy expended during activities that appear sedentary but require some level of muscular or metabolic effort;

- Based on *body accelerations*, measured through wearable devices, which offer another perspective but do not always capture qualitative aspects of sedentary behavior.

The recommendations suggest at least 150 minutes of moderate-to-vigorous physical activity per week, performed in sessions (bouts) of at least 10 minutes (Crespo-Salgado et al. 2014). However, these guidelines do not account for the time spent in a seated or reclined position. Consequently, a person can be physically active while also exhibiting sedentary behaviors. In fact, an individual who meets the recommendations for physical activity might still spend most of their remaining time in a highly sedentary state (Biswas et al. 2015; Katzmarzyk et al. 2012, Pirôpoet al 2021). In 2012, the Sedentary Behaviour Research Network (SBRN) (Tremblay et al. 2017), an international network of researchers and health professionals interested in the study of sedentariness, published a proposal for a definition aimed at clarifying the differences between “sedentary behavior” and “physical inactivity”. This effort received widespread acceptance, leading to the publication of the definitions in English and subsequent translations into other languages. However, the need for further refinement of these definitions remained, particularly to include terms emerging from modern society, such as screen time, standing time, sitting, and reclining. In 2017, through a participatory process involving a literature review, the creation of a steering committee, and consultations with SBRN members via an online survey, a conceptual model and a standard definition for sedentary behavior were developed. This definition, now widely recognized, is as follows:

"Any waking behavior characterized by an energy expenditure ≤1.5 metabolic equivalents (METs), while in a seated, reclined, or lying posture."

This definition is notable for its emphasis on both energy expenditure and posture, thereby integrating two fundamental aspects of sedentary behavior. Additionally, the developed conceptual model (*Fig. 2.1*) includes a comprehensive categorization of human activities over a 24-hour period, allowing sedentary behavior to be considered in relation to and contrasted with other actions, such as physical activity and sleep. This terminological standardization represents a crucial step toward improving consistency in research, facilitating study comparisons, and promoting targeted interventions to reduce sedentary time, with potential benefits for public health., The purpose of this thesis is not to analyze in detail the definition of sedentariness, but rather to deal with aspects of sedentary behavior—still difficult to fully enumerate even today—that contribute to the complex development of pathologies that, while initially silent, can manifest with symptomatic episodes at nonspecific moments in life. This relationship between sedentary behavior and the onset of diseases underscores the importance of a multidimensional approach that considers not only the duration of sedentary time but also the context in which it occurs, the interruptions between sedentary episodes, and the postures adopted. These factors can significantly influence the risk of developing metabolic, cardiovascular, and musculoskeletal disorders, as well as neurocognitive and psychological conditions (Tremblay et al. 2017).

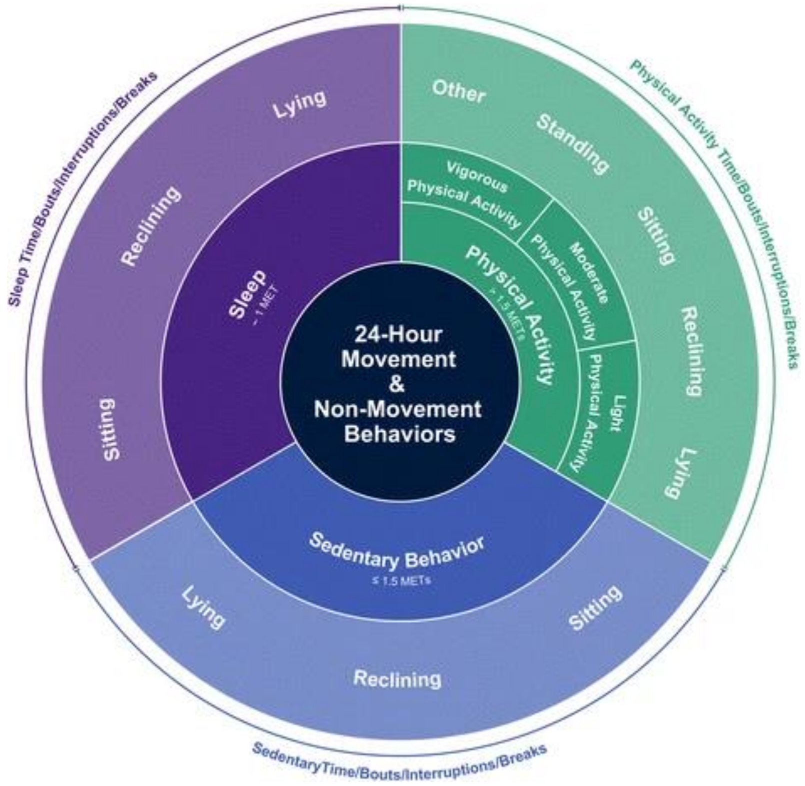

Fig. 2.1: Conceptual model from Tremblay et al. 2017. "Illustration of the final conceptual model of movement-based terminology arranged around a 24-h period. The figure organizes the movements that take place throughout the day into two components: The inner ring represents the main behavior categories using energy expenditure. The outer ring provides general categories using posture."

2.2 Prevalence in modern society

A sedentary lifestyle leads to insufficient physical activity, which represents a global issue requiring political interventions and evidence-based programs to reduce associated risks and improve public health. In 2016, 27.5% of adults globally did not meet the recommended levels of physical activity. The article by Guthold et al. (2018) highlights that WHO member states have agreed on a relative 10% reduction in the prevalence of insufficient physical activity by 2025, as one of the global targets for improving the prevention and treatment of non-communicable diseases. In this context, the need for urgent action to promote physical activity was emphasized, particularly in high-income countries and regions such as Latin America and South Asia. Although the target, which is difficult to achieve, has been set, specific action plans have been proposed, such as policies aimed at promoting infrastructure for walking and cycling, as well as the creation of public spaces, which are essential for increasing physical activity levels. More recently, Bull et al. (2024) declared a new goal for 2030, which is to further reduce physical inactivity levels. According to the study, in 2022, 31% of adults (about

1.8 billion people) did not meet the physical activity levels recommended by the WHO, i.e., at least 150 minutes of moderate activity or 75 minutes of vigorous activity per week. Furthermore, from 2010 to 2022, physical inactivity increased by 5 percentage points, rising from 26% to 31%. This alarming trend highlights the difficulty in achieving the set goals and underscores the urgency of implementing effective global strategies to tackle the issue. This growing trend of physical inactivity directly contributes to the rise of non-communicable diseases, such as cardiovascular diseases, type 2 diabetes, certain types of cancer, and other chronic conditions. Numerous studies have demonstrated a strong association between sedentary behavior and the onset of these diseases. For instance, the work by Lee et al. (2012) showed that physical inactivity is one of the main risk factors for premature mortality and chronic non-communicable diseases. Specifically, the analysis found that sedentary behavior is associated with an increased risk of cardiovascular diseases, diabetes, and certain forms of cancer. Additionally, a study by Tindle et al. (2020) demonstrated that physical inactivity is also linked to higher obesity rates, which is another risk factor for many chronic diseases. The study emphasized that promoting regular physical activity can significantly reduce the risk of developing these conditions.

Sedentarism not only contributes to the development of cardiovascular diseases, but also musculoskeletal disorders, such as back pain, joint pathologies, and muscle issues, which are commonly found in individuals who spend long hours in static positions. In particular, low back pain (LBP) is one of the most common musculoskeletal conditions associated with sedentarism. People who engage in work activities that require sitting for extended periods, such as office work, are particularly vulnerable to these issues. (Razavi 2020) Prolonged immobility leads to the weakening of support muscles, poor posture, and increased muscle tension, resulting in pain and dysfunction. Additionally, work-related sedentarism can also cause pain in the hands, such as carpal tunnel syndrome or other disorders related to excessive use of digital devices, which involve repetitive movements of the hands and fingers (Nunes et al. 2012). These disorders have become increasingly prevalent in modern work environments, particularly due to the prolonged use of computers and keyboards, with negative effects on musculoskeletal health. Therefore, the growing prevalence of physical inactivity is fuelling a true global public health crisis, and the need to intervene to promote physical activity has become more urgent than ever.

2.3 Challenges in the diagnosis of sedentary-related diseases

As highlighted earlier, the growing prevalence of physical inactivity is driving an unprecedented global health crisis, significantly contributing to the increase in sedentary-related diseases. These issues pose a major challenge for healthcare systems, as the early detection of such disorders is hindered by the complexity of behavioral and physiological responses associated with a sedentary lifestyle. One of the primary diagnostic challenges lies in the overlap of symptoms between sedentary-related disorders and other common conditions. For instance, symptoms such as muscle stiffness, chronic fatigue, and localized pain may not only indicate sedentary-related disorders but also other conditions, such as fibromyalgia, arthritis, or even stress-induced psychosomatic disorders. This lack of symptom specificity further complicates the diagnostic process, delaying both the identification of these conditions and the initiation of targeted interventions (Lee et al. 2012). Another factor contributing to diagnostic challenges is the considerable variability in individual movement patterns. Each person exhibits a wide range of movement behaviors, making it difficult to isolate unique characteristics clearly associated with a specific disorder. This variability not only hinders the establishment of standardized diagnostic criteria but also raises concerns about the applicability of personalized treatments (Kett et al. 2021). Studies like that of Knox et al. (2018) and have highlighted how postural patterns in individuals with low physical ability levels can vary significantly, even among those with similar symptoms. Similarly, Massé-Alarie et al. (2024) have demonstrated that biomechanical responses to sedentary behavior depend on individual factors, further complicating the development of generalizable diagnostic protocols. Another challenge stems from the limited availability of diagnostic tools capable of accurately distinguishing adaptive movements, which may represent beneficial bodily responses, from maladaptive ones that could exacerbate the condition. Although advanced technologies, such as biomechanical imaging and motion tracking systems, hold great promise, their widespread use remains limited, mainly due to high costs and restricted availability in routine clinical settings (Pinto et al. 2023). The early detection of these conditions is essential not only to prevent the chronic progression of diseases but also to tailor intervention strategies effectively. Timely diagnosis enables healthcare professionals to design customized therapeutic approaches that address the specific needs of each patient, breaking cycles of maladaptive adjustments that could worsen over time (Schubert et al. 2023).

2.4 Adaptive movements resulting from a sedentary lifestyle

The diagnostic complexity of sedentary-related diseases partly stems from the compensatory responses the body develops to prolonged inactivity. These biomechanical adaptations, referred to as adaptive movements, can have dual effects: in some cases, they help alleviate discomfort and mitigate musculoskeletal damage, while in others, they exacerbate the negative consequences of a sedentary lifestyle (Massé-Alarie et al 2024). This duality poses significant challenges for the early identification of these conditions and the design of targeted therapeutic interventions. Adaptive movements represent the body’s intrinsic biomechanical responses aimed at minimizing discomfort and preventing potential physical harm resulting from prolonged static postures. Common examples include postural shifts to redistribute body weight or adjustments in joint positioning to relieve localized pressure or tension. Additionally, these responses may involve voluntary movement restrictions intended to avoid or lessen pain and muscle stiffness. While these adjustments are intended to be beneficial, they can sometimes have adverse effects. For instance, limited movements or repetitive patterns can lead to maladaptive compensations, increasing strain on certain body structures. Over time, such adaptations may result in chronic dysfunctions, such as muscular imbalances, joint compressions, or asymmetric tensions, thereby heightening the risk of injury or persistent discomfort. A critical factor further complicating the diagnostic process is the significant interindividual variability in adaptive responses. This diversity is influenced by numerous factors, including:

- *Genetic predispositions*, which affect flexibility, muscle strength, and resilience to mechanical stress.
- *Individual biomechanics* encompass parameters such as joint angles, weight distribution, and postural alignment.
- *Previous levels of physical activity* determine the body’s ability to respond effectively to static or dynamic stimuli associated with sedentary behavior.

For instance, a common symptom such as postural modification can manifest in significantly different ways among individuals, influenced by variables like age, gender, body composition, and medical history. Some individuals may develop postural shifts that alleviate discomfort and reduce mechanical strain, while others may adopt maladaptive patterns that exacerbate musculoskeletal tension, worsening overall health. The aforementioned individual variability in movement patterns makes it challenging to establish standardized diagnostic criteria that are universally applicable. There is a clear need for the development of personalized diagnostic tools capable of distinguishing between beneficial biomechanical adaptations and maladaptive responses. These tools could leverage advanced technologies, such as motion tracking systems, real-time biomechanical analyses, and artificial intelligence algorithms, to identify specific movement patterns and suggest targeted interventions. Moreover, timely diagnosis using such tools could enable the implementation of personalized therapeutic strategies, reducing the risk of chronic progression in sedentary-related diseases. Early intervention to disrupt cycles of dysfunctional adaptations is essential not only for improving clinical outcomes but also for optimizing healthcare resources, ensuring more effective and targeted treatments (Massé-Alarie et al 2024; Freese et al. 2018).

In conclusion, gaining a deeper understanding of adaptive movements, their implications, and individual variations is a priority for enhancing the diagnostic and therapeutic approach to sedentary-related diseases. Achieving this goal requires a multidisciplinary effort that integrates biomechanical, physiological, and technological expertise to address diagnostic challenges and propose innovative solutions.

2.5 Major sedentary-related diseases: low back pain and musculoskeletal disorders of the hands

As previously discussed, sedentary behavior is an increasingly widespread issue in modern society, with more than half of the population engaged in activities characterized by prolonged sitting periods, such as watching television or using a computer (Owen et al., 2010; Park et al., 2021). These sedentary behaviors are associated with a wide range of negative health consequences, encompassing both cardiovascular and non-cardiovascular conditions. Among the most commonly associated illnesses are cardiovascular diseases, type 2 diabetes, obesity, and certain types of cancer (Biswas et al., 2015). However, the effects of sedentary behavior are not limited to internal organs; it also significantly impacts the musculoskeletal system. For instance, chronic LBP is one of the most frequently observed conditions, often exacerbated by poor posture or prolonged sitting. When the pain persists for more than 12 weeks, it is defined as chronic LBP. This condition not only reduces the quality of life but is also associated with an increased risk of disability. In developmental ages, reduced physical activity has even broader implications. In children and adolescents, sedentary behavior is linked to delays in the development of motor and cognitive skills, as well as a higher incidence of early-onset sarcopenia, characterized by the loss of muscle mass and strength at a young age. Additionally, lack of movement has been associated with an increased risk of mental disorders, including depression, schizophrenia, and bipolar disorder (Booth et al., 2012; Pirôpo et al., 2021). The diagnosis of chronic low back pain is primarily based on a detailed clinical assessment, including a comprehensive medical history, physical examination, and instrumental evaluation. During the patient's medical history review, information is gathered regarding their medical background, lifestyle, and occupational habits. The physical examination involves analyzing posture, mobility, and the presence of neurological signs. In some cases, instrumental tests such as X-rays or magnetic resonance imaging (MRI) are required to rule out specific pathologies. The treatment of chronic low back pain follows a multidisciplinary approach, which may include both non-pharmacological and pharmacological interventions, depending on the severity of the condition. Non-pharmacological interventions include physical therapy, focusing on targeted exercises to improve mobility and strengthen the back muscles (Kreiner et al., 2020; Urits et al., 2019). Complementary therapies such as tai chi (Hall et al., 2011), yoga, and relaxation techniques (Zhu et al., 2020) are often recommended. Pharmacological interventions involve the use of non-steroidal anti-inflammatory drugs (NSAIDs) to reduce inflammation and pain, analgesics for pain control, and, in cases of neuropathic pain, antidepressants or anticonvulsants. In selected cases, when other therapeutic options prove ineffective, surgical intervention may be considered (Koes et al 2017; Heneweer et al 2011).

A significant and perhaps less well-known example of musculoskeletal problems related to these behaviors is represented by issues with fine motor control of the hands, such as writer's cramp, a form of focal dystonia that manifests as muscle spasms and abnormal postures during repetitive movements or prolonged static positions. Such disorders, which affect fine motor control, frequently occur in older adults and the elderly and are often underestimated (Donati et al 2024; Ranney 1993). The absence of pain or the presence of intermittent pain, in fact, discourages medical consultations, making diagnosis challenging and often reliant solely on pain management. These conditions reflect the complex impact of sedentary behavior and work-related illnesses on the nervous and muscular systems (Nicholls et al., 2012; Franco, 2010). Thus, the diagnosis is often based on a careful evaluation of the patient's medical history, posture, and functional limitations, with treatments ranging from physical therapy and lifestyle modifications to more invasive procedures, such as injections or surgical interventions. In most cases, medication use is focused on pain management, employing analgesics, NSAIDs, or, in more severe cases, opioids and muscle relaxants to relieve discomfort and reduce inflammation (Makkouk et al 2008).

In conclusion, sedentary behavior represents a cross-cutting risk factor that affects multiple aspects of physical and mental health, requiring targeted interventions to promote more active lifestyles, enable early diagnosis of disorders, and reduce the time spent in inactivity.

2.6 Overview of Research Studies Submitted

Taking a deeper look at motor control allows us to promote healthier living, preventing the harms caused by sedentariness and improving overall well-being. It allows us to develop strategies and interventions aimed at counteracting the negative effects of sedentariness, a growing problem in modern society, especially in work environments. Understanding the mechanisms that regulate movement allows us to design exercise programs, ergonomic tools, and aids that encourage regular and correct motor activity. This is crucial for preventing musculoskeletal disorders, postural disorders, and other conditions related to lack of movement, such as obesity and cardiovascular disease. In addition, improving one's awareness and ability to control one's body promotes a more active and responsible approach to health, which not only reduces the risk of disease but also contributes to greater psychological well-being by improving mood and reducing stress. In addition, motor control plays a crucial role in building effective learning systems, both in rehabilitation and sports. The ability to understand and improve how the brain and body learn and refine new movements is essential for optimizing rehabilitation after injury, improving athletic performance, and promoting faster and longer-lasting motor learning. Improving one's awareness and ability to control one's body promotes a more active and responsible approach to health, which not only reduces the risk of disease but also contributes to greater psychological well-being by improving mood and reducing stress. This makes the study of motor control a core element in promoting a healthy and sustainable lifestyle. The importance of early diagnosis and targeted studies on motor control, even in the absence of evident symptoms such as pain, is now clear and necessary. A comprehensive understanding of the dynamics that regulate motor control represents a key element not only for the prevention of pathologies but also for motor rehabilitation following disorders or pathological conditions. In light of these premises, the research presented in this thesis aims to tackle two fundamental challenges in the field of motor control studies. The first focuses on one of the most widespread global pathologies, chronic LBP, with the objective of investigating motor strategies related to posture and pain management. The second challenge, on the other hand, addresses a less explored but equally crucial aspect: muscular synergies and fine motor control, starting with the study of the hands. These two complementary approaches allow us to address motor control from different perspectives: on one hand, analyzing the entire body (total body) concerning a widely prevalent condition such as LBP; on the other, delving into the foundations of motor control through the study of muscular and intramuscular synergies. This integrated approach aims to lay the groundwork for the development of innovative techniques in prevention, education, and motor rehabilitation, while simultaneously providing solid expertise in motor control research methodologies.

The first study aims to investigate anticipatory and compensatory motor strategies in response to self-induced perturbations in two groups of participants: healthy individuals and individuals with chronic generalized LBP who are currently asymptomatic for at least 10 days. The primary objective is to test motor adaptation patterns in individuals who have had the condition during an upright posture maintenance task. To this end, a wave-like structure designed to generate self-induced perturbations will be employed, combined with 14 EMG systems to record muscular activity. This approach will allow for the analysis of differences in muscle activation patterns between healthy and pathological subjects, providing useful insights for the development of strategies for the prevention and management of LBP. Since the individuals with LBP have been asymptomatic for at least 10 days, no significant performance differences are expected. However, the analysis will focus on their motor pre-programming strategies, investigating the deeper modifications and the residual traces the condition may leave even after recovery.

The second study, on the other hand, focuses on fine motor control of the hand, using specific and entirely distinct analytical models. This is because the biomechanical complexity of the hand, with its unique degrees of freedom, makes it impossible to apply the same analytical models used in the first study. Each body district requires a dedicated analytical approach tailored to its peculiarities. This study specifically focuses on investigating the synergies that stabilize accurate force production using the four fingers of the hand, examining three levels of neural control: (1) reciprocal and coactivation commands, (2) the forces produced by individual fingers, and (3) the activation of individual motor units (MU). The main goal is to determine how these synergies contribute to force stabilization at each of these levels, involving cortical, subcortical, and spinal circuits, and to verify whether correlations exist between these different levels of control. To this end, both the expression of force on customized cells and the MU recordings of two antagonistic muscles will be analyzed.

Both studies aim to cover a broad spectrum of knowledge on motor control, from posture and LBP management, which involves the entire body, to muscular synergies and fine motor control mechanisms of the hands. This dual perspective will not only enrich the scientific literature in a field of great clinical and theoretical relevance but will also provide a solid foundation for the development of more effective prevention and rehabilitation techniques. Furthermore, the experience gained through these studies will represent a significant contribution to the development of advanced skills in the study of motor control, ensuring valuable opportunities for future academic and professional advancements.

2.7 Thesis Structure

The structure of this thesis has been designed to provide an exhaustive and coherent presentation of the conducted studies, accompanied by critical analysis and theoretical reflections. The studies will be presented in detail, preceded by an introductory section that outlines the underlying theoretical and methodological principles. Before delving into the studies and their introductions, a dedicated section will provide an overview of motor control theory, which will be applied and referenced in the subsequent analysis of the studies. This section on motor control theory will serve as a foundation, offering a deeper understanding of the concepts and frameworks that will be used throughout the research. It will allow for a more thorough exploration of topics that would not be fully addressed within the scope of the articles themselves, ensuring a comprehension of the subject matter. After this theoretical introduction, each study will be followed by a discussion of the challenges encountered during the research process and additional insights that enrich the overall analysis. This methodological approach ensures that the original format of the studies, whether already published or in progress, is preserved, while also delving deeper into their key aspects. The complete bibliography is included at the end of the thesis to facilitate easy access to the referenced sources.

The first project focused on LBP, is currently in the writing phase and aims to be published by the end of the year.

The second project has already been published in *Neuroscience*: Benamati, A., Ricotta, J. M., De, S. D., & Latash, M. L. (2024). *Three levels of neural control contributing to performance-stabilizing synergies in multi-finger tasks.* Neuroscience.

3 MOTOR CONTROL

3.1 Importance of studying the control of action

Motor control is a discipline that seeks to answer questions such as: *How do we manage the movements of our body? How do we walk, run, and jump?* This field explores the laws governing the interactions between the central nervous system, the body, and the environment, aiming to understand the execution of both voluntary and involuntary movements (Latash & Zatsiorsky 2015). This chapter begins by acknowledging Nikolai Bernstein, a pioneering figure whose ground-breaking contributions laid the foundation for the study of motor control. It then delves into pivotal theoretical frameworks, starting with the Equilibrium Point Hypothesis (EPH), which provides insights into how the nervous system simplifies the control of complex movements. Building upon this, the section on single joint control and reciprocal and coactivation commands explores the role of muscular coordination strategies in motor execution. The chapter further investigates the Uncontrolled Manifold Hypothesis, a conceptual framework that highlights how variability in motor control can be a strategy to achieve task-specific goals rather than a sign of inefficiency. This structured progression ensures a comprehensive understanding of the analysis and approach followed, for better setting the stage for the detailed exploration of specific studies later in the thesis.

3.2 Nikolai Bernstein: founding father of the study of motor control

Nikolai Bernstein, a Russian neurophysiologist, is considered the founding father of motor control studies. With his brilliance and limited research tools, Bernstein was able to demonstrate and predict fundamental principles that still form the theoretical foundations of this field today. One of his most famous contributions is the experiment known as “the redundancy problem.” By observing the movements of expert blacksmiths as they hammered a specific point with precision, Bernstein discovered that, despite the hammer always striking the target with accuracy, the movements of the joints varied continuously. There was no rigid or predefined trajectory; each strike represented a unique combination of joint movements. With this observation, Bernstein demonstrated that the human body is redundant, meaning there are multiple ways to achieve the same motor outcome. The joints can move in different combinations, yet the final result remains precise and unchanged. From this, Bernstein deduced that motor control is not a rigid sequence of instructions, as in a computer. The brain and nervous system do not control each joint movement in detail but rather work to achieve a final goal (Latash, 2006; Lacquaniti & Ivanenko, 2020).

Subsequently, many researchers focused on explaining and theorizing how the body selects a specific solution from the many possible options to achieve a motor goal. Among these, Anatol Feldman, a physicist and follower of Bernstein's theories, refined the modern theoretical model known as the Equilibrium Point Hypothesis (EPH). This model provides an innovative interpretation of motor control, not focusing on controlling each element individually ("one by one") but considering the body as an integrated system. The EPH, along with its extension (the theory of control by reference coordinates), is an example of a parametric control model. These models describe the control strategies that guide the movements of biological systems, suggesting that movement is not regulated by calculating every detail but by setting parameters or reference points (such as desired positions) that the body strives to achieve. For example, when moving an arm, the central nervous system may establish an endpoint towards which to direct the movement, allowing muscles and joints to naturally work to reach it, utilizing their elastic properties and adapting to external forces.

3.3 The first attempt to define muscle synergies

In common usage, the concept of muscle synergy refers to the coordinated action of multiple muscles working together toward a specific goal, namely, the manner in which groups of muscles cooperate to produce movement. However, this concept can at times appear vague or imprecise. For this reason, various research groups have attempted to formalize and define it more rigorously. Notably, the definitions that have emerged tend to be closely tied to the analytical methods used to compute synergies. Indeed, several computational approaches exist, each carrying its own distinct conceptual nuance.

Broadly speaking, two major methodological paradigms can be identified.

The first includes techniques such as Independent Component Analysis (ICA), Principal Component Analysis (PCA) (with or without rotations and factor selection), Non-negative Matrix Factorization (NNMF), and other similar algorithms. These methods share a common objective: reducing the dimensionality of original datasets - such as EMG signals - into a smaller set of components that explain the underlying structure of movement (Latash & Zatsiorsky, 2015).

In this framework, muscle synergies are interpreted as fixed spatial patterns of muscle co-activation that can be temporally combined to generate a wide variety of movements. In other words, they are conceived as stable motor modules that serve to simplify motor control. Each movement results from the linear combination of a limited number of synergies, with each synergy representing a specific balance of muscle activations (Tresch, Cheung, & d'Avella, 2006).

For instance, NNMF enables the decomposition of EMG signals into a reduced number of spatial modules and their corresponding temporal coefficients. Unlike PCA, which imposes no sign constraints and yields orthogonal components, NNMF enforces non-negativity and produces non-orthogonal components, which are generally more physiologically interpretable (Rabbi et al., 2020).

Other methods, such as ICA and Factor Analysis (FA), differ primarily in their underlying statistical assumptions. ICA assumes that the sources of the observed signals are statistically independent and non-Gaussian, whereas FA posits that observed variables are linear combinations of latent factors that are Gaussian distributed, with uncorrelated error terms (Zhao et al., 2022).

The second major paradigm is grounded in a different theoretical foundation, centered on the principles of motor redundancy and movement stability. In this view, muscle synergies are not merely algorithmically derived patterns, but rather functional strategies that allow the motor system to maintain both stability and adaptability in the face of internal or external variability.

This perspective has led to the development of theoretical models such as the Uncontrolled Manifold (UCM) hypothesis, proposed by Schöner in 1995. According to this framework, the motor system does not aim to control every single movement variable directly. Instead, it stabilizes only those components of movement that are critical for task success, allowing variability in task-irrelevant dimensions (see Chapter 3) (Latash, 2024).

In either approach, the core idea that synergies represent functional units of motor control—potentially linked to specific neural structures such as spinal circuits or cortical areas—is widely shared across research groups. However, the debate remains open as to whether synergies reflect genuine neural control strategies or are instead mathematical constructs devised to model the complexities of motor behavior.

In summary, while the first paradigm seeks to identify consistent patterns, the second focuses on how variability along task-relevant dimensions (i.e., "good variability") contributes to successful motor execution.

3.4 Equilibrium Point Hypothesis (EPH)

One of the fundamental principles of biology indicates that the force a muscle can generate depends on its length. When a muscle is stretched slowly, the force it produces derives from two factors: passive properties, i.e., connective tissues (such as tendons and ligaments) resisting stretching, and active response, which is the stretch reflex that activates the muscle, causing it to contract. The stretch reflex only starts working when the muscle reaches a certain length, called the stretch reflex threshold (λ). According to the EPH, the nervous system does not directly control force or movement; instead, it regulates the threshold of the tonic stretch reflex, denoted as λ. This parameter defines the length at which a muscle begins to actively respond (contract) in reaction to stretching. By adjusting λ, the central nervous system (CNS) can "set" the position where the muscle achieves equilibrium between the force it generates and the force exerted by an external load. At any given moment, there are multiple possible equilibrium points that the system can reach. Depending on external conditions (e.g., the weight of a load or the desired position), the CNS adjusts the λ threshold to select the most appropriate equilibrium point.

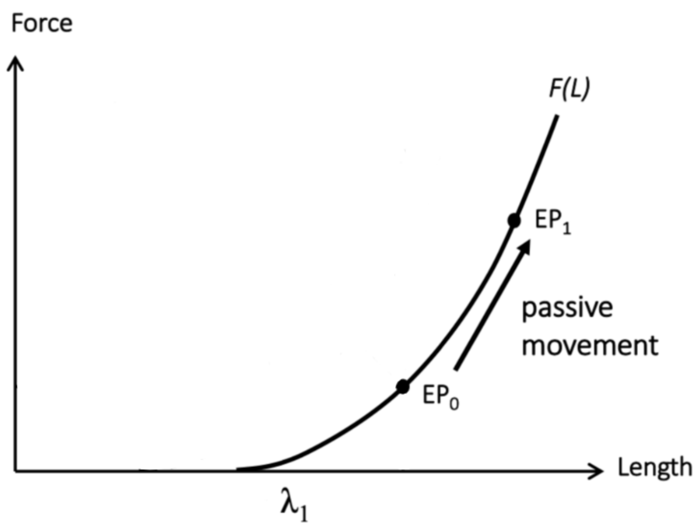

Fig. 3.1:Relationship between the force generated and muscle length, highlighting the role of the central nervous system (CNS) in regulating movement through the parameter λ, which represents the threshold of the tonic stretch reflex. The curve F(L) describes the passive properties of the muscle, showing how force increases with elongation due to the elasticity of connective tissues. The points EP0 and EP1 represent different equilibrium states of the muscle-load system: the transition from EP0 to EP1 corresponds to a passive movement in which the muscle lengthens.

Fig. 3.1 illustrates the relationship between muscle force and muscle length, highlighting the role of the CNS in regulating movement and equilibrium through the λ parameter, corresponding to the tonic stretch reflex threshold. The x-axis indicates muscle length, while the y-axis represents the generated force. The F*(L)* curve describes the passive properties of the muscle, showing how force increases with length due to the elasticity of connective tissues. The points EP_0 and EP_1 represent different equilibrium states of the muscle-load system. The transition from EP_0 to EP_1 occurs in response to an increase in external load, which passively stretches the muscle without activating the reflex. This phenomenon corresponds to passive movement, where the system adapts to increased external force by achieving a new equilibrium along the F*(L)* curve. For instance, imagine lifting a heavy bag with a relaxed arm. The weight of the bag passively stretches the bicep (the muscle does not actively contract), leading the system to a state of equilibrium on the F*(L)* curve.

A change in the λ threshold, from λ_1 to λ_2 as depicted in *Figure 2*, results in an active modification of the system's state. Using the same example of the bag, let us assume that at λ_1, the arm is semi-flexed, and the muscle-load system is in equilibrium (e.g., at EP_1) to keep the bag stationary. If we decide to actively lift the bag higher, the brain sends neural signals to the muscle, increasing the activation threshold to λ_2. The muscle contracts more forcefully, generating greater force, and the arm shortens as the system moves toward a new equilibrium, say EP_3 (refer to Fig 3.2).

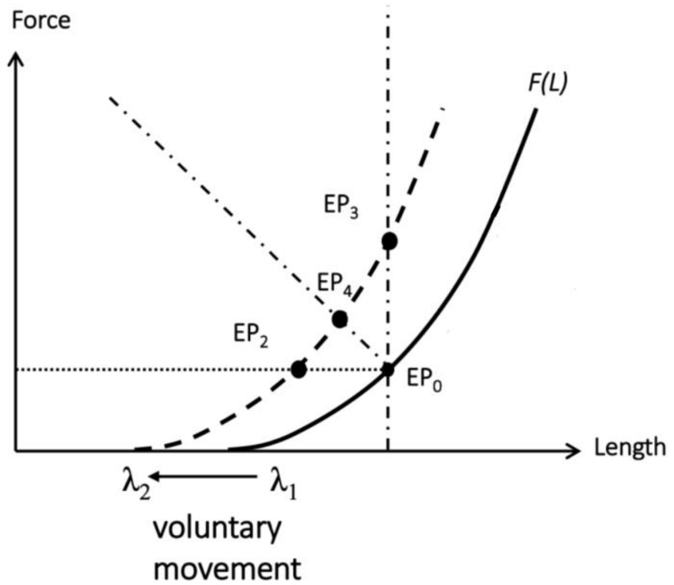

Fig. 3.2: Representation of the different equilibrium conditions achievable based on variations in the parameter λ and external conditions. EP2: in isotonic conditions, the muscle shortens or lengthens at a constant force. EP3: in isometric conditions, the muscle varies the force while maintaining a constant length. EP4: in elastic/mixed conditions, both force and length vary, reaching an equilibrium determined by both variables.

Depending on external conditions, various scenarios can occur. For instance, under isometric conditions, where muscle length remains constant, the muscle increases or decreases the generated force, shifting to a new equilibrium, EP_3. Under isotonic conditions, characterized by a constant force, the muscle shortens or lengthens, moving the system to a new equilibrium, EP_2. Finally, under elastic/mixed conditions, which combine variations in both force and length, the system reaches EP_4, an equilibrium determined by both variables.

3.5 Single joint control and reciprocal and coactivation commands

The generalization of the EPH to the control of a joint with one degree of kinematic freedom is relatively straightforward, particularly when considering a simple joint crossed by two opposing muscles, referred to as the agonist and the antagonist. Assuming that the agonist and antagonist produce positive and negative torque, respectively, their tonic stretch characteristics can be represented in *Fig. 4*. A joint can generally be described as controlled by a flexor muscle and an extensor muscle. According to the described model, the joint's behavior results from the interaction between the tonic stretch reflex (TSR) threshold of the flexor (λ_{FL}) and that of the extensor (λ_{EX}). The alternative commands that regulate the motor behavior of a joint are defined as the R-command and the C-command. The R-command is referred to as "reciprocal" because when one of the two muscles (flexor or extensor) is activated to generate more force, the other is inhibited and produces less force. In other words, when the flexor works harder, the extensor works less, and vice versa. The distance between λ_{FL} and λ_{EX} represents the level of cocontraction, or the degree of simultaneous activation of both muscles. An increase in this distance corresponds to greater co-contraction, which makes the joint more stable and resistant to sudden angular perturbations, as both muscles collaborate to maintain joint stability. The concept of co-contraction is particularly relevant in the context of the C-command, which occurs when both muscles (agonist and antagonist) are simultaneously active. Under the C-command, the resulting force along the spatial coordinate X (such as the joint angle) depends on the combined activity of both muscles. In contrast, the R-command defines the position where the sum of the muscular forces is zero, meaning the flexor and extensor exactly balance each other.

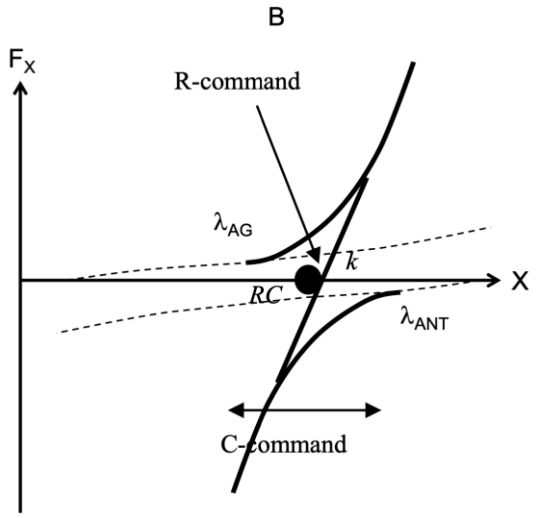

Fig. 3.3: Schematic representation of joint control according to the Equilibrium Point Hypothesis (EP) in a single degree-of-freedom joint. The figure shows the relationship between the tonic stretch properties of the flexor muscle (λ_{FL}) and the extensor muscle (λ_{EX}) and illustration of reciprocal (R-command) and co-contraction (C-command) controls for joint control.

In summary, the R-command determines the intercept of the muscular force, while the C-command defines the slope of the joint response, which results from the combined characteristics of both muscle groups. Fig. 3.3 illustrates the concept of control through reference coordinates, showing that for any effector acting along a spatial coordinate X, the joint can be described by a mechanical variable, such as the joint angle. The muscles involved can be classified into two main groups: those that generate force (or torque, in the case of joints) in the desired direction along X (agonists) and those that generate force in the opposite direction (antagonists). It is assumed that each muscle group can be controlled by a specific parameter: λ_{AG} for the agonist muscles and λ_{ANT} for the antagonist muscles.

The study of the agonist muscle in relation to its antagonist will be addressed in both proposed studies. In particular, the first study, focused on subjects with Low Back Pain (LBP), will delve deeper into this concept by extending it to the entire body, examining the relationships between ventral muscles and their dorsal antagonists. This approach will provide a better understanding of how compensatory mechanisms and muscular imbalances contribute to the development and persistence of chronic low back pain.

A key aspect of the investigation will be the analysis of muscle activation indices, specifically the R-index (Reciprocal Index) and C-index (Coactivation Index), which offer detailed insights into the coordination and interaction between agonist and antagonist muscles. The R-index measures the degree of reciprocal inhibition between the two muscle groups, a parameter that can reveal dysfunctions in neuromuscular regulation. In contrast, the C-index evaluates the level of simultaneous co-activation, useful for identifying stabilization or compensation strategies adopted by the muscular system.

These indices make it possible to detect subtle alterations in muscle activation patterns that often escape visual or qualitative analysis. For instance, in individuals with LBP, an imbalance in the agonist-antagonist relationship may present as excessive co-activation of dorsal muscles relative to ventral ones, indicating a compensatory attempt to enhance lumbar stability at the expense of functional mobility. Conversely, altered reciprocal inhibition may suggest impaired regulation of muscle tone, contributing to dysfunctional posture or inefficient movement.

3.6 The Uncontrolled Manifold Hypothesis

The Uncontrolled Manifold (UCM) hypothesis (Scholz and Schöner, 1999) will be one of the tools utilized in one of the following studies to evaluate the quality of the performed task. Initially, this hypothesis was developed to address the question: "How does the central nervous system select one specific movement over another?". According to the UCM hypothesis, variance across successive trials in a high-dimensional space of elemental variables is quantified within two subspaces. One is the subspace where the salient performance variable remains unchanged, defined as the UCM for that variable. The other is orthogonal to the UCM subspace and is referred to as ORT. If a performance variable is stabilized within a system, the UCM hypothesis predicts greater variance in the UCM subspace, where the salient performance variable remains constant, compared to the ORT subspace, where greater variance suggests changes in the performance variable or instability in the task. In other words, the UCM subspace, where the performance variable is not affected by changes in elemental variables across trials, does not require active control, justifying the term "uncontrolled." Conversely, the amount of variability in the orthogonal subspace requires monitoring and intervention by the controller, as it affects the performance variable and introduces errors into the task execution. Consequently, in a synergistic task, directions within the UCM subspace are expected to exhibit low stability, whereas those within the ORT subspace demonstrate high stability. It is important to note that the CNS does not necessarily focus exclusively on stabilizing the performance variable explicitly defined by the task. The CNS might instead prioritize the stabilization of another performance variable not explicitly instructed, potentially due to evolutionary tendencies or other functional preferences. These dynamics are expressed in the principle $V_{UCM}>V_{ORT}$.

For clarification, consider an example where a participant is instructed to apply a combined force of 20 N using two fingers across 100 consecutive trials. Multiple combinations can achieve this goal, such as 10 N with one finger and 10 N with the other, or 15 N with one finger and 5 N with the other, or even 20 N with one finger and 0 N with the other. When these data are plotted on a graph, with the force from one finger on the X axis (F1) and the force from the other finger on the Y axis (F2), the combinations satisfying the task will lie along a continuous diagonal line (*Fig. 3.4*). This diagonal represents good variability (V_{UCM}), as every point along it fully meets the task's requirements. Conversely, deviations from this diagonal, indicated by points along a dashed line, represent bad variability (V_{ORT}), indicating a departure from task optimization. If the data from the 100 trials cluster predominantly around the diagonal representing good variability, this indicates synergistic coordination between the fingers. On the other hand, if the results deviate orthogonally from the diagonal, synergistic coordination is absent. It is therefore important to note that UCM analysis is an excellent toolbox for analyzing salient elemental variables; however, it is based on certain fundamental assumptions, including the linearization of UCM and ORT subspaces and the assumption of normality in the distributions of elemental variables.

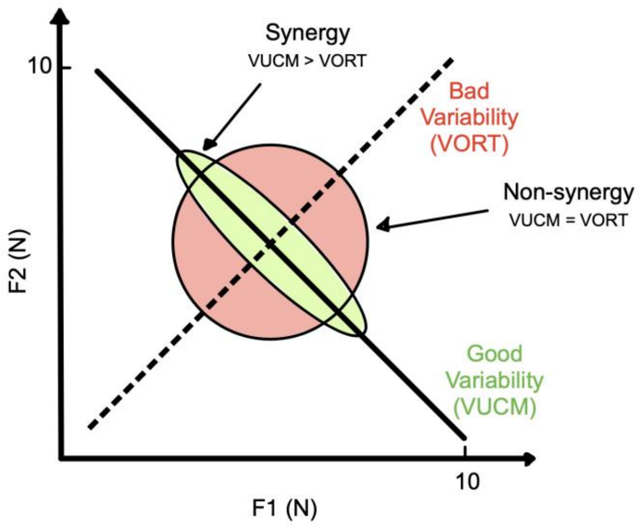

Fig. 3.4: Graphical representation of the Uncontrolled Manifold (UCM) analysis. The X and Y axes represent the forces applied by the first and second fingers, respectively. The diagonal line shows the combinations of forces that meet the task goal, indicating "good variability" (V_{UCM}). Deviations from this line, represented by the dashed line, reflect "bad variability" (V_{ORT}), which leads to task performance errors. The UCM subspace shows low stability, while the orthogonal subspace (ORT) exhibits high stability.

This investigative technique will be the focal point of the second proposed study. The UCM method allows for the identification of an optimal zone, a sort of "solution cloud," within which the task can be considered effectively performed. It is an exceptional tool that makes it possible, despite the infinite possibilities for executing a task, to determine whether the performance falls within a set of optimal solutions or not. In the experiment focused on the hand, this calculation will be further expanded and applied to the level of motor units and force exertion.

To sum up, the process used to analyze the Uncontrolled Manifold (UCM) and quantify motor synergies through a data processing pipeline. The starting point is the execution of a motor task, during which raw data is collected, such as motor unit activity (f_{MU}, often filtered using a Hann window) and the generated force. The data is pre-processed to remove noise and artifacts, and then analyzed using Principal Component Analysis (PCA), which identifies the primary motor modes (MU-modes), i.e., linear combinations of muscle activities that explain the predominant variance. These modes are then used to construct the J matrix, which represents the linear relationship between the motor modes and the observable behavior of the task (e.g., force). From J, the null space (null(J) is calculated, approximating the UCM and defining the directions in the space of motor variables where variations do not affect task outcomes. A variance analysis is then performed, decomposing total variance into two components: VUCM, the variance along the UCM (directions that do not influence the task), and VORT, the variance orthogonal to the UCM (directions that do influence the task). Finally, the Synergy Index is computed as the difference between these two components, providing a quantitative measure of the neuromotor system's effectiveness in organizing the degrees of freedom to meet task demands, thereby highlighting the role of motor synergies in movement control. The image illustrates the process.

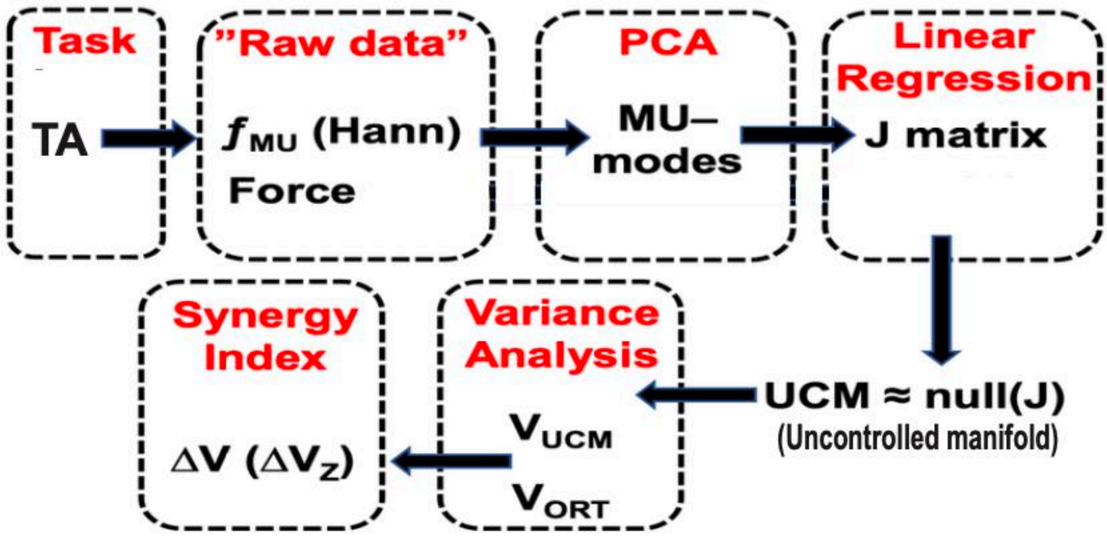

Fig. 3.5: The process used to analyze the Uncontrolled Manifold (UCM) and quantify motor synergies through a data processing pipeline

3.7 The general rational of the study

Consider, for instance, the body and the upper arm and hand postures kept by a sedentary office worker; when in action, they are functionally interconnected; the hand mouse manipulation and the digits' pressures on the keyboard are reciprocally affected by the posture of the entire body. Moreover, when these movements are kept for extended periods, continuous compensatory actions for managing individual muscular stiffness become the main phenomenon in interconnecting the general (body posture) with the focal (hand posture) action compensations. Based on this idea, we thought that we could run two studies that complement each other by offering a broader and more integrated view of how fine motor control and postural regulation interact in the prevention of musculoskeletal dysfunctions.

Interestingly, in the literature, body posture and manual dexterity have often been studied in two separate setups, partly due to historical distinctions in research traditions but also due to the main relevance that postures present in the presence of specific pathologies. Postural control has traditionally been investigated within the context of gross motor movement, considering mainly the middle-aged population (average age 45) some of whom affected by low back pain, while hand function has received greater attention from the standpoint of central motor control due to the movements being highly adapted for fine quick and precise actions where the overuse give rise to pathologies as the writer cramp. No wonder that in several instances, the hand has been referred to as an "extension of the brain," and following the metaphor, many neuroscientists became interested in hand action and hand control. This is why manual dexterity has been examined mostly in a young population (average age 24).

Recently, the literature has shown interest in studying the combination of hand and body relationships. The study by Alizadeh et al. (2023) on pain in monogenic forms of Parkinson's disease underscores how pain, mostly low back pain and hand pain, can be an early and significant manifestation of the disorder. Such findings strengthen the hypothesis that manual dexterity and postural control are tightly interdependent functions and are central to understanding both neurodegenerative and musculoskeletal conditions.

In a different context, the study by Joumaa et al. (2022) highlights that botulinum toxin injections (BTX-A), widely used to treat muscle hyperactivity disorders such as spasticity, dystonia, and back pain, selectively reduce specific force and shortening velocity in fast-twitch fibers of the paraspinal muscles. These effects, combined with the well-documented association between poor posture, repetitive movements, and conditions such as focal hand dystonia and low back pain, suggest that BTX-A-induced muscular changes may contribute to the worsening of such disorders.

Therefore, returning to the example of the sedentary worker, it is far from trivial to unify posture and dexterity within a single theoretical framework and to explore both functions jointly using the concepts of referent coordinates and motor synergies. Precisely because this integration is complex, the first step of this research involved addressing the two functions separately, each with dedicated analyses and methodologies grounded in well-established literature. What links the two studies and enables their convergence is the conceptual framework of referent coordination and motor synergy.

In both experimental tasks, modulation of motor synergies by the central nervous system is expected. In particular, with regard to postural stability, we hypothesize that it is primarily regulated through reciprocal co-contractions between agonist and antagonist muscles. If this hypothesis is confirmed, it would pave the way for studying postural control and manual dexterity within a unified and coherent experimental design.

In conclusion, the current literature appears to lack a direct and systematic connection between two essential motor functions: adequate manual dexterity and the corresponding postural control. The present research project aims to explore whether, and to what extent, these two domains of motor control can be analyzed jointly, and whether meaningful results can be obtained in terms of motor synergies. The central hypothesis driving this work is the possibility of describing and quantifying such synergies through a combined analysis of the control strategies involved.

A central concept emerging consistently across the two studies is the organization of motor control in terms of referent coordinates (RC). This theoretical approach, rooted in the equilibrium-point hypothesis and later formalized by Feldman and Latash, posits that the central nervous system does not directly command muscle forces or activations. Instead, it sets spatial reference coordinates toward which effectors are oriented. Within this framework, movement and postural stabilization result from the interaction between two principal neural commands: the reciprocal command (R-command), which defines the virtual equilibrium position, and the coactivation command (C-command), which regulates the degree of coactivation between agonist and antagonist muscles, thereby influencing the system's apparent stiffness.

In the first of the two studies, which focused on postural stability in individuals with chronic low back pain but free from acute symptoms, the use of R and C indices allowed for an analysis of anticipatory and compensatory muscular strategies in response to controlled postural perturbations. In this context, the C-command proved particularly sensitive in differentiating motor strategies between individuals with low back pain and healthy controls, suggesting that increased co-contraction may represent a learned and persistent stabilization mechanism. The R-command establishes the intended location of the body within the motor system—not through physical displacement, but by setting an internal target. The neuromuscular system then acts to minimize the discrepancy between the actual and desired position, where the target position is understood as the referent coordinate. Subjects knowing the direction of the perturbation correctly "calculated" the projection of their bodies to counter the perturbation. The C-command, on the other hand, determines the extent to which agonist and antagonist muscles are simultaneously activated. Higher coactivation corresponds to greater stiffness, which enhances the system's resistance to perturbations. This is reflected by the parameter k, the apparent stiffness.

In parallel, the second study, which investigated isometric multi-finger force production, applied the referent coordinate concept in a mechanical sense, through direct identification of the parameters R, C and k, which serve as operational manifestations of the neural R- and C-commands, respectively. In other words, R and C refer to the virtual position at which, if the finger could physically pass through the surface, the force would become zero. The parameter k reflects the slope of the force-position relationship and indicates how "stiff" or resistant the muscular response is to displacement. These values are not measured directly from neural or muscular activity but are instead derived mechanically from force and position data, and thus serve as indirect reflections of the underlying neural commands.

The use of controlled perturbations, combined with an analytical framework based on the Uncontrolled Manifold (UCM) hypothesis, enabled quantification of stabilizing synergies at multiple levels of the control hierarchy, including individual finger forces and motor unit activity. Despite the differing experimental contexts—one clinical and postural, the other biomechanical and analytical—both studies support the idea that motor control operates through anticipatory setting of spatial reference coordinates. Furthermore, the stability of the musculoskeletal system, whether at the global or distal level, is maintained through the hierarchical organization of motor synergies. The application of the referent coordinate framework thus provided a coherent interpretative basis for integrating the two experimental paradigms under a unified logic of control, offering insight into the motor strategies employed in both postural compensation and fine neuromuscular precision tasks.

4 Project #1: LBP

4.1 Project #1 presentation

Numerous studies have sought to investigate the onset and underlying mechanisms of postural adjustments, focusing on two main categories: anticipatory postural adjustments (APAs) and compensatory postural adjustments (CPAs). APAs are proactive postural adjustments executed by the nervous system before an action, while CPAs are corrective responses that occur after a perturbation has taken place. However, the findings from these studies have often been inconsistent, increasing uncertainty about how the postural system responds in individuals with LBP. Several factors — such as the type of task performed, the magnitude and nature of the perturbation, the environment in which the subject is placed, and their perception of their physical abilities — significantly influence the postural response in individuals with LBP. However, these factors have not always been standardized across experiments, resulting in varied responses and inconsistent findings between studies.

An interesting study by Piscitelli et al. (2017) explored APAs and CPAs by adding another layer of analysis, examining the Reciprocal Command (R-Index) and the Coactivation Command (C-Index) as proposed by Latash and Zatsiorsky (1993), in healthy subjects. The experimental paradigm consisted of releasing a weight while attempting to maintain balance. To better understand the R-command and C-command at the whole-body level, *Fig. 4.1* schematically illustrates body control in the antero-posterior direction. During standing, the center of mass projects in front of the ankle joints and generates a moment that tends to rotate the body forward. AO represents the actual orientation of the body in the field of gravity. The R-command defines the referent orientation of the body (RO), and the difference between RO and AO leads to the generation of the moment of force acting against gravity. The C-command defines a spatial (angular) range, in which opposing muscle groups exhibit non-zero levels of activation. In terms of mechanics, the C-command determines the apparent stiffness of the ankle joint (cf. Latash and Zatsiorsky 1993). They found healthy people prefer reciprocal activation patterns, while people with impaired postural control show more agonist and antagonist muscle co-activation, even in relatively simple tasks (Piscitelli et al. 2017). Conversely, other studies on pathological subjects reported that these individuals tended to favor co-contraction patterns even in simple tasks.

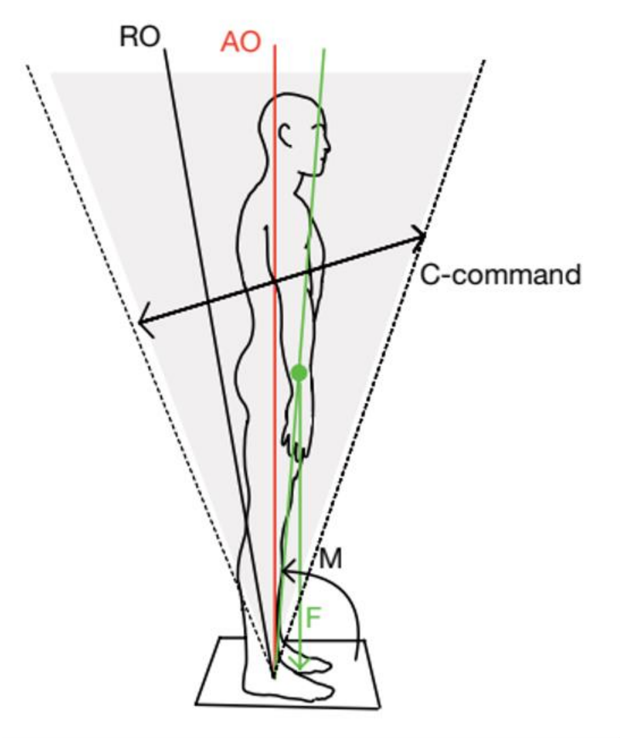

Fig. 4.1: Schematic representation of postural control in the antero-posterior direction. The center of mass is projected in front of the ankle joints (F). The AO represents the person's current orientation. R-index is an active force moment that counteracts the force of gravity, maintaining balance. C-index regulates co-activation of antagonist and agonist muscles, increasing apparent joint stiffness and allowing rapid postural correction in response to minor perturbations.

A subsequent study extended this line of research by investigating healthy individuals using a similar weight-release paradigm but incorporating a torso twist (Pascucci et al., 2023). The researchers found that muscle activation indices were generally higher on the side of the body opposite the direction of rotation. However, this hypothesis was not consistently confirmed in all cases. Finally, changes in postural stability did not produce significant variations in all the analyzed indices (R-Index and C-Index); often, changes were observed in only one index or neither.

This method of analysis proved to be an interesting approach, as it does not limit itself to detecting the presence of APAs and CPAs but explores the synergistic work between pairs of agonist and antagonist muscles at the joint level. We evaluated this method as a promising strategy to obtain a detailed characterization of the postural behavior of the whole body in response to a perturbation. Consequently, we decided to adopt this methodology to study subjects with LBP.

.

4.2 Abstract

Chronic low back pain (LBP) is one of the most prevalent conditions worldwide, associated with pain and motor alterations that impair postural stability. However, evidence regarding changes in trunk muscle activity in individuals with LBP is conflicting. Some studies have identified movements significantly different from those of healthy individuals, while others have not observed variations substantial enough to be considered characteristic of the pathology. This inconsistency highlights the lack of a unified consensus on the nature of postural changes associated with LBP, emphasizing the need for further targeted investigations.

This study analyzed postural control in individuals with chronic LBP, free from pain, by comparing them with a healthy group matched for sex and age. The aim was to investigate the mechanisms of anticipatory (APAs) and compensatory postural adjustments (CPAs) by evaluating reciprocal activation (R-Index) and coactivation commands (C-Index) to identify the muscle synergies involved in maintaining vertical posture during a load-release task performed under varying stability conditions.

4.3 Introduction

Low-back pain (LBP) is a prevalent condition worldwide and is characterized by pain, discomfort, and/or muscle tension located in the lower trunk up to the gluteal muscles (Koes et al 2006). It presents significant medical and economic challenges, and there is currently no effective cure (Itz et al. 2012). This pathology has been proven to be associated with impaired control of movements and stability in the vertical posture (Knox et al., 2018, Massé-Alarie et al, 2024), producing different patterns of action in different individuals that might be highly variable with no agreement on whether they represent direct consequences of LBP or adaptive reaction to this condition (O’Sullivan, P. 2005). The state of the art is that eighty-five percent of chronic LBP have no diagnosis and are categorized as nonspecific LBP, leaving the treatment in a vacuum (O’Sullivan, 2005).

One of the most important issues clinicians raise is that for efficient prevention, it is necessary to establish whether behavioral responses expressed by LBP patients reflect adaptive responses as a supportive strategy for recovering or whether behavioral responses reflect a vicious cycle that will develop into a chronic negative pattern of actions. Following the literature, two models have been proposed for explaining the changes in trunk muscle activity and pain perception in LBP patients. On one side, the pain-spasm-pain model sustains that pain results in increased muscle activity, which in turn causes chronic pain (Roland MO, 1986; J. Travell, S. Rinzter, M. Herman, 1942). On the other side, the pain adaptation model postulates that under pain, there is a reduction of the activation of muscles when active as an agonist and increased activation of muscles when active as an antagonist. This will decrease movement velocity and range of motion, which will prevent the mechanical provocation of pain (J.P. Lund, R. Donga, C.G. Widmer, C.S. Stohler 1991). A recent review tested the strength of the prediction of the two models in more than 30 clinical studies (van Diee, Selen, Cholewicki, 2003) and found that neither one of the two models was able to predict the effect of back pain systematically and unambiguously on trunk muscle activation. In some cases, there has been found evidence for reduced activation in line with the adaptation model (Marras et al., 1999), while in some other cases, an increase in activation was predominantly in line with the spasm-pain model (Hemborg and Moriz, 1985).

The inconsistency among results could be found in the methodology applied: the analysis considered each muscle individually, and no muscle-sharing activity was present. When muscle-sharing activation was included, considering, for instance, the combined activation between abdominal muscles, it was found that while the individual activation levels of the internal oblique and rectus abdominus muscles were not different between patients and controls, the ratio between the two muscles showed a difference with higher activation of rectus abdominus relative to the internal oblique in the patient's group (O'Sullivan et al.1997). In the same vein, the electromyographic amplitudes taken as a ratio between the lumbar over the thoracic erector spinae were greater in LBP patients than in the control group, indicating the presence of specific muscular synergies functional for enhancing spinal stability (van Diee, Selen, Cholewicki, 2003). Overall, research largely concentrated on individual muscle activity rather than examining the coordinated activation of multiple muscles, a prerequisite for collectively contributing to maintaining the correct postures in action. Expanding the focus to including larger groups of muscles could provide a more comprehensive insight into the control applied for producing coordinated actions through synergies. Analyzing the collective behavior of numerous muscles could yield valuable new information about the control of posture across the entire body, offering a broader understanding of the mechanisms underlying postural adjustments in individuals affected by LBP (Knox et al., 2018).

An additional open question related to LBP is related to the origin of the pain. A growing interest has been recently developed for studying the nervous system and its involvement in pain perception by documenting complex neuro-modulatory changes at both peripheral and central levels (Moseley, 2003; Wright e Zusman, 2004). There is growing evidence showing that the nervous system, while dynamically changing its cortical mapping, establishes a memory of pain that makes it pre-sensitized to the recurrence of pain (Zusman, 2022). This has changed the way in which clinical attention is devoted to pathologies affected by pain, to try to intervene specifically on both central and or peripheral pain processing (Bogduk, 2004). Either pathological effects, such as nerve pain, intravertebral disc, and joint degeneration (Elvey and O'Sullivan, 2004) or psychological components, such as anxiety, depression, and somatization (Hodges and Moseley, 2003), have been shown to alter motor behavior when in the presence of pain.

Changes in motor coordination observed in individuals affected by LBP, particularly considering the trunk muscles, might be related to different excitability of the descending cortico-motor inputs. When the amount of activity of the descending motor inputs toward the superficial trunk muscles was compared between healthy individuals and patients affected by LBP, the increment was higher under the presence of LBP (Arendt-Nielsen et al. 1996; Radebold et al. 2001; Tsao et al. 2011) suggesting a functional role of the increment, as an adaptive strategy for stabilizing and protecting the spine from potential stress and injuries (Hodges and Moseley, 2003). Moreover, when the background activity of the corticomotor excitability was compared in the presence or the absence of pain, the two modulations were comparable (Tsao et al. 2011), showing that it is during the action that different muscular strategies are produced. Together, the results sustain the idea that the increase in cortico-motor activity is consistent with the aim of the central nervous system to protect the body from potential perturbations by, for instance, reducing the spine's mobility (Hodges et al. 2006).

In general, one might think that by virtue of the plasticity of cortical maps, adaptive movements could emerge as a defense and/or as a new learning of motor strategies and that both action pre-programming and action execution could affect the different patterns of movements observed in individuals affected by LBP both in the presence and the absence of pain. Indices in anticipatory (APAs) and compensatory postural adjustments (CPAs) are the measures often used to assess the control of postures in both healthy persons and those suffering from a variety of conditions associated with stability problems (Belenkii et al 1967; reviewed in Aruin 2003). APAs are defined as changes in the baseline muscle activation levels observed about 120-200 ms before predictable and/or self-triggered perturbations and reflect the person's prediction of the mechanical effects of the perturbation on the vertical posture (Masson 1992; Bertucco & Cesari, 2010; Bertucco et al., 2013). CPAs represent phasic changes in muscle activation, initiated a few tens of milliseconds after the perturbation, and their aim is to restore balance (Bertucco et al, 2021; Cesari et al, 2022). While APAs act in a feedforward manner, involved in anticipating the actions, the CPAs are initiated by sensory feedback signals (Aruin et al. 2015, Tsao et al. 2008). Studies on the control of vertical posture in persons affected by LBP have quantified the onset of the APAs in the trunk muscles using fast arm movement as an auto-inflicted postural perturbation (Hodges et al. 1999; Liebetrau et al. 2013; Knox et al. 2018; Massé-Alarie et al. 2015). These studies demonstrated a delay in the APAs onset, but no consistency was present when the amount of muscle activation was measured. Overall, the reported delays in the APA onset have been interpreted as an impairment in the feedforward control, which could exacerbate or perpetuate the pain and movement dysfunction.

In this study, we focus on postural control in individuals with low back pain (LBP) who are not in an acute phase of pain. They have been free from pain for at least 10 days but have a confirmed diagnosis of chronic or recurrent low back pain. We decided to recruit free-from-pain individuals to ensure that the pain per se will not influence results but, instead, reflect the underlying postural control mechanisms in the absence of immediate symptoms. We examined anticipatory postural adjustments (APAs) and compensatory postural adjustments (CPAs), analyzing several muscle groups acting around individual joints. To emphasize the control via muscle synergies, we have accepted the theoretical approach that considers the control of the vertical posture as a result of two commands sent in a feedforward manner to the agonist and antagonist muscles defined as the Reciprocal Command (R-Index) and the Coactivation Command (C-Index) (Latash and Zatsiorsky 1993).

Within the framework of the equilibrium point hypothesis (reviewed in Feldman, 1986, 2015; Latash, 2010, 2021), the R-command defines the referent orientation of the body (RO), and the difference between RO and AO leads to the generation of the active moment of force against the moment of force of gravity. The C-command defines a spatial (angular) range, in which opposing muscle groups exhibit non-zero levels of activation. In terms of mechanics, the C-command determines the apparent stiffness of the ankle joint (cf. Latash and Zatsiorsky 1993). Typically, healthy people prefer reciprocal activation patterns, while people with impaired postural control show more agonist and antagonist muscle co-activation, even in relatively simple tasks (Piscitelli et al. 2017, Nardon et al., 2022). The task requested of the participants was to maintain a stable upright posture and release a load held while keeping the arms straight. We compared conditions that included different levels of challenged stabilities and body rotation postures.

We expected to find the same amount of individual muscle activation either for APAs as well as for CPAs for both groups (LBP and Control), while in the muscular synergies, we expect differences in the coordination pattern between groups (Arendt-Nielsen et al. 1996; Radebold et al. 2001; Tsao et al. 2011) (Hypothesis 1). As a consequence, differences when R and C-indexes were considered particularly higher C-index values for APAs in the LBP group. For this latter group, anticipating an incoming perturbation through a co-contraction agonist-antagonist of the trunk muscles might have been functional for a safe strategy when stability was at risk. In other words, we anticipated that LBP individuals to correctly pre-program the self-triggered perturbation while anticipating the incoming perturbation with an increment of their joint stiffness to enhance their body stability. Moreover, since our LBP group was in the absence of pain, we might see the anticipatory strategies diverging from the control group, particularly when the task became more challenging, as when participants performed the task while standing on the most unstable platform. Finally, we hypothesized that CPAs would have remained unchanged. As the appropriate strategy to preserve an upright posture had already been adopted during the anticipatory phase (APAs), there was no further need to apply additional compensations after the perturbation.

4.4 Experimental set-up

4.4.1 Subjects

Fifteen participants with a clinical diagnosis of LBP and fifteen age-matched healthy participants were recruited for the study (8 male mean age 47 ± 11, 7 female mean age 43 ± 14). Participants with LBP were required to be either symptom-free for at least 10 days, in need of an MRI for diagnostic purposes (indicated for common back pain symptoms) or already have an MRI dated no more than 30 days and a clinical assessment considering the status of the general functional system using the WOMAC scale (Wolfe 1999). All participants underwent a rehabilitation program and now appear to have recovered. The side of the spine diagnosed could be either left or right, or no side specifically prevailed. For both groups, participants with a history of neuromotor disorder or musculoskeletal disorder affecting the motor or sensory function of the upper extremity were excluded from enrollment. All the participants provided informed written consent using procedures approved by the University of Verona. The local Ethical Committee approved the study protocol (No. 26.R2/2021) and conformed to the most recent revisions of the Declaration of Helsinki.

4.4.2 Apparatus

Kinematic data were collected using an 8-camera 3-D motion capture system (MX 13, VICON, Oxfordshire, UK). Four passive reflective markers were affixed to the upper arm to assess the proper execution of the task at the right and left acromion and the jugular notch. One was attached to the handle of the setup to verify the correct execution of the task (see Methods).

Electromyographic (EMG) signals were recorded using a wireless low-power signal conditioning electronics device (Zero Wire Aurion, Milan, Italy). EMG electrodes were attached to the external oblique (EO), rectus abdominis (RA), rectus femoris (RF), tibialis anterior (TA), erector spinae longissimus (ES) biceps femoris long head (BF), and soleus (SOL) muscles on both sides of the body. The electrodes were taped to the skin after shaving and cleaning the skin surface with denatured alcohol. Motion capture and EMG data were collected at a sample rate of 100 Hz and 1000 Hz, respectively. All apparatus has been synchronized with MATLAB (R2018a, version 9.4; MathWorks Inc., MA, Natick, USA), including the trigger from the magnet system (see procedures below).

EMG signals were synchronized and monitored using the Vicon system. The start of kinematic and EMG data recording was managed by MATLAB, which also recorded the timing of when the electromagnets were turned off.

4.4.3 Procedures

Participants were instructed to stand on a wooden board measuring in cm 45 x 45 x 1. To ensure consistency in the initial foot position across all trials and conditions, foot placement was marked with a tape on the board surface. The board was classified as either 'balanced' or 'unbalanced.' The 'balanced' board was made such as it maintained full contact with the floor, providing a highly stable and solid base of support for the participants. In contrast, the 'unbalanced' version contacted the floor through a narrow wooden beam, measuring 45 cm in length, 3 cm in width, and 1 cm in height, that was fixed along the midline of the underside of the board. This design created an unstable surface, thereby challenging the participants' postural control in the anteroposterior direction.

At the two extremes of a frame pulley system two identical loads where attached, each representing 3% of the participant's body weight. The two loads hanging one in front and the other behind participant, were suspended from the frame by a pulley mechanism. The two loads were connected to a handle equipped with a trigger mechanism. The handle allowed the participant to control the release of the electromagnets that secured each weight by pressing a button. When the button was pressed, the trigger released one of the two weights, causing an instantaneous loose of balance by inducing a shift of the participant's center of mass. By systematically releasing one weight and keeping the other stationary, the system created a sudden unbalance for participants, forcing them to react and adjust their posture to maintain the stationary position. Henceforth, backward loose of balance identifies the load released in front having as a consequence the participant pushed toward a backward direction, on the contrary, forward loose of balance identifies the load released behind having as a consequence the participant pushed toward the forward direction (see *Figure 1*).

It is important to underline that the time between the pushed of the button and the weight release was instantaneous. This meticulous arrangement made it possible to have total control of the timing of the perturbation, simulating real situations in which sudden weight shifts can occur.

The task required participants to maintain over time their body stability while releasing a load and after the load was released (either in front of or behind the body). Initial posture was kept while adopting three different trunk rotations: standing by facing the body forward, rotating the body 45° to the right, and 45° to the left with respect to the front body line. Participants performed the task by standing on two different platforms: on one stable and on the other unstable.

With their arms outstretched forward, participants were instructed to grasp the handle and push the button to release the weight at their own pace, they were asked then to keep their balance for at least 3 seconds after. They were informed in advance at each trial about the weight that would be released: whether the one on the front or the one on the back.

To verify the correctness of the execution of the task, an experimenter was positioned close to the participant for checking the body alignment and the arms firmness during the weight release, moreover, in a post-processing phase, passive markers recorded by the cameras were used to confirm that any swinging of the arms was present. A trial was discarded if the participant's arm swing exceeded 20 cm. Each participant completed twelve trials for each condition, resulting in a total of 144 trials (3 Rotation (Left, Front, Right), 2 Platform (Stable Unstable), and 2 Direction (Weight Forward (WF), Weight Backward (WB) for weight release). A participant would be excluded from the experiment if after five trials he she was unable to perform the task correctly; however, this scenario never occurred. The order of presentation for direction of body rotation and type of board utilized, was randomized across participants. Fatigue was not a concern, as a two-minute break was permitted after each change in experimental condition. In any case breaks were allowed at any time when requested. For each participant considering preparation and data collection the experiment lasted approximately two hours.

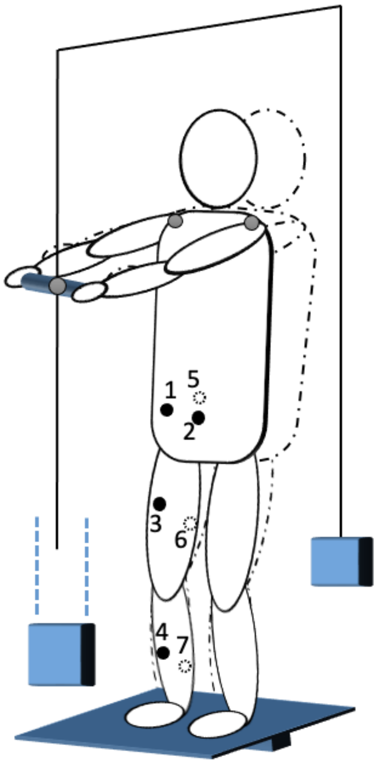

Fig. 4.2: Schematic representation of the task during platform instability when releasing weight forward. The subjects are pushed backward by the weight that remains attached. Gray dots represent passive markers, black dots indicate the anterior muscles recorded

4.5 Data analysis

Data were processed offline with MATLAB software (R2022a, version 9.12). EMG signals were filtered with 5-450 Hz bandpass, fourth-order, zero-phase digital Butterworth filter, then rectified and 50 Hz low pass filter, 4^{th}-order. For each trial, the instant of release of the load was identified by the trigger as t0.

4.5.1 Kinematics

The maximum displacement of the handle marker was calculated in a three-dimensional coordinate system (x, y, z) during the entire APA and CPA windows. For each time point during the window, the displacement was calculated by measuring the distance between the current position of the marker and its previous position. This sequential calculation involved the following steps:

$$D_i = \sqrt{(\,(x_i - x_{(i-1)}\,)^2 \;+\; (y_i - y_{(i-1)}\,)^2 \;+\; (z_i - z_{(i-1)}\,)^2}$$

where is the displacement between the current position (x_i, y_i, z_i) and previous position $x_{(i-1)}, y_{(i-1)}, z_{(i-1)})$. The maximum displacement was identified by finding the largest value among all calculated displacements.

If this displacement exceeded 20 cm, the trial was discarded. The other markers were used for two reasons: to ensure a minimum number of markers to create a rigid figure for recording with the Vicon system, and to provide reference points for reconstructing the tracker in case the handle marker was lost. This situation did not occur throughout the entire execution of the experiment.

4.5.2 Electromyography data

Anticipatory Postural Adjustments (APA) were defined as the integral signal from -200 to +50 ms with respect to t0, subtracting baseline activity. Compensatory Postural Adjustments (CPA) were defined as the integral signal from +50 to +300 ms with respect to t0, subtracting the baseline activity (Cesari et al. 2022).

$$APA = \int_{-200}^{50} EMG - EMGbaseline$$

$$CPA = \int_{50}^{250} EMG - EMGbaseline$$

Each muscle's APA and CPA values were normalized based on the maximum absolute magnitude for each phase across all trials, separately for each participant. This normalization ensured that all indices fell within the –1 to +1 range. (Pascucci et al. 2023) We choose to select fixed time intervals to calculate C-Index and R-Indexes within the framework of the equilibrium-point hypothesis (Feldman 1986, Feldman, 2015).

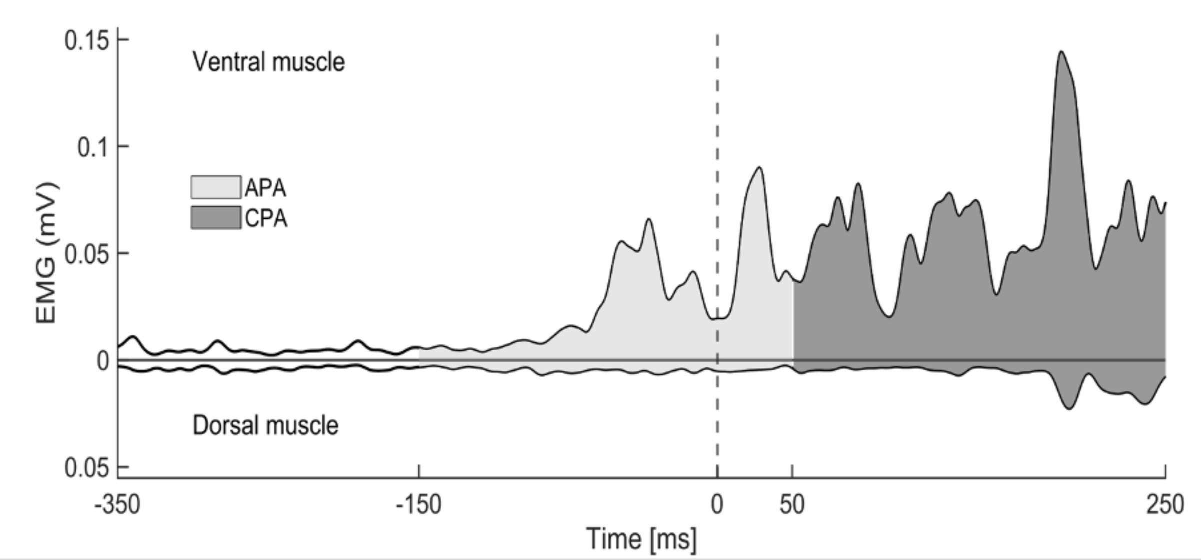

Fig. 4.3: illustrates an example of a filtered muscle pair, highlighting t0 (the instant of release), along with the calculation windows for APA (shaded in light gray) and CPA (shaded in dark gray). To enhance visual clarity and emphasize the antagonist.

The C and R indexes were calculated individually for APA e CPA. R-index calculated the ventral muscle's integrals (EMGv) by subtracting its dorsal antagonist's integral (EMDd). C-index was zero if the integrals of the two agonist and antagonist muscles had different signs; if they had the same sign, C-index is the minimum of the absolute values of the two integrals. (Yamagata et al 2018).

The three muscle pairs considered are TA–SO, RF–BF, and RA–ES. Another muscle pair, EO–ES, was also included. Although they do not have a functional antagonist role, we can define the erector spinae as the muscle that provides sufficient resistance to the external oblique, since both muscles are active during postural adjustments and are anatomically positioned oppositely— with the external oblique located ventrally and the erector spinae located dorsally (Iscoe, 1998).

$$R - index = \int EMGv - \int EMGd$$

$$C - index = \begin{cases} 0 & if \int EMGv \;\; and \int EMGd \;\; have\, different\, sign \\ min\{|EMGv|; |EMGd|\} & if \int EMGv \;\; and \int EMGd \;\; have \;\; sign \end{cases}$$

The R and C indexes for each pair of muscles were normalized with respect to the absolute maximum magnitude for each phase across all experimental trials. The R and C indexes for each pair of muscles were normalized with respect to the absolute maximum magnitude for each phase across all experimental trials. After normalization, the C and R indexes for all muscle pairs of each subject were summed separately, resulting in a single C-index and a single R-index representing the whole body for each individual.

The rationale for summing the C and R indexes across all muscle pairs is to provide a comprehensive, global measure of postural control. Postural adjustments are not limited to the activation of isolated muscle groups; rather, they involve the coordinated effort of multiple muscle pairs working in synergy to maintain stability. By summing the indexes, we capture an overall measure of muscle co-contraction (C-index) and postural orientation (R-index) for the entire body, rather than analyzing each pair independently. This whole-body approach enables a more robust comparison between groups, allowing us to investigate how individuals with low back pain and healthy controls manage postural adjustments at the system level, reflecting the overall strategy of coordination and stability.

4.6 Statistical analysis

The Jamovi software (The jamovi project, 2024, Version 2.3.26.0, https://www.jamovi.org) was used for statistical analysis (Şahin et al., 2019). Data are presented as mean ± standard error, unless otherwise specified.

Data from the release of the weight forward (WF) were analyzed separately from the data from the release of the weight backward (WB), as the primary muscles involved were the ventral and dorsal muscles, respectively.

The analysis considered APAs and CPAs separately, and for each of them, C and R indices. A repeated measures ANOVA was conducted, with the following factors: Group (LBP and Control), Rotation (Left, Front, Right), and Platform (Stable and Unstable). When significant effects were found, pairwise contrasts with Tukey corrections were applied. Normality was tested using the Shapiro-Wilk test, and in cases where the assumption of normality was violated, appropriate non-parametric tests were employed (Bertucco, 2021; Cesari, 2022). In all repeated measures ANOVA, whenever Mauchly's test of sphericity was not satisfied, the Greenhouse–Geisser correction was applied. The level of significance was set at $p < 0.05$.

4.7 Result

4.7.1 Kinematics

Arm swing during perturbation did not exceed 20 cm (LBP: 8.28±3.66 Control: 8.02±2.87). No trials were disqualified for this reason.

4.7.2 APA and CPA

When releasing the weight forward (WF), the body was pushed towards the back, and consequently, all subjects in both groups presented higher activation for ventral than dorsal muscles. Similarly, when the weight was released backward (WB), the body was pushed forward, and consequently, all subjects in both groups exhibited greater activation of the dorsal muscles compared to the ventral muscles. Comparing each muscle between subjects with LBP and controls for both the WF and WB conditions in APA and CPA, we found no statistical differences, except for the left tibialis during the CPA window in the WB condition ($F_{[1,27]}=0.70$, $p=0.015$). Fig.4.4 shows the average values for the APA and CPA groups under both WF and WB conditions. The data were averaged across all conditions and left and right muscles to provide a clearer and more concise representation of the overall muscle behavior. Displaying all individual conditions would have resulted in an excessive number of figures, complicating the interpretation of the general patterns. This averaging was performed solely for the purpose of visualization and did not affect the subsequent statistical analyses, where all conditions and muscles were considered individually.

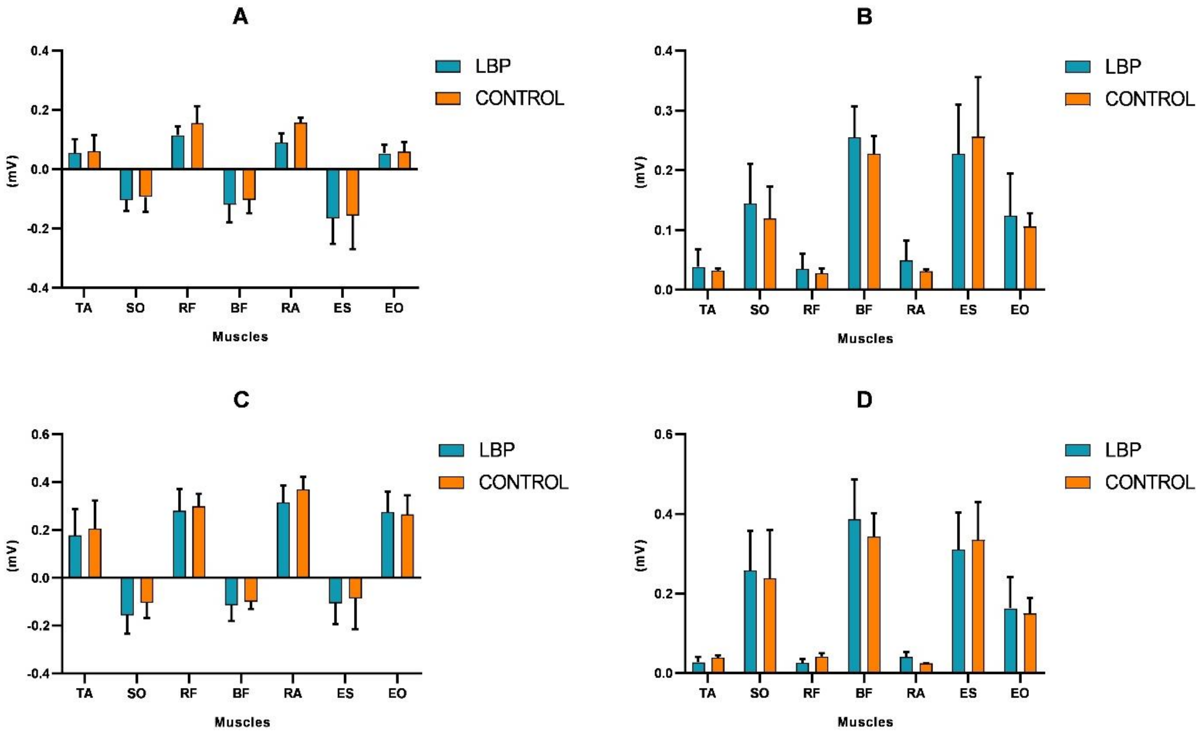

Fig. 4.4: APA and CPA values averaged across all conditions and for both left and right muscles: A) APA in the WF condition, B) APA in the WB condition, C) CPA in the WF condition, D) CPA in the WB condition.

4.7.3 C-index APA

In the WF condition, the LBP group showed a higher C-index than the control group (0.063±0.03 vs. 0.058±0.03, respectively), although this difference was not statistically significant.(Fig. 4.5) Both groups for *direction* factor presented a higher C-index during rightward rotation (left: 0.056±0.03, front: 0.057±0.03, right: 0.069±0.03), with a statistically significant increase ($F_{[2,56]}$=5.303, p=0.008) showing greater values for both the leftward (p=0.017) and front (p=0.033) (Fig. 4.6).

Similarly, in the WB condition, there were no significant differences between the LBP group (0.134±0.05) and the control group (0.128±0.04) (Fig. 4.5). However, the *direction* factor was significant ($F_{[2,56]}$=7.26, p=0.002), showing a lower C-index in the front position compared to leftward and rightward rotations (p=0.012 and p=0.004, respectively).(Fig.4.6) The *Platform* × *Groups* interaction was also significant ($F_{[1,28]}$=11.46, p=0.002), showing similar C-index values for the LBP group in both stable (0.131±0.04) and unstable (0.137±0.05) conditions. In contrast, the control group showed a higher C-index in the unstable condition compared to the stable condition (stable: 0.114±0.03, unstable: 0.142±0.04), with a significant difference between the two conditions (p=0.003) (Fig.4.7).

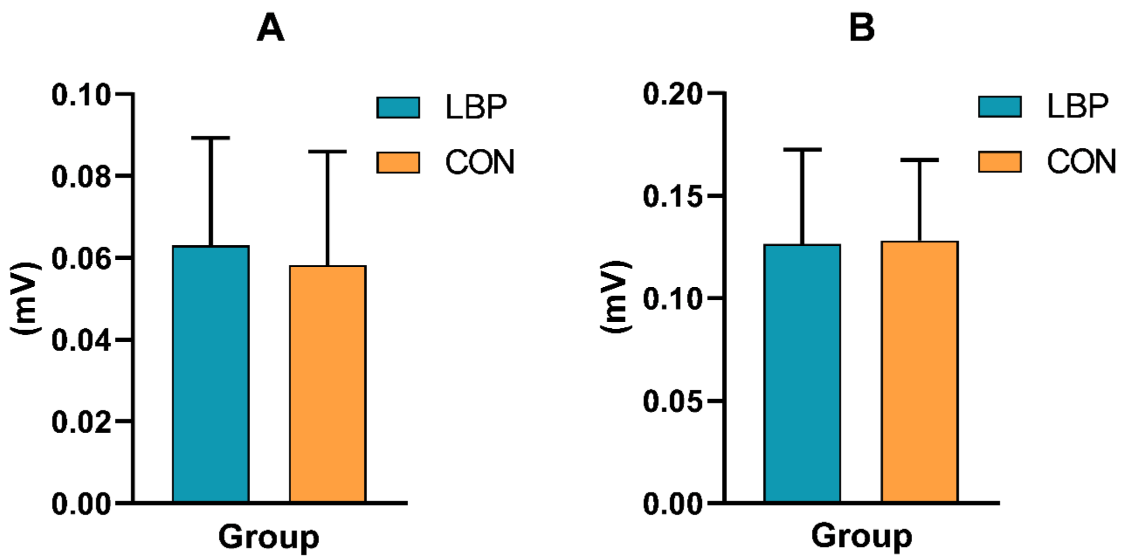

Fig. 4.5: C-index in the APA window: A) During WF condition. B) WB condition. Comparisons between groups low back pain (LBP) and control (CON)

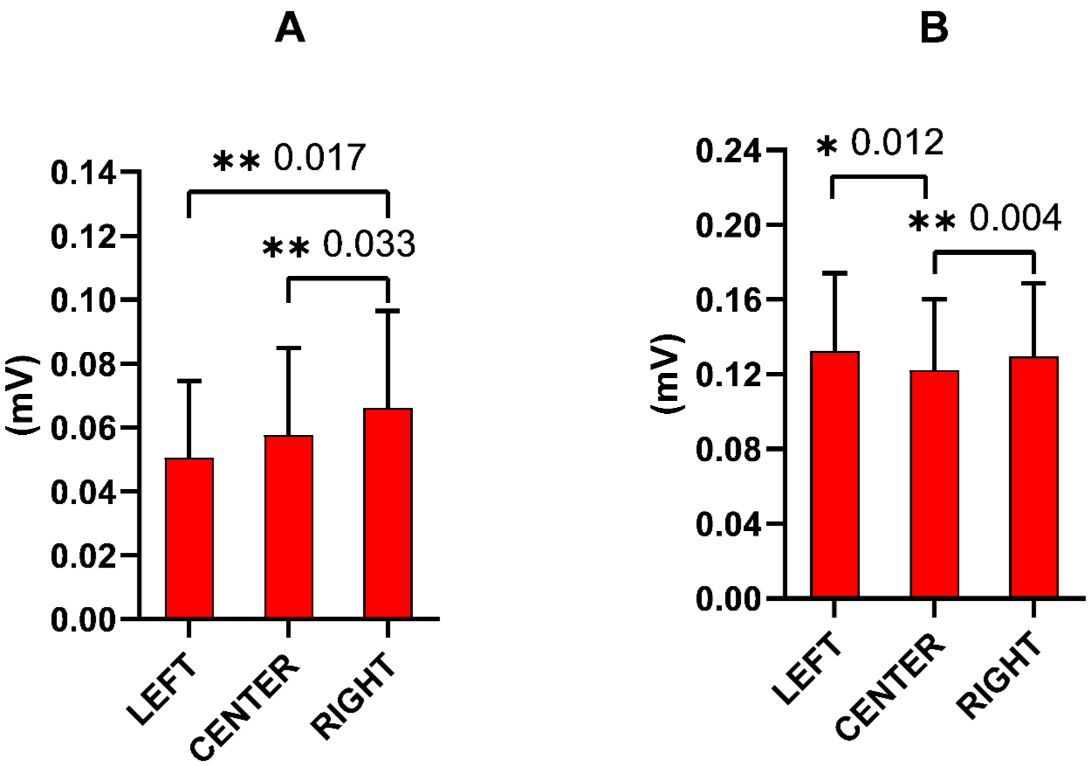

Fig. 4.6: C-index in the APA window: A) Directions During WF condition. B) Directions WB condition.

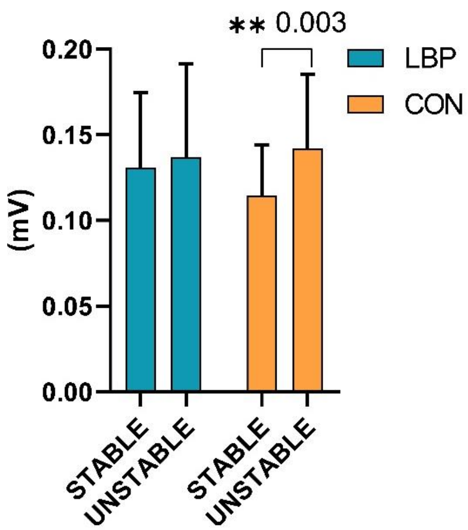

Fig. 4.7: C-index in the APA window Interaction Platform x Group for WB condition.

4.7.4 R-index APA

During the WF condition, the control group showed slightly higher values compared to the experimental group (0.018±0.08 vs. 0.174±0.19, respectively), but this difference was not statistically significant. (Fig. 4.8) The factor *direction* demonstrated a statistically significant difference ($F_{[2,56]}$=3.65, p=0.032), with the highest R-index values occurring during the frontal condition (-0.193±0.12) compared to the left (-0.163±0.10, p=0.044) but not compare to the right conditions (-0.185±0.11). (Fig. 4.9)

In the WB condition, the LBP group had slightly higher R-index values compared to the control group (-0.179±0.13 vs. -0.182±0.09), though this difference was not statistically significant. (Fig. 4.8) However, the factor *direction* showed statistical significance ($F_{[2,56]}$=4.972, p=0.01), with higher R-index values in the leftward rotation (-0.163±0.10) compared to the frontal (-0.193±0.12) and rightward (-0.185±0.11) rotations (p=0.028 and p=0.032, respectively). (Fig. 4.9) Additionally, the *Direction* × *Groups* interaction was significant ($F_{[2,56]}$=7.948, p<0.001), indicating differential effects of rotation direction between the two groups. In the control group, the leftward rotation (-0.162±0.079) produced significantly higher R-index values than the rightward rotation (-0.207±0.25) (p=0.008). Conversely, in the LBP group, the frontal condition (-0.210±0.14) showed significantly lower values compared to the rightward rotation (-0.164±0.11) (p=0.031).(Fig.4.10)

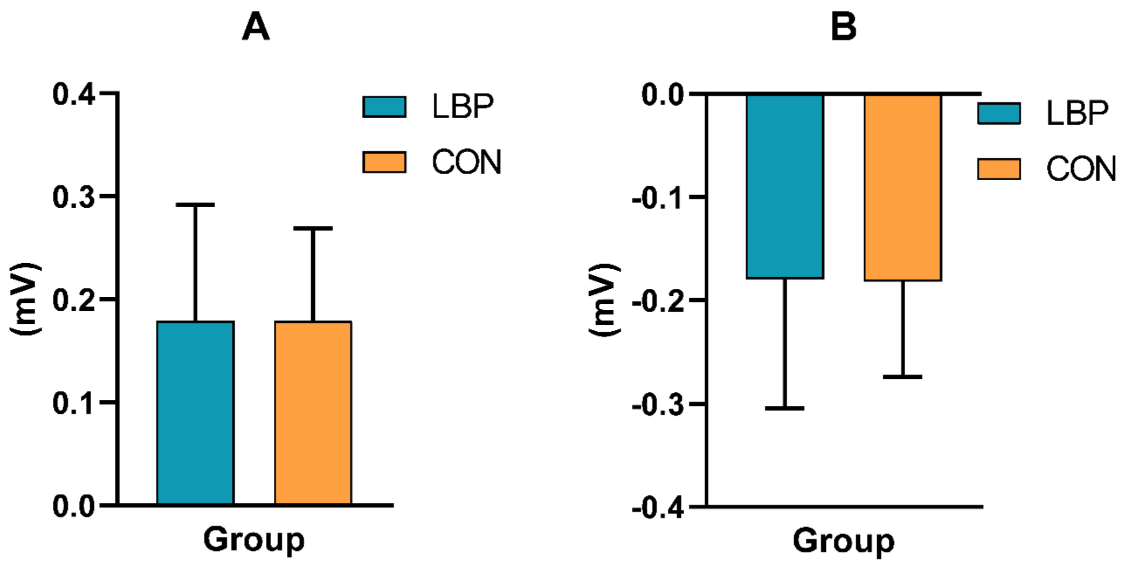

Fig. 4.8: R-index in the APA window: A) During WF condition. B) WB condition.

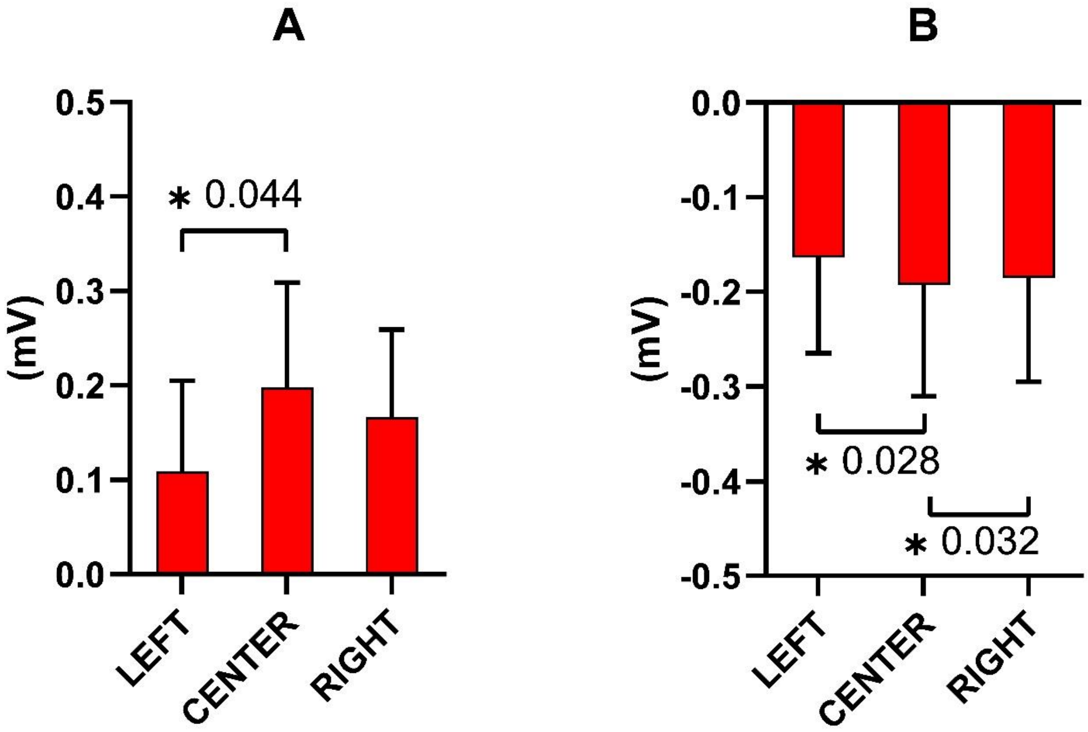

Fig. 4.9: R-index in the APA window: A) Direction during WF condition. B) Direction during WB condition.

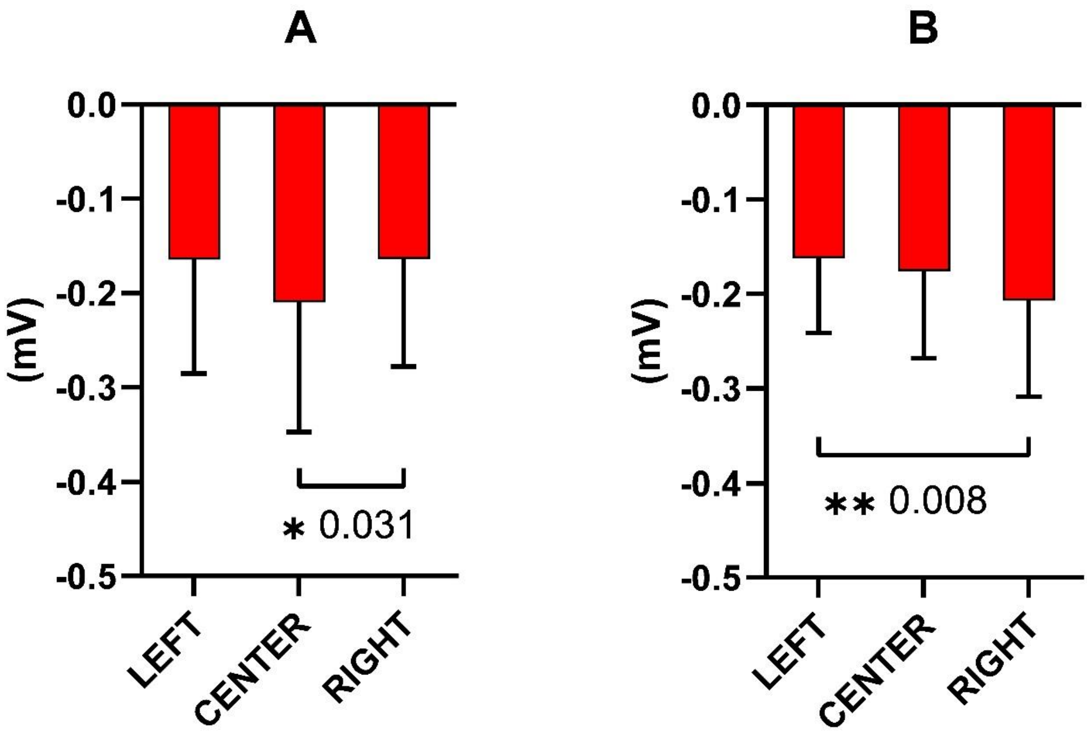

Fig. 4.10: R-Index APA in WB condition - direction X group: A) LBP group, B) Control group.

4.7.5 C-index CPA

After the perturbation under WF conditions, the mean C-index values for the two groups were very similar (LBP: 0.034±0.05, Control group: 0.033±0.04). No significant differences were found between the groups. Only the *direction* factor reached statistical significance ($F_{[2,56]}$=12.59, p<0.001), with rightward rotation (0.053±0.06) being significantly greater than both leftward (0.024±0.03) and frontal (0.023±0.02) conditions (p=0.003 for both comparisons).(Fig.4.11)

A similar pattern was observed under WB conditions. On average, the C-index values were higher in the control group (LBP: 0.133±0.06, Control group: 0.150±0.07), but no significant differences were found between the groups. Only the *direction* factor was statistically significant ($F_{[2,56]}$=7.60, p=0.001), with higher values for rightward rotation (0.158±0.06) compared to the center (0.132±0.06) and leftward (0.135±0.06) conditions (p=0.003 and p=0.008 for the respective comparisons).(Fig. 4.11)

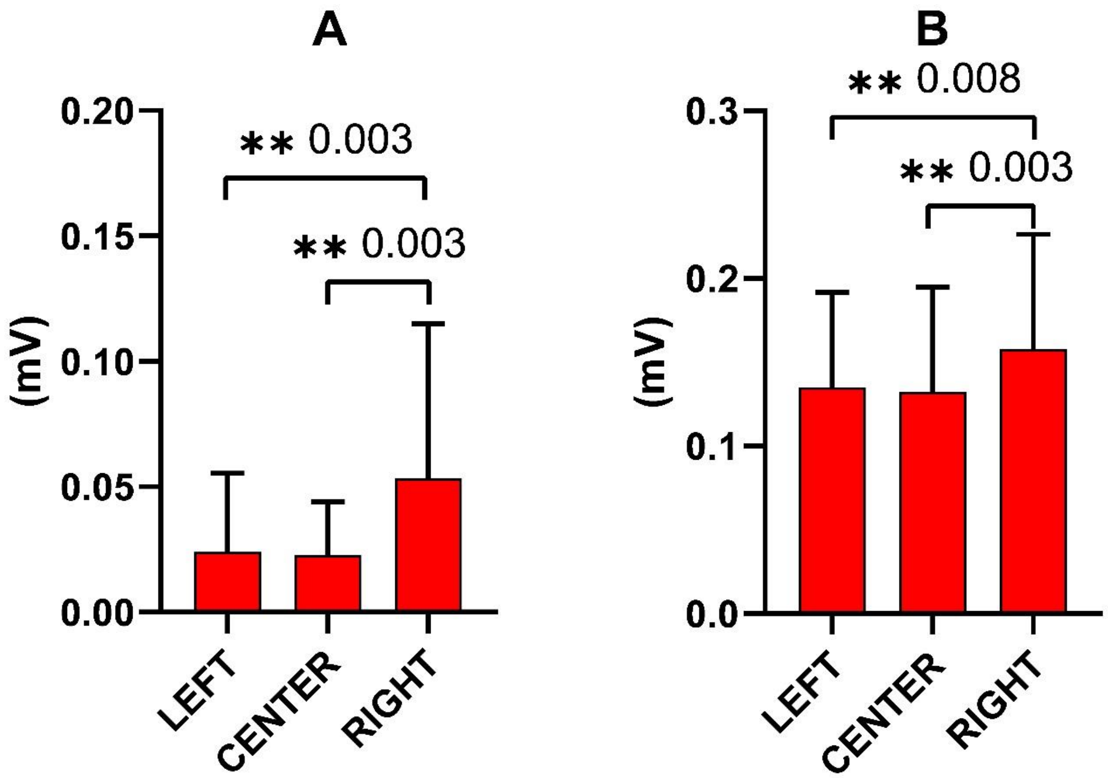

Fig. 4.11: C-index in the CPA window: A) Directions During WF condition. B) Directions WB condition.

4.7.6 R-index CPA

During the WF condition, the control group displayed slightly higher R-index values compared to the experimental group (0.279±0.14 vs. 0.227±0.14, respectively), though this difference was not statistically significant. The factor *direction* had a statistically significant effect ($F_{[2,56]} = 9.001$, $p < 0.001$), with the highest R-index values observed during the frontal condition (0.286 ± 0.13) compared to the left (0.237±0.15) and right (0.236±0.13) conditions (p=0.006 for both comparisons). (Fig. 4.12) Additionally, a significant interaction between *direction* and *group* was found ($F_{[2,56]}=3.850$, p=0.027), indicating differences in central values relative to some rotations within each group. In the control group, the frontal condition (0.310±0.14) was significantly greater than the leftward rotation (0.244±0.12) (p=0.039). In the LBP group, the central condition (0.262±0.13) was significantly greater than the rightward rotation (0.192±0.14) (p=0.020).

In the WB condition, the R-index levels of the LBP group were slightly higher than those of the control group, although the difference did not reach statistical significance (-0.207±0.23 vs -0.214±0.100, respectively). A significant effect of platform type was observed ($F_{[1,28]}=31.850$, $p<0.001$), with higher values recorded for the unstable platform compared to the stable platform (-0.236±0.27 vs -0.185±0.1). The *direction* factor also yielded a significant effect ($F_{[2,56]}=15.812$, $p<0.001$), showing lower values for the central condition (-0.243±0.11) compared to both leftward (-0.199±0.11) and rightward (-0.190±0.1) rotations ($p<0.001$ for both comparisons). (Fig. 4.12) Additionally, a significant interaction between *direction* and *group* was found ($F_{[2,56]}=3.230$, $p<0.001$), indicating differential effects of rotation direction within each group. In the control group, the central condition (-0.24±0.11) showed significantly lower values compared to leftward rotation (-0.194±0.10) ($p=0.05$). Similarly, in the LBP group, the central condition (-0.025±0.15) demonstrated significantly lower values than rightward rotation (-0.172±0.11) ($p<0.01$).(Fig.4.13)

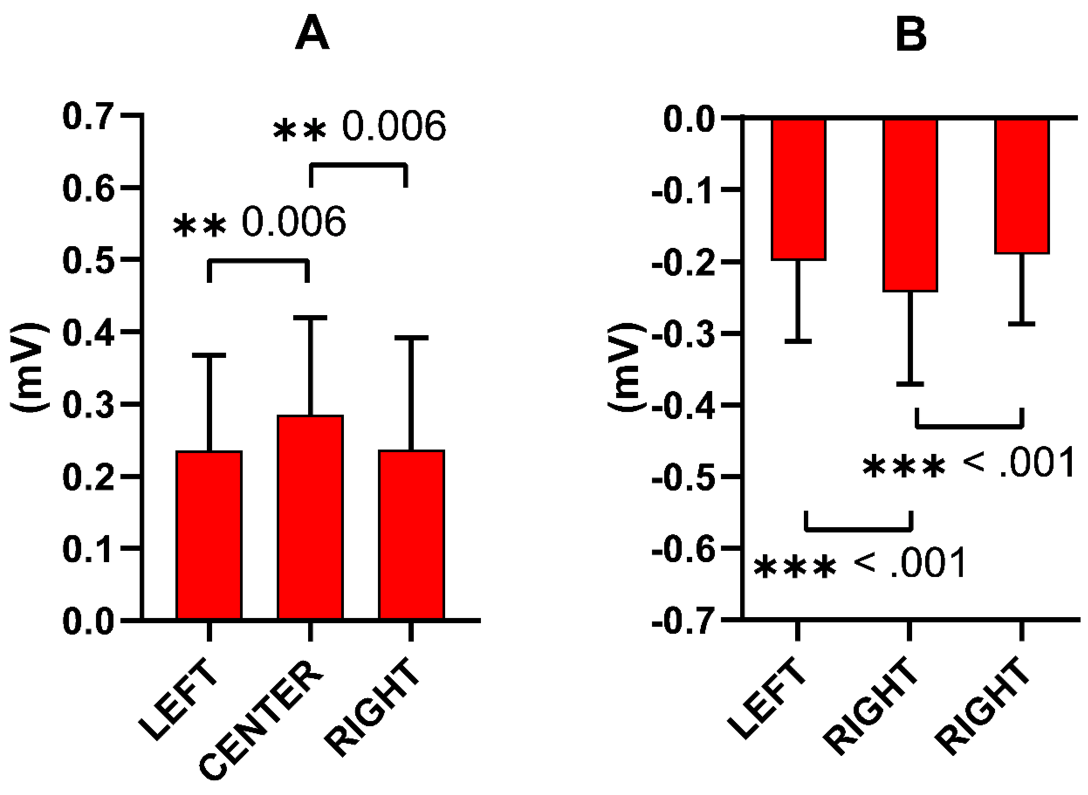

Fig. 4.12: R-index in the CPA window: A) Directions During WF condition. B) Directions WB condition.

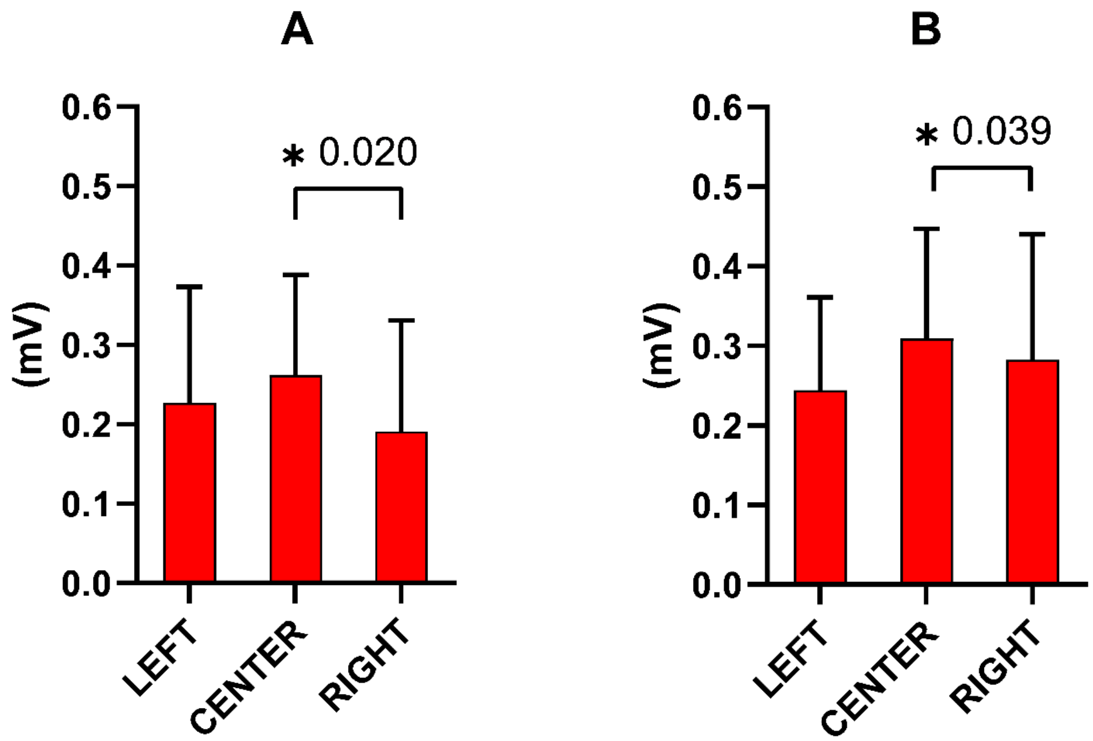

Fig. 4.13: R-index in the CPA window, directions X group - WF condition: A) LBP group, B) Control group

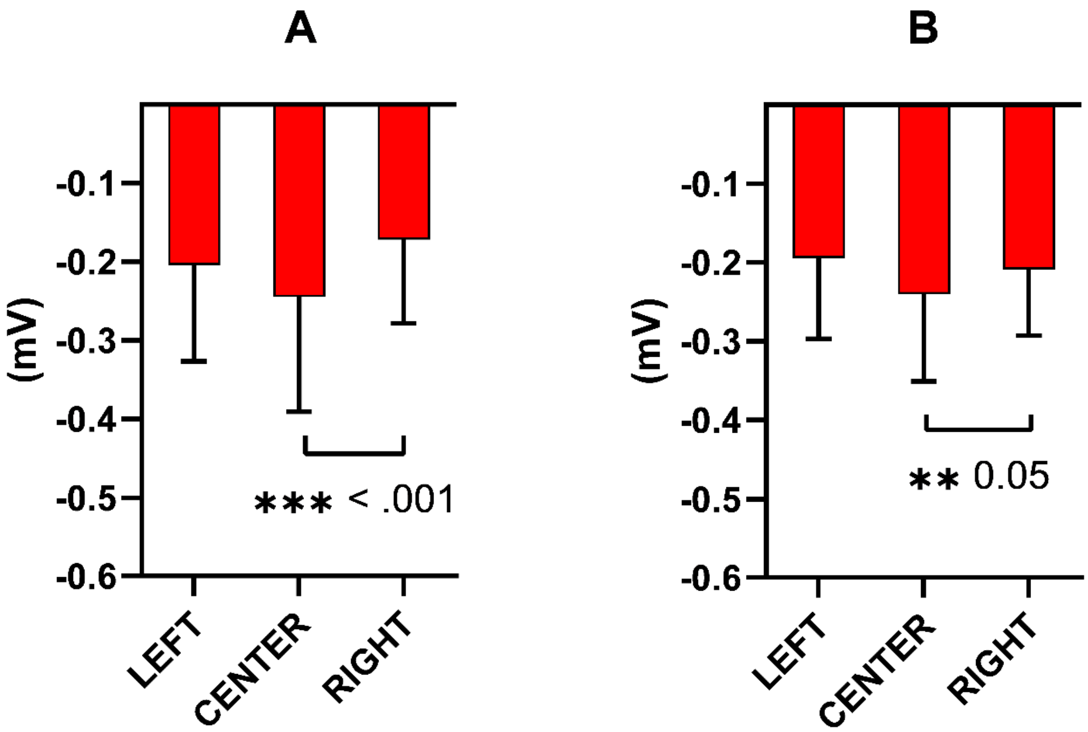

Fig. 4.14: R-index in the CPA window, directions X group - WB condition: A) LBP group, B) Control group

4.8 Discussion

The main aim of this research was to reveal the presence of adaptive patterns of action that patients may develop in response to Low Back Pain (LBP). Although LBP may initially be considered an acute and temporary event, a chronic evolution may induce altered movements, either as adaptive strategies to protect the spine or as maladaptive strategies that perpetuate the dysfunction (O'Sullivan, 2005). We were interested to know whether the above-mentioned patterns of action will remain present over time even after the pain has disappeared and whether it will be detected at the level of action planning, as indicated by APAs measures, and or during the actual action, as indicated by CPAs measures. Here, we show that LBP individuals, in the absence of pain, act against perturbations that destabilize their postural balance by applying similar muscle activations as healthy individuals, while they presented dissimilar anticipatory muscle activations compared to healthy individuals, indicating the development and then the maintenance of different central commands necessary for anticipating an incoming postural disturbance. This study had the merit of exploring these anticipatory and compensatory postural responses considering several muscles involved in the maintenance of the upright posture, rather than limiting the analysis to a single muscle. Following we will discuss the results in more detail.

At first, it is important to recall that the task proposed included two conditions of weight release: forward and backward. When releasing the weight forward (WF), the body was pushed towards the back, and consequently, we were expecting to find higher activation for ventral muscles. When releasing the weight backward (WB) the body was pushed forward, and consequently, we were expecting higher activation for the dorsal muscles.

Comparing the groups, considering an overall analysis of APAs and CPAs, we found nonsignificant results, indicating that both groups expressed the same amount of muscle activation in preparation (APAs) as well as during the execution (CPAs) of the action. Moreover, both groups activated principally the ventral muscles during the release of the weight forward and the dorsal muscles during the release of the weight backward. We expected to find this result as the recruited patients had not felt pain for several days, and therefore, the physical exercise required for the motor task could be performed normally.

We expected instead to find differences in the indices for the reciprocal command (R-index) and the coactivation command (C-index). In fact, we found differences between the groups regarding the level of co-contraction (C-index), but interestingly, only during the preparation of the action (APAs) did the group LBP present higher muscle activity than the control group while during action execution (CPA) none difference between groups was present.

The co-contraction strategy has been observed in various pathologies involving impaired postural stability, such as Parkinson's disease and multiple sclerosis. For instance, in individuals with Parkinson’s disease, an increased use of muscle co-contraction as a strategy to improve postural control and reduce the risk of falls has been documented (Ricotta & Latash, 2021). Likewise, in patients with multiple sclerosis, changes in muscle activation strategies, including increased co-contraction, have been observed to compensate for instability and improve motor control (Molina-Rueda et al., 2023). These findings suggest that muscle co-contraction may represent a common response in disorders affecting postural stability. The novelty found in our research is that we were able to detect the presence of this strategy in the anticipatory part of the action, in other words, in action preparation and not in action execution, since our LBP individuals were diagnosed as cured as they had no longer felt pain for several days.

Interestingly these co-contraction strategies are mainly observed in the LBP group during the APAs but in the WB condition, as the dorsal muscles are more involved in maintaining stability. In the WB condition, muscles such as the tibialis anterior, paraspinal muscles, and glutes are more consistently activated, as they are crucial for supporting the spine and preventing a postural collapse in individuals with LBP (Ghamkhar & Kahlaee, 2019; Seyed & Asghar, 2010). Specifically, the dorsal muscles play a key role during the preparation phase of the action to sustain an erect posture and maintain spinal stability during perturbations.

Interestingly, the same co-contraction strategy is applied by individuals with LBP regardless of the task conditions' level of stability: the stable or unstable platforms; by contrast, healthy individuals modulate muscle activation based on the task difficulty. Studies in healthy subjects have shown that, under conditions of postural instability, such as with an unstable platform, muscle activation tends to be more dynamically modulated according to task difficulty (Smeets & Schalley, 2017). On the other hand, individuals with LBP seem to apply a more rigid and standard strategy, involving, in general, a greater muscle co-contraction.

Healthy individuals showed a significant increase in the C-index when moving from a stable to an unstable platform, indicating their ability to evaluate the amount of incoming perturbation, and based on that, they prepare their muscle co-contraction adequately in response to the expected amount of instability.

LBP individuals showed ability as well to evaluate the amount of incoming perturbation, but for them, the strategy to apply was more conservative than the one used by the control group, and they preferred to apply a greater and stable amount of muscle co-contraction independently by the task conditions: stable or nonstable platform.

Again, as mentioned above, this conservative strategy has been shown on multiple occasions in the literature, especially in musculoskeletal and neurological disorders, but importantly, this strategy has been observed particularly during action execution. For example, muscle co-contraction has been described as a protective response in chronic low back pain (Schinkel-Ivy et al., 2013), but also in other pathologies such as stroke, where patients often use co-contraction to improve postural stability during motor recovery (Souissi et al., 2018). Moreover, it has been observed in patients with knee instability, where co-contraction helps reduce the risk of injuries and improve joint stability (Smith et al., 2019). Finally, in neurodegenerative conditions such as dystonia, co-contraction has been used to counteract involuntary muscle contractions and enhance postural control (Malfait & Sanger, 2007).

Here LBP group exhibited during APAs similar C-index values for both stable and unstable platforms, possibly indicating a reduced sensitivity or adaptability to changes in postural demands. In other words, while the control group adjusted their co-contraction strategy by increasing it as the task became more challenging, the LBP group failed to show a similar adaptive response, suggesting potential deficits in their postural control mechanisms. The C-index values for the LBP group were slightly higher than those of the control group during the stable condition and slightly lower during the unstable condition, suggesting that individuals with LBP may adopt a less flexible postural control strategy. This could indicate an over-reliance on co-contraction during simpler, stable tasks, potentially as a protective mechanism. However, when faced with increased postural demands, such as during unstable conditions, their ability to further adjust or increase muscle co-contraction appears to be limited. This lack of adaptability could contribute to an overall less efficient postural control system in individuals with LBP, leaving them more vulnerable to instability or future episodes of pain. In the CPA phase, after the perturbation, C-index values remained comparable between the two groups, though a consistent trend was noted where rightward rotation elicited the highest C-index values. This may suggest a general biomechanical preference or greater muscular recruitment in managing perturbations directed towards the right side, regardless of group. The lack of significant differences between the LBP and control groups indicates that individuals with LBP maintain a similar ability to employ co-contraction strategies as controls. This preference for rightward co-contraction could be due to asymmetric motor patterns or habitual postural responses developed over time. However, these findings raise the question of whether such asymmetrical strategies could be due to external factors, such as a slight misalignment in the setup relative to the participants' natural rotation. Nevertheless, since this phenomenon was observed in both the LBP and control groups, it seems more likely that these are natural asymmetries rather than setup-related issues. Such natural asymmetries might contribute to long-term postural imbalances or an over-reliance on certain muscle groups. To sum up, the control group appeared to adapt more to platform instability by increasing preparatory co-contraction, while the LBP group’s responses were less sensitive to changes in stability, potentially indicating altered motor control strategies. In other words, although these individuals correctly anticipate the self-triggered perturbation, we expect them to show increased apparent joint stiffness, potentially linked to underlying fragilities. Despite the absence of pain, these latent issues may be difficult to detect but could provide valuable insights for physiatrists and physiotherapists. Identifying these subtle postural control changes could guide specific training and maintenance interventions to prevent further episodes or mitigate the risk of recurrence.

Despite the absence of pain, individuals with LBP nevertheless seem to manifest a certain fear of relapse, which could be linked to a learned neurophysiological response modulated by cognitive processes. Indeed, these individuals may develop a kind of 'brain mapping' that influences their motor behaviour even in the absence of overt painful stimuli. This neural mapping, linked to pain memory, could generate greater postural rigidity or excessive response to perturbations that, while not causing pain, are perceived as potentially dangerous. In practice, the fear of a new painful phase could alter their perception of movement and negatively influence postural control (REF).

Our results indicate that individuals with low back pain (LBP), when they are not subjected to movement and are observed in a quiet situation, do not manifest overt relevant physiological changes. In the absence of motor activity, these individuals may appear healthy, showing no signs of impaired motor behaviour. However, changes in postural control become evident when subjects are exposed to perturbations or postural challenges that require dynamic motor adaptations. This suggests that although they do not show signs of pain or dysfunction at rest, their ability to adapt to situations involving postural changes or instability may be impaired.

To date, the treatment of low back pain (LBP) has mainly focused on action execution and not on action preparation, with muscle re-education exercises focused on the painful area and the use of drugs (such as NSAIDs) to control acute pain. However, an approach that also considers in combination the anticipatory and executory movement synergies might be relevant. In this sense, APA, CPA, and the R and C indices could serve as sensitive indicators of the central component of postural control. These parameters could, in fact, reveal early signs of alterations in motor control mechanisms, which could lead to a progression of the pathology. The integration of these tools in the analysis and treatment of LBP could be useful to prevent the onset of pain and improve long-term management, promoting a more comprehensive approach focused on the centrality of motor control and cognitive responses of patients.

Interestingly, for the R-index both in the APA and CPA phases, no significant differences between the groups were found. Moreover, the R-index never detected differences between he stable and unstable conditions. R-index was systematically letting merge for both APAs and CPAs differences among directions Front Right and Left. In general, the highest R-index values were observed mostly during the frontal rotation condition, suggesting that both groups expected and then required greater muscular adjustments when facing forward, a posture that might pose additional postural challenges compared to lateral rotations.

This could suggest that both groups adopt different strategies depending on the direction of the post-perturbation rotations, influenced by factors such as personal motor habits, preferences, or confidence levels in handling perturbations.

4.9 Conclusion

The main objective of this paper is to highlight changes in motor strategies in subjects with chronic and/or latent low back pain, which could pave the way for future research on motor control reeducation and different rehabilitation strategies.

We wanted to investigate any discrepancies present in the results of previous research. Knowing how to modulate motor responses in health-acceptable ranges, based on the difficulties and disturbances presented to us in daily life, is the key to primary prevention of the condition.

This study highlights the potential of using specific tasks involving trunk rotations to uncover subtle differences in postural control strategies, particularly through the analysis of C-index and R-index values. Developing such investigative tasks can significantly enhance our understanding of the underlying mechanisms of postural control in conditions like low back pain (LBP). By revealing how the body compensates for disruptions in kinetic chains, these tasks provide valuable insights into the motor adaptations associated with postural pathologies.

Future research should further explore the factors contributing to these differences, including the role of muscle coordination and the impact of chronic pain on motor planning. Additionally, investigating specific rehabilitation strategies aimed at improving postural control in individuals with LBP could yield important insights for clinical practice and enhance outcomes for this population. Ultimately, this knowledge can inform the design of more effective rehabilitation programs tailored to address the specific compensatory patterns and functional deficits observed in individuals with postural impairments.

5 Three levels of neural control contributing to performance-stabilizing synergies in multi-finger tasks.

5.1 Project #2 presentation

The human hand as a joint is uniquely designed with its many degrees of freedom to perform a wide variety of motor actions. Just think that it is a structure comprising 14 phalangeal bones in the fingers, 5 metacarpal bones in the palm and 8 carpal bones in the wrist, and approximately 36 muscles that interact to modulate movement with a dense network of tendons. Among the main muscles recorded in the hand are the flexor digitorum superficialis (FDS), which through its tendons flexes the proximal interphalangeal joint of the fingers; the flexor digitorum profundus (FDP), which flexes the distal phalanges; the extensor digitorum communis (EDC), which sends tendons to the middle and distal phalanges, allowing extension of the fingers (Schwarz & Taylor 1955).

At the neurological level, the human hand benefits from advanced cortical control mechanisms. The primary motor cortex and corticospinal tract are essential for its functioning. Individual neurons within the corticospinal tract exert excitatory and inhibitory effects on the alpha motor neurons of the hand muscles on the contralateral side of the body. The corticospinal tract's direct input to the alpha motor neurons allows fine control of hand movements. Damage to the primary motor cortex can result in muscle weakness and impaired independent finger movement. Several conditions, such as Amyotrophic Lateral Sclerosis (ALS) (Dutta et al., 2011; Shefner et al., 1992), strokes affecting the motor cortex (Balasubramanian, 2015), or head trauma causing direct damage to the motor cortex or its connections (Carron et al., 2016; Blennow et al., 2016), are associated with such deficits.

To gain detailed insights into the functioning of motor units, we employed EMG sensors, specifically the Trigno Galileo sensor (Delsys Inc., Natick, MA, USA). These sensors consist of four closely placed EMG electrodes. Motor units, comprising a motor neuron and its innervated muscle fibers, generate a synchronized wave of electrical signals when activated by an action potential. These electrical signals produce a current detectable by surface EMG. The amplitude of the EMG signal increases when multiple motor units are engaged, reflecting muscle activity levels. However, interpreting these signals is challenging due to noise from overlapping signals, a phenomenon known as "amplitude cancellation," which complicates precise readings.

Surface EMG arrays, which record signals from multiple muscle positions through a network of electrodes, provide valuable data on motor unit activity. These recordings can identify motor unit discharge times during low-force contractions, remodelling of motor unit territories in neurological disorders, localization of neuromuscular junctions, and estimation of muscle fiber conduction velocity. Despite these capabilities, current technology limits high-density surface EMG applications to detecting surface motor unit activity during isometric contractions at low force levels. This indirect measurement method has limitations, including potential misidentification or omission of motor unit action potentials. Wearable electrodes only capture information on motor units near the electrode tip.

The concept of "average innervation number" highlights the variability in motor unit composition across muscles. For instance, small muscles, such as those in the eyes or ears, have an innervation number between 5 and 10 fibers per motor neuron, while larger muscles, such as the medial gastrocnemius, can have around 1,750 fibers. This distribution follows an exponential pattern, with numerous motor units producing small forces and fewer units capable of generating high forces. The fibers of a motor unit are often confined to specific sub-volumes within a muscle rather than being uniformly distributed (Harris et al., 2005). In some muscles, motor units are organized into distinct compartments, creating a regional functional structure with specific physiological roles (Butler et al., 2005). This anatomical organization significantly impacts the activation strategies of the central nervous system, which must account for such complexity to coordinate movement effectively.

5.2 Early Studies

Within the theory of referent spatial coordinates (RC), as reviewed in Feldman (2015), several research studies (Ambike et al., 2016a, b; Reschechtko and Latash, 2017) have documented significant variations in RC and kkk when a healthy person attempts to produce the same level of force multiple times by pressing with a finger under isometric conditions. These values exhibited significant co-variation across trials, suggesting that both RC and kkk can be considered mechanical proxies for neural commands.

In 2021, Madarshahian and colleagues explored a different aspect of motor control: determining whether motor unit-based synergies exist within a muscle. Using the concept of synergistic control and the theoretical framework of the uncontrolled manifold hypothesis, they demonstrated that motor units (MUs) within a muscle, specifically the flexor digitorum superficialis (FDS), organize into stable groups called "MU-modes." These MU-modes contribute to stabilizing the force produced during finger exercises.

Subsequently, Madarshahian et al. (2022) expanded their investigation by studying the synergistic relationship between the motor units of an agonist muscle and its antagonist. In a task like the previous one, they recorded the activity of the flexor digitorum superficialis (FDS) and the extensor digitorum communis (EDC). Using the same analytical techniques, they examined whether stable synergies existed within each muscle individually and whether such synergies were present when both muscles were analyzed together as a single functional system.

For the first time, this study aims to integrate and compare three levels of analysis within the same task to provide a more comprehensive understanding of motor synergies. Specifically, the analysis will include: synergies at the level of Referent Coordinates (RC), synergies between the agonist (FDS) and antagonist (EDC) muscles, analyzed both individually and as a unified functional system.

This integrated analysis is particularly relevant in the context of pathological conditions such as cerebellar disorders or basal ganglia dysfunction. In such cases, synergies are impaired, leading to less precise and coordinated control of finger movements. For instance, a patient with Parkinson's disease may struggle to properly coordinate the forces between fingers, making it difficult to grasp objects securely and stably.

5.3 Abstract

We tested a hypothesis on force-stabilizing synergies during four-finger accurate force production at three levels: (1) The level of the reciprocal and coactivation commands, estimated as the referent coordinate and apparent stiffness of all four fingers combined; (2) The level of individual finger forces; and (3) The level of firing of individual motor units (MU). Young, healthy participants performed accurate four-finger force produc- tion at a comfortable, non-fatiguing level under visual feedback on the total force magnitude. Mechanical reflections of the reciprocal and coactivation commands were estimated using small, smooth finger perturbations applied by the “inverse piano” device. Firing frequencies of motor units in the flexor digitorum superficialis (FDS) and extensor digitorum communis (EDC) were estimated using surface recording. Principal component analysis was used to identify robust MU groups (MU-modes) with parallel changes in the firing frequency. The framework of the uncontrolled

manifold hypothesis was used to compute synergy indices in the spaces of referent coordinate and apparent stiffness, finger forces, and MU-mode magnitudes. Force-stabilizing synergies were seen at all three levels. They were present in the MU-mode spaces defined for MUs in FDS, in EDC, and pooled over both muscles. No effects of hand dominance were seen. The synergy indices defined at different levels of analysis showed no correlations across the participants. The findings are interpreted within the theory of control with spatial referent coordinates for the effectors. We conclude that force stabilization gets contributions from three levels of neural control, likely associated with cortical, subcortical, and spinal circuitry.

5.4 Introduction

The concept of synergies in the field of motor control was developed by Nikolai Bernstein (1947; translation in Latash 2020a) who introduced a hierarchical scheme of movement control with the second level termed "The level of synergies and patterns or the thalamo-pallidar level". According to Bernstein, this level of control was responsible for two important functions. First, it united the numerous muscles into a relatively small number of groups. Second, it ensured dynamical stability of salient performance variables. The first feature of synergies has been explored by many groups using various matrix factorization methods applied to correlation or covariation matrices (reviewed in Ting and McKay, 2007; Tresch and Jarc, 2009; Latash 2020b). The second feature had been mostly overlooked until the introduction of the uncontrolled manifold (UCM) hypothesis (Scholz and Schöner, 1999), which offered a toolbox to estimate dynamical stability of salient performance variables produced by multiple elements, which generate an abundant set of elemental variables (cf. Gelfand and Latash, 1998; Latash, 2012). The UCM hypothesis assumes that, if a salient performance variable is stabilized by covaried contributions of elemental variables, inter-trial variance in the space of elemental variables is primarily constrained to a subspace where the salient variable does not change (UCM for that variable). As a result, in a linear approximation, inter-trial variance within the UCM is expected to be larger than in the space orthogonal to the UCM: $V_{UCM} > V_{ORT}$.

Many of the early studies used the UCM framework to estimate synergies in spaces of elemental variables representing activation levels of muscle groups, joint rotations, digit forces, etc. (reviewed in Latash et al., 2007; Latash, 2021). Recently, this method has been developed in two directions. First, the concept of *intra-muscle synergies* has been introduced (Madarshahian et al., 2021; reviewed in Latash et al., 2023). Within this concept, motor units (MUs) within a muscle form robust groups (MU-modes) and these groups are recruited with gains that co-vary to stabilize muscle action, e.g., force is isometric conditions. Such intra-muscle synergies have been assumed to reflect action of spinal circuits including reflex feedback loops, recurrent inhibition, etc. Second, the concept of synergies has been used within the theory of motor control with spatial referent coordinates, RC (reviewed in Feldman, 2015), which is a development of the equilibrium-point hypothesis (Feldman, 1966, 1986). Within this theory, any effector acting along a spatial coordinate *X* is viewed as controlled by two opposing muscle groups, agonists and antagonists (Fig. 1A). Involvement of each muscle group is controlled with a single neural variable corresponding to the threshold of stretch reflex, λ_{AG} and λ_{ANT}, for the agonist and antagonist, respectively. Equivalently, the control of the effector can be described with two basic commands, the reciprocal command (R-command), which defines the coordinate where the resultant force of the opposing muscle groups is zero (shown in Fig. 1A as *RC* for the effector), and the coactivation command (C-command, also addressed as "C-zone", Feldman, 2015), which is defined as the spatial range where both agonist and antagonist muscles are active simultaneously. As in earlier studies (Ambike et al., 2016a,b; Reschechtko and Latash, 2017), we assume that changing the C-command leads to monotonic changes in the slope of the force coordinate characteristic, i.e., its apparent stiffness (*k* in Fig. 5.1A, cf. Latash and Zatsiorsky, 1993) and that, under isometric conditions, *k* values reflect changes in the C-command. Both *RC* and *k* are viewed as mechanical proxies of the neural commands. A series of studies have documented broadly varying RC and k values when a healthy person tries to produce the same force level multiple times by pressing with a finger in isometric conditions. These values co-varied across trials to be constrained primarily to the hyperbolic UCM for the required force magnitude (Ambike et al., 2016a; Reschechtko and Latash, 2017).

In this study, for the first time, we applied three methods of analysis reflecting different levels of control to the task of accurate multi-finger total force (F_{TOT}) production. These levels are illustrated schematically in Fig. 5.1B. At the highest task level, F_{TOT} is viewed as produced by co-varying adjustments of the *RC* and *k* to the hand. At the next level, F_{TOT} is viewed as being produced by co-varying forces by the individual fingers, index (I), middle (M), ring (R), and little (L). At the lowest level, F_{TOT} is viewed as produced by co-varying MU-modes within the extrinsic flexor and extensor muscles. The top two levels are likely to involve brain circuitry. In particular, multi-finger synergies are significantly impaired in patients with cerebellar and/or basal ganglia disorders (reviewed in Latash and Huang, 2015). It remains unknown what structures are involved in {*RC*; *k*}-based synergies. As mentioned earlier, MU-mode synergies are likely organized at the spinal level. They stabilize reflex-induced force changes, which are not stabilized at the level of sharing F_{TOT} across the four fingers (Madarshahian et al., 2022). Our first hypothesis was that all three methods would demonstrate F_{TOT}-stabilizing synergies during accurate constant force production. Further, we explored relations among the synergy indices computed using the three methods. Since the methods potentially reflect different neural circuits contributing to F_{TOT} stabilization, we expected their independence (Hypothesis 2). At the intra-muscle level of analysis, we also explored F_{TOT}-stabilizing synergies within spaces of MU-modes defined for the agonist (flexor digitorum superficialis, FDS), for the antagonist (extensor digitorum communis, EDC), and for MUs pooled over both muscles. An earlier study produced rather unexpected results, showing strong synergies by co-varied MU-modes within each muscle but not across the two muscles, although clearly, at the level of mechanics, F_{TOT} is the resultant of the opposing actions of the flexor and extensor muscles. Another exploration was related to possible effects of hand dominance, which were reported in studies of multi-finger synergies, but not $\{RC; k\}$-based and not intra-muscle synergies (Park et al., 2012; de Freitas et al., 2019; Ambike et al., 2016a,b; Madarshahian and Latash, 2022b). To test the main hypothesis and perform the mentioned exploratory analysis, we asked a group of healthy, young participants to perform steady force production tasks under continuous visual feedback on the force magnitude while pressing with four fingers of a hand on individual force sensors. The $\{RC; k\}$-based synergies were estimated using the "inverse piano" method (Martin et al., 2011; Ambike et al., 2015). Multi-finger synergies were estimated as in earlier studies (Latash et al., 2001; Scholz et al., 2002). MU-modes and synergies were estimated in spaces of MU firing frequencies recorded with surface EMG recording (as in Madarshahian et al., 2021). Both hands were tested to explore effects of dominance.

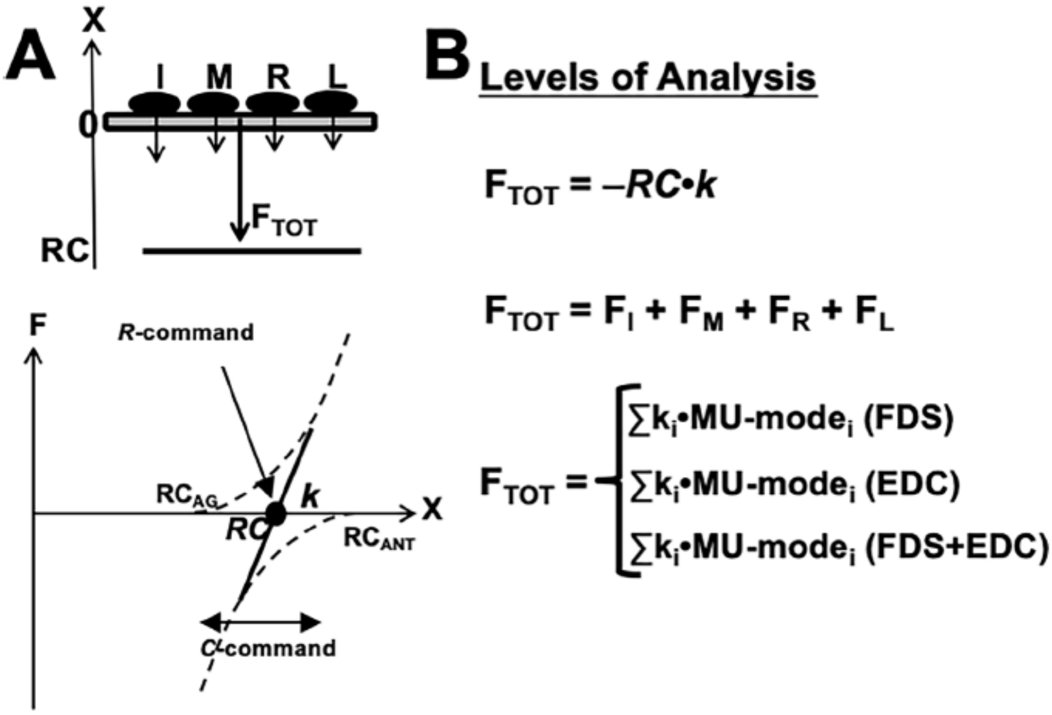

Fig. 5.1: A: The top panel shows the production of total force (F_{TOT}) with four fingers (I – index, M – middle, R – ring, and L – little) as a result of specifying a referent coordinate (RC) for the hand under the surface of contact. The bottom panel shows schematically the two basic commands to the agonist and antagonist muscles (RC_{AG} and RC_{ANT}), which lead to values of the reciprocal command (R-command) defining the RC for the effector and the coactivation command (C-command) defining the apparent stiffness (k). B: The three level of analysis for the task shown in part A. F_{TOT} can be seen as the product of –RC and k, as the sum of individual finger forces, and as the result of action of motor unit groups (MU-modes) defined for the agonist (flexor digitorum superficialis, FDS), for the antagonist (extensor digitorum communis, EDC), and for both muscles together (FDS + EDC).

5.5 Experimental procedures

5.5.1 Participants

Sixteen participants (9 males, and 7 females, 24 ± 4 years old, mean ± SD) participated in the study. All participants were right-handed based on their hand use during writing and eating. The participants were free of neurological or peripheral disorders affecting the hands. They had normal or corrected to normal vision. All participants provided written consent in accordance with procedures approved by the Office for Research Protections of the Pennsylvania State University.

5.5.2 Apparatus

The “inverse piano” setup was used to record finger forces and apply smooth positional perturbations to the fingers (Martin et al., 2011). This device consists of four cylindrical piezoelectric sensors (PCB Piezotronics, Depew, NY, USA) placed within a frame with the centers of the sensors spaced by 2.4 cm. The location of the sensors could be adjusted in the forward–backward direction to fit the individual participant's hand anatomy. Each sensor had a dedicated linear actuator (PS01-2380; Linmot, Spruitenback, Switzerland), which could lead to its controlled displacement in the vertical direction. The actuators were controlled by a four-channel servo drive (Linmot E400-AT). Analog signals from the force sensors were transmitted through a signal conditioner (model 484B06; PCB Piezotronics) to a 16-bit analog-to-digital converter (BNC 2110; National Instruments, Austin, TX, USA). LabView program (National Instruments, USA) was used to acquire finger force data and control the sensor movement. Force data were sampled at 500 Hz with a 16-bit resolution. A 19-inch Dell monitor was placed about 0.8 m in front of the participant at eye level and used to provide feedback on the total force produced by the four fingers together (Fig. 5.2A). Two wireless surface EMG sensors (Trigno Galileo sensor, Delsys Inc., Natick, MA, USA) were used to record the activation of flexor digitorum superficialis (FDS) and extensor digitorum communis (EDC). The FDS muscle belly was identified between 3 and 7 cm distal to the medial epicondyle, following a line towards the lunate. The EDC muscle belly was identified along a line from the lateral epicondyle to the scaphoid (Fig. 5.2B). Before taping the sensors over the muscle bellies, the skin was shaved and cleaned with alcohol swabs. Each sensor body, which houses two stabilizing reference electrodes, was affixed to the distal antebrachium. The head of each sensor, which houses four active electrodes spaced 5 mm apart in a diamond formation was placed over the respective muscle belly. The EMG was originally sampled by the system at 2222.2 Hz and later downsampled to 100 Hz with on-board filtering from 20 to 450 Hz performed automatically by the data acquisition software (an example of raw EMG signals is shown in Fig. 2C). The signal quality was assessed using EMGWorks (Delsys Inc.) and continuously monitored throughout the procedures.

5.5.3 Procedures

Participants sat comfortably in a chair in front of the setup with their forearms resting on the wooden board and the four fingertips of one of the hands resting on the respective force sensors. The interphalangeal and metacarpophalangeal joints were slightly flexed, and the hand formed a dome. There were two tasks, maximal voluntary contraction (MVC) and the Main task. The two hands were tested in a random order. An experimenter was at all times watching the participant to ensure that no change in the position of the body and hand took place. First, the participants performed the MVC task by pressing "as strongly as you can" with all four fingers within 5 s. Total force (F_{TOT}) was shown on the screen. Three MVC trials were performed in a row with at least 30-s breaks after each trial. The trial with the highest F_{TOT} value was chosen to set the targets for the Main task (see later).

The main body of the experiment consisted of five identical trials. Each trial lasted 105 s and consisted of five episodes following each other with 3-s breaks in-between. During the breaks, the participant relaxed the hand with the fingers resting on the sensors, and the sensor readings were reset to zero to avoid drift accumulation. As a result, only active downward force was recorded. During the first episode, the participant was required to follow a sine wave shown on the computer screen with the cursor showing the current F_{TOT} magnitude. This episode, referred to as the cyclical task, lasted 18 s. The sine wave was set at 1 Hz with the peaks and troughs at 35% and 15% MVC, respectively. The next four episodes were identical. Each of them lasted for 18 s. The participant was asked to match F_{TOT} cursor with the target corresponding to 25% MVC and keep it for the entire episode. The force sensors were raised and then lowered by 1 cm at 2 cm/s by the “inverse piano” three times per each episode. The time intervals with sensor motion are going to be addressed as “IP-tests”. The participant was instructed not to react to possible force changes during the sensor motion and keep F_{TOT} at the target level of 25% MVC at all times in-between the IP-tests. The entire experiment lasted about 1 h, and none of the participants reported fatigue. Fig. 5.3A shows a typical episode with the cyclical task.

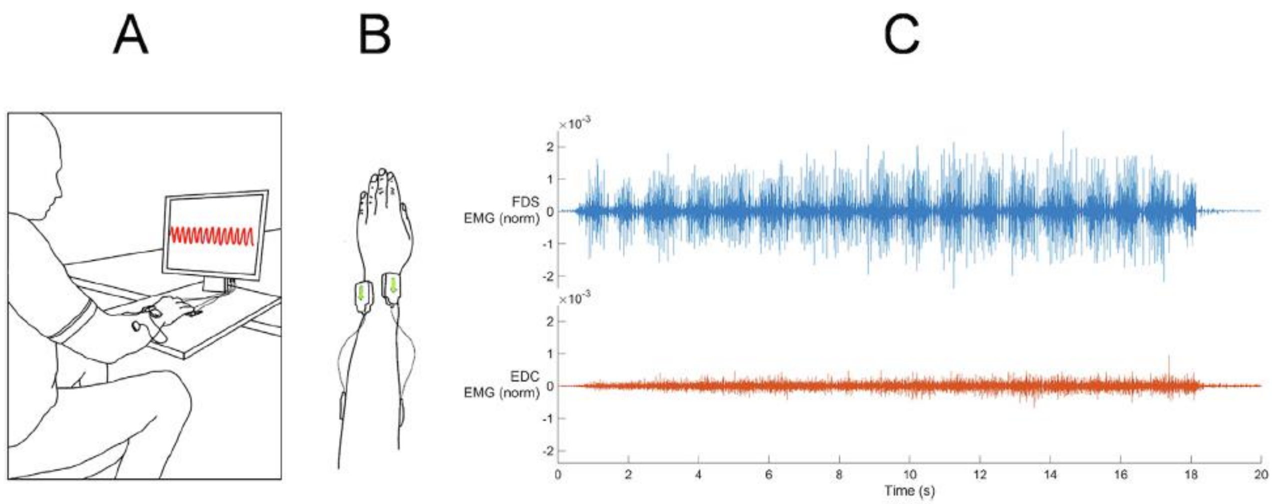

Fig. 5.2: A: An illustration of the experimental setup showing the position of the subjects and tested arm and the feedback monitor. B: The location of the electrodes. C: A sample of EMG recording during the cyclical force change in one of the recording sites from the flexor digitorum superficialis (FDS, top) and extensor digitorum communis (EDC, bottom).

5.6 Data analysis

The data processing procedures were implemented using a custommade Matlab code specifically tailored for the analysis. The force data were digitally low-pass filtered at 10 Hz using a fourth-order zero-lag Butterworth filter. The MU waveforms and firing times were extracted from the EMG signals collected by each sensor separately over each of the Main trials. The NeuroMap software (NeuroMap software; Delsys Inc.; De Luca et al., 2015) was used to identify MU action potentials using the signal decomposition algorithms. The software produces the raster plots for each MU, i.e., discrete sequences of action potentials. To convert these discrete signals into a differentiable time function, a 1-s Hann window filter was used to generate the MU firing rate (f_{MU}) time functions (see Fig. 5.3B). The Hann filter replaces discrete events with sine-like functions centered at the time of the event, effectively integrating the effects of both MU intermittent recruitment and frequency modulation into a single smooth function necessary for the analysis of synergies (see below). For more detail, we refer to a previous study, which explored Hann filters with different parameters (Madarshahian et al., 2021). The software also employs the decompose-synthesize-decompose-compare method (Nawab et al., 2010) to accept MUs at an accuracy setting of 80%. Note that this value is a setting in the software, not the actual percentage of properly identified MUs (cf. Farina and Enoka, 2011). This setting was used in our previous studies and produced consistent results with an acceptable number of identified MUs per muscle. The current software identifies MU action potentials only within a single trial. As a result, identifying a MU within one trial with a MU in another trial is next to impossible and may lead to major errors. This is a major limitation, which affected our experimental design. Hence, each trial was processed separately. The number of identified MUs per muscle varied across participants and trials from zero to 53 (see Table 1). In earlier studies (Madarshahian et al., 2021; Madarshahian and Latash, 2022a), only data with at least 7 MUs per muscle were accepted. We accepted this criterion for consistency and as a practical decision, which disqualified a large number of trials. Three participants were discarded in their entirety due to the insufficient number of MUs found. For consistency, we have decided to perform further analysis in the space of MUs using only the "best trial" for each hand and each participant. The "best trial" was defined as the one with the largest number of MUs in EDC, which always had fewer identified MUs as compared to FDS. In cases when this number was the same for two or more trials, we selected the trial with the highest value of variance accounted for (VAF) at the level of Jacobian computation (see below). Analysis of force-stabilizing synergies in the other two space, those of finger forces and of $\{RC; k\}$, used the data acquired over all five trials.

5.6.1 Defining MU modes

The MU-modes were identified using the first (cyclical) episode of the selected "best trial". Principal component analysis (PCA) was applied to the f_{MU} covariation matrix using the cycles of F_{TOT} production that satisfied the criterion of their duration being within 20% of the nominal one. A minimum of 13 to a maximum of 16 cycles were accepted. Each accepted cycle was divided into 20 phase windows, 5% of the cycle time each.

The data formed a matrix $Nm \times n$ where N represents the number of cycles accepted, $m = 20$ phase windows for each cycle, and n is the number of MUs identified for that trial. A factor was accepted if at least one MU exhibited a significant loading factor (with the absolute magnitude > 0.5), and the corresponding eigenvalue exceeded 1.0. These criteria were consistently met for two factors across all subjects. Accepting the two first factors was also consistent with previous studies (Madarshahian et al. 2021; reviewed in Latash et al. 2023). These factors are referred to as MU-modes, which are further used as elemental variables in the UCM-based analysis of variance (reviewed in Latash 2022; Latash et al. 2023). This analysis was performed separately for the sets of MUs identified in FDS, in EDC, and to the combined set of MUs over both muscles, addressed further as "FDS+EDC". At this stage of processing, VAF by the two factors ranged from 70% to 98% (across the accepted trials); these values for each subject are shown in Table 1 for the dominant (D) and non-dominant (nD) hands. The magnitudes of the MU-modes ($\underline{MUmode}$) were obtained by multiplying the loading factors of the MU-modes by the f_{MU} vector:

$$\underline{MUmode} = LF_{mode} \cdot f_{MU} \tag{1}$$

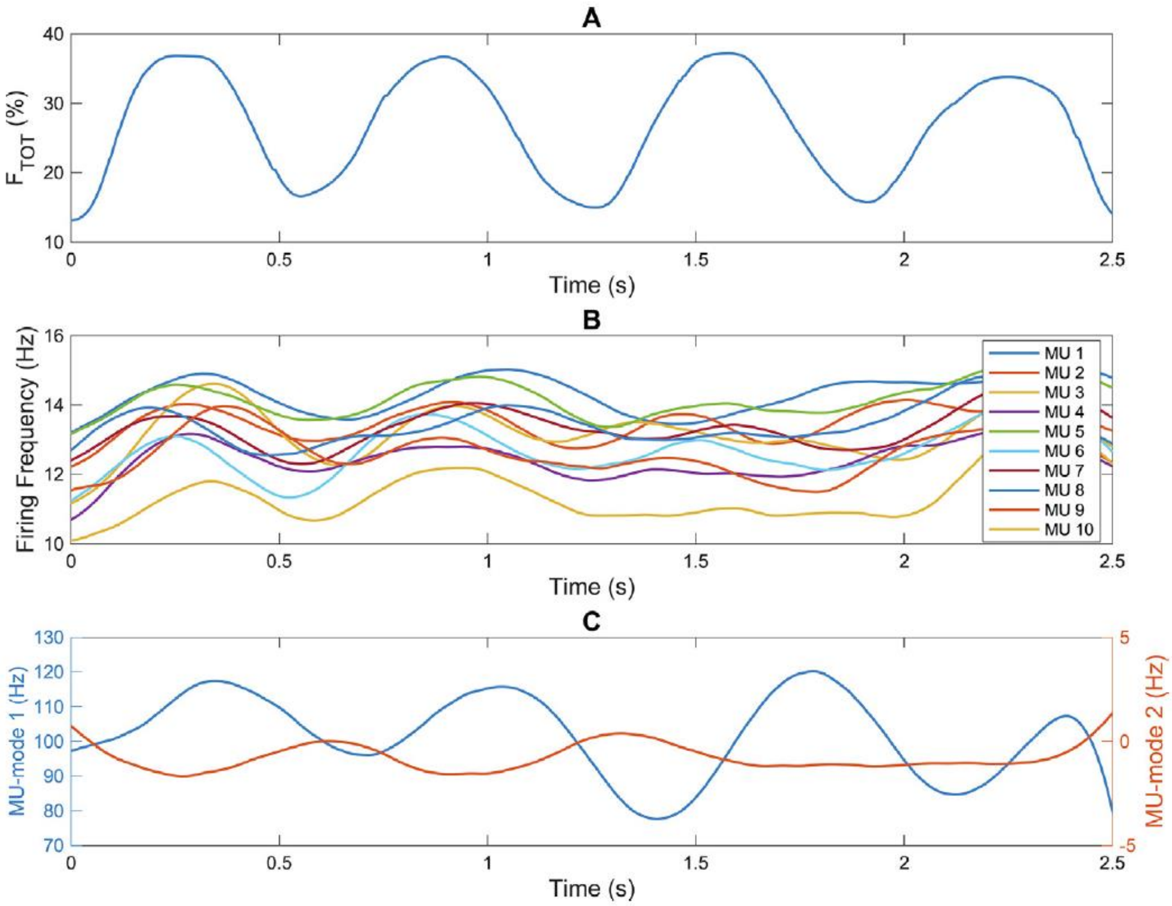

Fig. 5.3: A: An illustration of the total force (F_{TOT}) time series during the cyclical F_{TOT} production task for a representative participant. B: The firing frequency (f_{MU}) of a subset of motor units recorded in the flexor digitorum superficialis during the task shown in A. C: The time profiles of the two motor unit groups (MU-modes).

5.6.2 Defining the Jacobian Matrix

Analysis of synergies within the UCM hypothesis requires mapping between two spaces, the abundant space of elemental variables and the low-dimensional space of salient performance variables. In the analysis within the MU-mode space, the dimensionality of the elemental variables space is two, and the performance variable (F_{TOT}) is one-dimensional. The mapping from small changes in MU-modes and in F_{TOT} was done with the help of the Jacobian matrix (J), which is composed of the partial derivatives of F_{TOT} with respect to each of the MU-modes. Multiple linear regression was used:

$$\Delta F_{TOT} = k1\Delta MUmode1 + k2\Delta MUmode2 \quad (2)$$

where k1 and k2 are constants. This analysis was performed using the changes in F_{TOT} (ΔF_{TOT}) and MU-modes (ΔMU-mode$_i$, i = 1, 2) between successive phase windows within the force cycle in the cyclical task. Before computing these values, the values of F_{TOT} and MU-modes were averaged across all the accepted cycles to avoid effects of the large variance in the MU-mode space along the UCM (where $\Delta F_{TOT} = 0$). The Jacobian, $\mathbf{J} = [k_1\ k_2]$ was computed separately for the MU-mode sets based on the MUs in FDS, in EDC, and in (FDS+EDC). The VAF (the coefficient of determination squared, R^2) accounted for by the linear mode ranged from 43% to 100%. The values for individual subjects are presented in Table 5.1.

Tab. 5.1: The number of motor units (MU) and variance accounted for (VAF). The number of identified motor units (MUs) in the "best trial" and variance accounted for (VAF, in %) at the level of principal component analysis (PCA) and Jacobian identification (J). The data are shown separately for each subject, each hand (dominant – D and non-dominant – nD), and flexor digitorum superficialis (FDS) and extensor digitorum communis (EDC). Empty cells mean lack of acceptable data based on the criteria described in the text. The data for subjects 7, 8, and 14 were discarded due to few identified MUs (see Methods). The bottom rows present the median values for FDS, EDC, and both muscles combined (FDS + EDC).

Subject	Muscle	MUs (#)	VAF (%) (PCA)	VAF (%) (J)	MUs (#)	VAF (%) (PCA)	VAF (%) (J)
		D Hand	D Hand	D Hand	nD Hand	nD Hand	nD Hand
1	FDS	39	89	96	36	92	94
	EDC	31	96	97	10	97	82
2	FDS	17	79	92	46	92	83
	EDC	8	74	62	20	89	84
3	FDS	51	86	97	46	79	97
	EDC	7	89	98	7	90	98
4	FDS	35	90	96	37	87	95
	EDC	34	93	88	29	97	95
5	FDS	–	–	–	36	74	90
	EDC	–	–	–	9	84	89
6	FDS	16	98	70	31	92	95
	EDC	13	88	72	17	93	91
9	FDS	–	–	–	22	80	95
	EDC	–	–	–	12	73	95
10	FDS	41	82	86	31	94	100
	EDC	18	95	91	14	93	99
11	FDS	35	95	98	53	90	97
	EDC	24	74	98	24	90	97
12	FDS	31	76	92	29	81	94
	EDC	28	94	76	7	95	94
13	FDS	–	–	–	51	83	71
	EDC	–	–	–	10	70	71
15	FDS	40	81	88	38	87	94
	EDC	11	94	90	12	97	43
16	FDS	51	94	91	47	94	68
	EDC	41	96	96	7	96	94
Median	FDS	35	86.19	92	36.5	85	94

	EDC	18	93.45	90	11	90	93
	FDS + EDC	59	84	93	50	88	92

5.6.3 Analysis based on the UCM framework

The UCM hypothesis (Scholz and Schöner 1999), offers a method to estimate stability of a performance variable in a linear approximation using inter-trial (inter-cycle) variance in two subspaces within the space of elemental variables, UCM – where the performance variable does not change, and ORT – orthogonal to the UCM, where the performance variable changes. As in a number of earlier studies (reviewed in Latash et al. 2002, 2007), we used the null-space of **J** as a linear approximation of the UCM. During analysis in the two-dimensional MU-mode space, **J** = [k_1 k_2] as shown in Eq. (2). During the analysis in the space of individual finger forces, **J** = [1 1 1 1] because F_{TOT} is the sum of the forces produced by the individual four fingers. This method cannot be used in synergy analysis in the $\{RC;\ k\}$ space because, as mentioned earlier, the UCM is hyperbolic and cannot be linearized. We described an alternative analysis later.

5.6.4 Analysis in the MU-mode space

Two 0.5-s windows were identified during steady force production prior to each IP-test (see Fig. 1). The first window ended 0.5 s prior to the IP application, and the second one ended 1.5 s prior to the IP application. Mean values of both MU-modes were computed over each time window. This resulted in a set of 24 pairs of MU-mode values computed over the "best trial" for each subject and each hand: Two time windows × three IP-tests × four episodes.

Mean-free values of MU-modes were computed over the 24 time windows. This average magnitude was then subtracted from the individual MU-mode magnitudes, resulting in mean-free values of the MU-modes:

$$\Delta MUmode_{demeaned} = \underline{MUmode} - \underline{\underline{MUmode}} \tag{3}$$

Subsequently, the data in the MU-mode space were projected onto the null-space of J, which represented the UCM, as well as onto its orthogonal complement, ORT:

$$f_{UCM} = ((\varepsilon)^T \cdot \Delta MUmode_{demeaned})^T \cdot (\varepsilon)^T \tag{4}$$

$$f_{ORT} = \Delta MUmode_{demeaned} - (f_{UCM})^T$$

where ε is the basis vector spanning the null-space of J. VUCM and VORT were computed as:

$$V_{UCM} = \sigma^2{}_{UCM} = \frac{1}{N}\sum_{i=1}^{N} \quad f^2{}_{UCM} \tag{5}$$

$$V_{ORT} = \sigma^2{}_{ORT} = \frac{1}{N}\sum_{i=1}^{N} \quad f^2{}_{ORT} \tag{6}$$

Here, N represents the number of points (N = 24). The force-stabilizing synergy index was computed as the normalized difference between V_{UCM} and V_{ORT}:

$$\Delta V = (V_{UCM} - V_{ORT})/V_{TOT} \tag{7}$$

where V_{TOT} stands for total variance. Positive ΔV values indicate the presence of a force-stabilizing synergy, while ΔV ≤ 0 indicates the absence of a force-stabilizing synergy.

5.6.5 Analysis in the finger force space

A similar computational procedure was applied to the individual finger forces. Briefly, the average values of the finger forces were computed within each of the 24 time windows. Further, demeaned values were projected onto the null-space of **J** = [1 1 1 1] and onto its orthogonal complement (see Eq. (4)). Variance indices were computed as in Eqs. (5) and (6). The synergy index was computed as in Eq. (7). The only difference is in the lack of normalization per degree-offreedom in the analysis of ΔV in the MU-mode space because both UCM and ORT are one-dimensional, and in the presence of such normalization for the analysis in the finger force space because ORT is one-dimensional and UCM is three-dimensional. Further, ΔV was converted into ΔV_Z using Fisher's z-transformation modified given the computational boundaries of ΔV (Solnik et al., 2013).

5.6.6 Analysis in the {RC;k} space

This analysis involved two distinct steps. First, we used the ascending portion of each IP-test (i.e., finger motion upward) to estimate *RC* and *k* for that particular trial. This method is described in earlier publications (Ambike et al., 2016a,b). Briefly, we accepted the middle 0.3-s portion of the 0.5-s phase when the fingers were lifted to avoid edge effects and minimize chances of the participant's unintentional reaction to the sensor motion. F_{TOT} was plotted as a function of sensor coordinate (X, assuming that the original coordinate $X_0 = 0$), and linear regression analysis was performed. Only IP-tests with R > 0.9 were accepted. We also rejected trials with obvious reactions by the participant as reflected in transient force spikes. The median number of accepted IP-tests per participant was 99, ranging from 21 to 117. The data for Participant 5 for the D (right) hand were discarded because of fewer than five acceptable pairs of RC and k (see Table 2). The accepted regressions were used to compute the intercept (RC) and slope (k). An illustration of typical sensor force and coordinate time profiles are shown in Fig. 4A, B. The regression is shown in Fig. 4C. Further, for each participant and each hand, all the accepted $\{RC; k\}$ pairs were plotted, and hyperbolic regression analysis was run. R^2 of the hyperbolic regression was taken as one of the indices of force stabilizing synergy by co-varying values of RC and k.

We also used a randomization method, which creates surrogate, covariation free, data sets by accepting RC and k values from different IP-tests, $\{RC_i; k_j\}$, i ≠ j. (cf. Müller and Sternad, 2003; Ambike et al., 2016a,b; Nardon et al., 2022). These values were used to compute expected surrogate F_{TOT} values as the products of RCi and kj. We refer to such values of force corresponding to the surrogate $\{RC_i; k_j\}$pairs as F_{SUR}. This analysis was performed 100 times for each participant and hand combination. Note that F_{SUR} is created by {RC; k} pairs with the same mean and standard deviation values as the original set but without co-variation. Further, we computed the values of the F_{TOT} and F_{SUR} variance, $V(F_{ACT})$ and $V(F_{SUR})$ and used the ratio between the two variance values as an index of force-stabilizing co-variation in the original data: $\Delta V_{SUR} = V(F_{SUR}) / V(F_{ACT})$. Note that $\Delta V(F_{ACT}) > 1$ indicates covariation of RC and k in the original data set reducing force variability, i.e., a force-stabilizing synergy.

Tab. 5.2: Descriptive data on the {RC, k} − based analysis. Mean and standard deviation values for referent coordinate and apparent stiffness (RC and k). The coefficient of determination for the hyperbolic regression (R^2) between RC and k and the synergy index (ΔV_{SUR} – see Methods) are also shown. The data are shown separately for each subject, each hand (dominant – D and non-dominant – nD). Empty cells mean lack of acceptable data based on the criteria described in the text. The bottom rows present the median values.

Subject	Hand	Mean RC (cm)	S.D. RC	Mean k (MVC/cm)	S.D. k	R²	ΔVSUR
1	nD	−1.15	0.27	0.23	0.05	0.95	147
	D	−1.12	0.32	0.26	0.07	0.97	76.9

2	nD	−1.72	0.56	0.15	0.05	0.91	83.3
	D	−1.40	0.4	0.19	0.04	0.94	101
3	nD	−1.25	0.27	0.20	0.04	0.91	200
	D	−1.02	0.25	0.25	0.05	0.96	140
4	nD	−2.05	0.46	0.13	0.02	0.98	175
	D	−1.85	0.54	0.14	0.04	0.95	71.4
5	nD	−1.94	0.46	0.13	0.03	0.94	151
	D	–	–	–	–	–	–
6	nD	−1.33	0.41	0.19	0.05	0.96	90.9
	D	−1.25	0.33	0.21	0.06	0.91	90.9
7	nD	−1.00	0.13	0.26	0.02	0.87	588
	D	−0.77	0.12	0.35	0.05	0.91	384
8	nD	−1.10	0.16	0.23	0.03	0.87	434
	D	−0.69	0.12	0.40	0.07	0.91	208
9	nD	−1.43	0.57	0.19	0.08	0.89	38.5
	D	−1.41	0.19	0.17	0.02	0.90	454
10	nD	−1.42	0.27	0.17	0.03	0.97	270
	D	−1.62	0.26	0.15	0.02	0.92	357
11	nD	−2.08	0.5	0.12	0.03	0.97	142

	D	−1.86	0.37	0.13	0.03	0.98	196
12	nD	−1.10	0.2	0.25	0.03	0.93	278
	D	−1.26	0.34	0.24	0.05	0.96	100
13	nD	−1.36	0.29	0.19	0.04	0.95	181
	D	−1.20	0.3	0.22	0.04	0.88	142
14	nD	−1.35	0.45	0.20	0.06	0.95	71.4
	D	−1.76	0.5	0.14	0.04	0.94	104
15	nD	−1.12	0.6	0.28	0.15	0.94	15.2
	D	−0.88	0.64	0.35	0.19	0.87	11.4
16	nD	−2.18	0.79	0.12	0.03	0.97	27.0
	D	−1.97	0.46	0.13	0.03	0.95	158
Median	nD	−1.36		0.19		0.95	149.00
	D	−1.26		0.21		0.94	140.00

5.6.7 Statistics

The data are presented in the text and figures as means with standard errors or as medians with quartiles. Before using methods of parametric statistics, all data were checked for normality and sphericity.

Variables were log-transformed if violations of the normality assumption were detected. In cases of sphericity violations, corrections were applied to degrees-of-freedom. For all statistics, the *z*-transform was applied to the synergy index ΔV to obtain ΔV_Z.

To test the first hypothesis formulated in the Introduction we used ANOVA with repeated measures with the factors Space (UCM and ORT), Muscle (FDS, EDC and FDS + EDC), and Hand (D and non-D) applied to the variance indices computed in the space of MU-modes. To test this hypothesis in the space of finger forces, ANOVA was used with the factors Space and Hand. An interaction Space × Hand was expected to reflect effects of dominance. To test this hypothesis in the $\{RC; k\}$ space, we explored the values of R^2 and ΔV_{SUR} using non-parametric methods (Wilcoxson's signed-rank test). To explore the second hypothesis, we computed linear regression between pairs of synergy indices for the analyses in the three spaces as well as for the analysis within the MUmode space across the three muscle levels (FDS, EDC and FDS + EDC). The data were analyzed across the male and female participants combined because we saw no sex differences (no effects of Sex factor and no significant interactions in pilot statistical analysis). Significant effects in ANOVAs were further explored using pairwise contrasts with Bonferroni corrections. The level of significance was set at $p < 0.05$. Jamovi software (v. 2.3) was used for statistical analysis.

5.7 Results

5.7.1 Motor units and MU-modes

The number of identified motor units (MUs) within the "best trial" accepted for further data processing for FDS ranged from a minimum of 16 MUs units to a maximum of 53 MUs, and for EDC from a minimum of 7 MUs to a maximum of 41 MUs (see Table 5.1, which presents the values for the "best trial"). The PCA resulted in the extraction of two MU-modes (see above) with the total VAF values ranging from 74% to 98% for FDS, from 70% to 97% for EDC, and from 70% to 94% for (FDS + EDC). Two-way ANOVA Hand × Muscle on the log-transformed VAF values for the PCA demonstrated no significant effects of Hand ($F_{[1,63]} = 0.025$, $p = 0.875$), Muscle ($F_{[2,63]} = 2.180$, $p = 0.121$), and no interaction ($F_{[2,63]} = 0.016$, $p = 0.984$).

5.7.2 Jacobian identification

Analysis of the relations between small changes in the MU-modes and F_{TOT}, i.e., the identification of the Jacobian matrix (**J**, see Methods) produced VAF values ranging from 68% to 99% for the sets of MU-modes in FDS, from 43% to 99% for the sets of MU-modes in the EDC, from 73% to 99% for the sets of MU-modes combined over the two muscles, FDS +

EDC (see Table 1). Two-way ANOVA Hand × Muscle on the log-transformed VAF values demonstrated no significant effects and no interactions ($F < 1.1$, $p > 0.34$).

5.7.3 MU-mode synergies

The null-space of the **J** matrix was used as a linear approximation of the UCM. Consistently, the amount of variance in the space corresponding to no change in F_{TOT} (the UCM for F_{TOT}) was larger than within the orthogonal to the UCM space (ORT) for the analysis performed for the MU-mode spaces for FDS and for EDC. Fig. 5 illustrates the individual data as well as box-and-whiskers bars with the medians, quartiles, and 5–95% ranges. Note that the difference between V_{UCM} and V_{ORT} was smaller for the analysis using the MU-modes defined across the two muscles, FDS + EDC. ANOVA showed the effects of Space ($F_{[1,126]} = 113.794$, $p < 0.001$), reflecting VUCM > VORT, and of Hand ($F_{[1,126]}= 7.330$, $p =0.008$). The effect of Muscle was significant ($F_{[2,126]} = 27.338$, $p < 0.001$) reflecting the larger log-transformed variance magnitudes for the (FDS + EDC) analysis (6.39 ± 0.31) as compared to the FDS analysis (4.76 ± 0.47, $p = 0.002$) and EDC analysis (3.20 ± 0.44, $p < 0.001$). The higher variance magnitudes for the (FDS + EDC) analysis was primarily due to higher values of V_{ORT}, not of V_{UCM}, as supported by the Muscle × Space significant interaction ($F_{[2,126]} = 6.003$, $p = 0.003$). The effect of Hand reflected the overall larger variance indices in the D hand compared to the nD hand. These effects were, however, not different between V_{UCM} and V_{ORT} leading to similar magnitudes of the synergy index as described in the next paragraph. The significant differences between V_{UCM} and V_{ORT} were reflected in the overall positive values of the synergy index ΔV_Z. ANOVA showed no effect of Hand ($F_{[1,63]} = 1.68$, $p = 0.284$) but there was an effect of Muscle ($F_{[1,63]} = 8.18$, $p < 0.001$). Specifically, the ΔV_Z index was larger for FDS (2.68 ± 0.20) than for EDC (1.60 ± 0.33, p = 0.017) and for FDS + EDC (1.28 ± 0.21, p < 0.001). However, there was no difference between EDC and FDS + EDC (p = 0.905).

5.7.4 Finger force synergies

Force-stabilizing synergies in the space of individual finger forces were estimated using the indices of inter-trial variance within the UCM and ORT (see Methods). $V_{UCM} > V_{ORT}$ was confirmed in both D and non-D hands (effect of Space, $F_{[1,42]} = 4.822$, $p = 0.034$) with no significant differences between the Hands ($F_{[1,42]} = 1.932$, $p = 0.172$). There was no Hand × Variance interaction ($F_{[1,42]} = 0.209$, $p = 0.65$). These results are illustrated in Fig. 5.6. On average, the synergy index value for the non-D hand was 0.31 ± 0.08, while for the D hand it was 0.19 ± 0.11. In spite of the nearly two-fold difference between the hands, it was below the significance level ($F_{[1,21]} = 1.29$, $p = 0.27$).

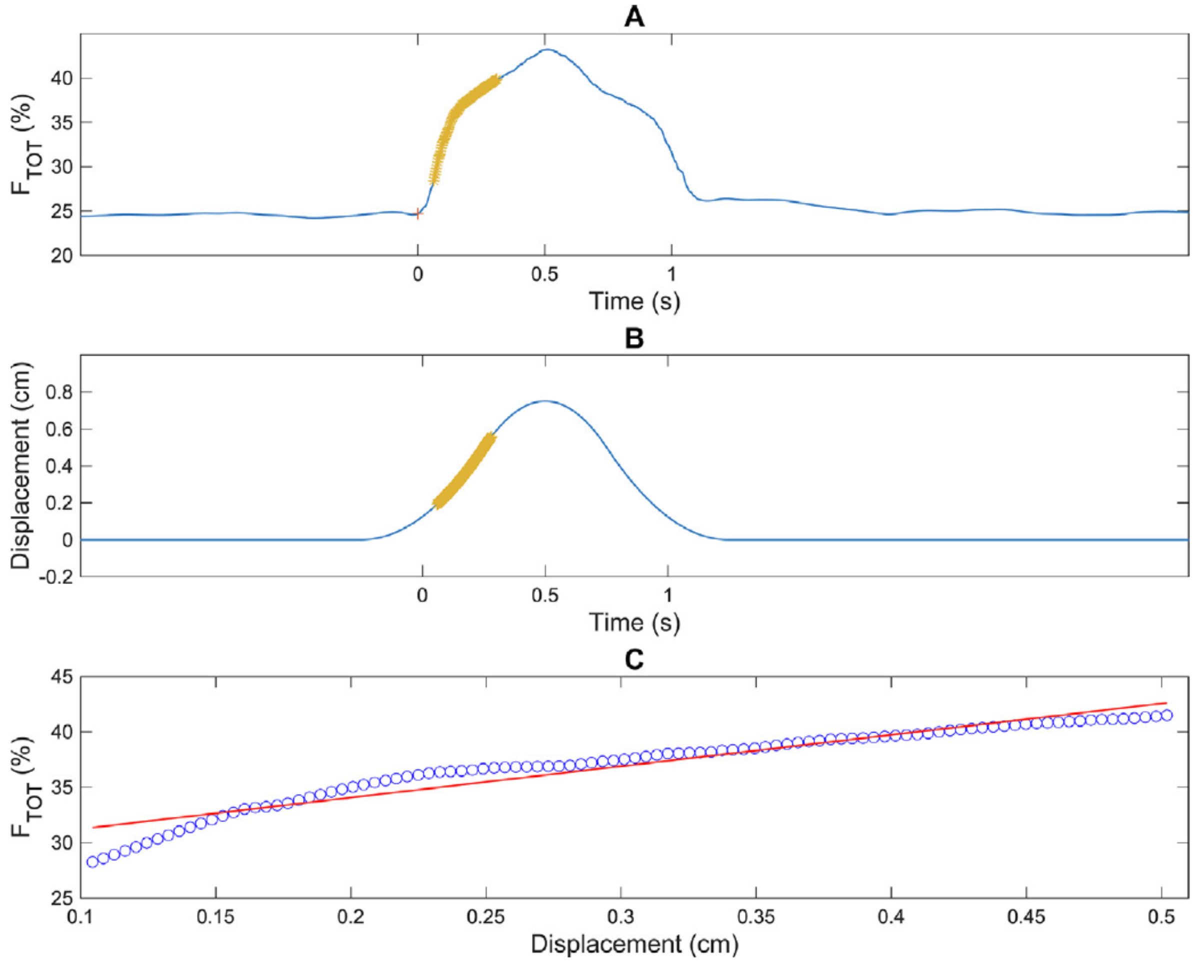

Fig. 5.4: A: An illustration of the total force profile during an episode with the "inverse piano" (IP) lifting the fingers smoothly in a typical participant. B: The vertical sensor displacement during the IP episode shown in A. The thick yellow line in A and B shows the data taken for the linear regression analysis. C: The linear regression between the F_{TOT} and finger coordinate, which was used to compute the intercept (referent coordinate, RC) and slope (apparent stiffness, k). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

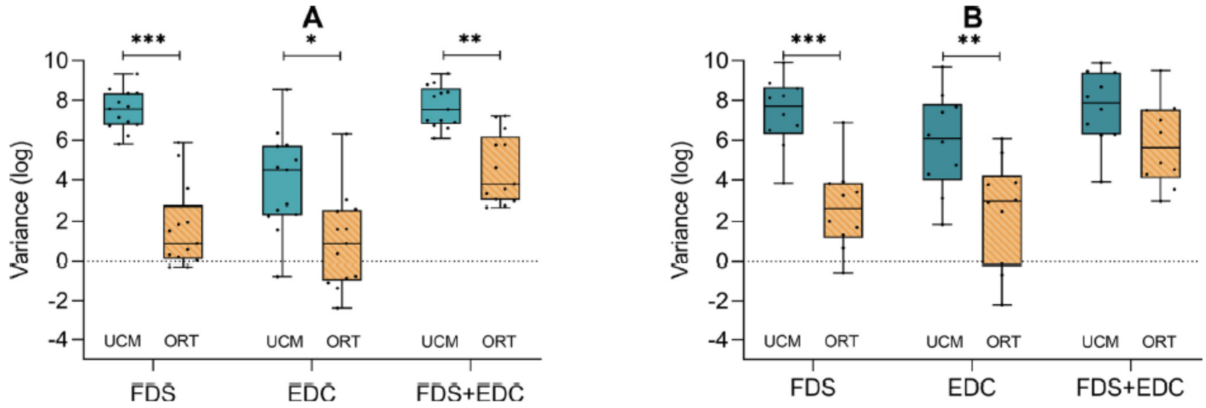

*Fig. 5.5: Synergy analysis at the level of motor unit groups (MU-modes). Individual values and medians with quartiles and 5–95% whiskers are shown for the interepisode variance within the uncontrolled manifold (V_{UCM}) for total force and within the orthogonal to the UCM space (V_{ORT}). The values are shown for the sets of MU-mode identified in the flexor digitorum superficialis (FDS), extensor digitorum communis (EDC), and pooled over both muscles (FDS+EDC). The data for the non-dominant (left) hand are shown in A while the data for the dominant (right) hand are shown in B. Note VUCM > VORT consistently across the analyses. Note also the log scale of the ordinate axes. *p < 0.05; **p < 0.01; ***p < 0.001.*

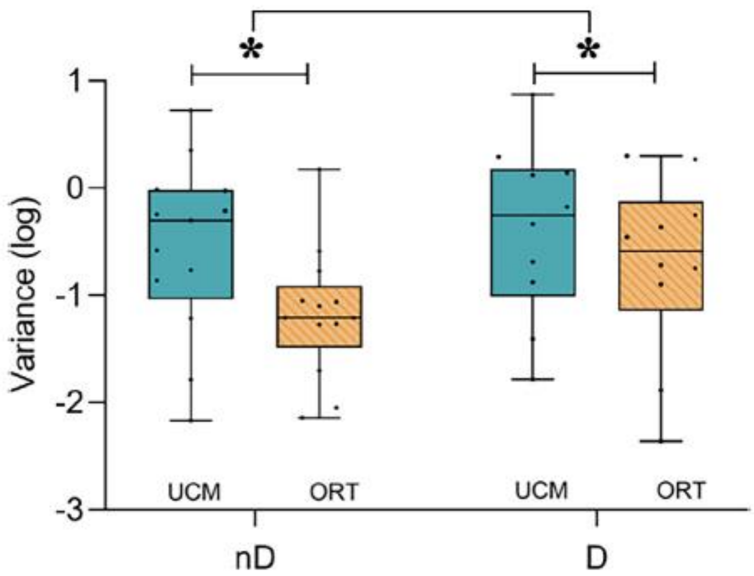

*Fig. 5.6: Synergy analysis at the level of individual finger force. Individual data as well as medians with quartiles and 5–95% whiskers are shown for the interepisode variance within the uncontrolled manifold (V_{UCM}) for total force and within the orthogonal to the UCM space (V_{ORT}). The data are shown for the non-dominant (left) and dominant (right) hands. Note V_{UCM} > V_{ORT}(*p < 0.05 for the main effect). Note also the log scale of the ordinate axes.*

5.7.5 *Synergies in the {RC;k} space*

The magnitudes of the intercept (*RC*) and slope (*k*) of the linear regressions between total force and fingertip coordinate varied across trials for individual participants. The grand average values of *RC* and *k* were –1.49 ± 0.08 cm and 0.19 ± 0.01 N·cm. No significant difference between the D and non-D hand was found for either variable, *RC* ($F_{[1,29]} = 0.915$, $p = 0.347$) and k ($F_{[1,29]} = 1.67$, $p = 0.206$).

Within each participant, the magnitudes of *RC* and *k* varied broadly across trials with a strong hyperbolic covariation. An example for a representative participant performing the task with the D hand is presented in Fig. 5.7. Note the very high R^2 value. The median R^2 value was 0.95 (quartiles: 0.92–0.97). Across participants, the log-transformed R^2values for the hyperbolic regressions showed no significant difference between the D and non-D hands ($F_{[1,29]} = 0.185$, $p = 0.670$). Using the surrogate data sets produced much larger variance of the computed F_{TOT} values, $V(F_{SUR})$, as compared to the variance computed over the actual force values, $V(F_{ACT})$. The values of the ratio between $V(F_{SUR})$ and $V(F_{ACT})$, ΔV_{SUR}(see Methods) are shown in Table 5.2. There was no significant difference between the D and non-D hand ($F_{[1,29]} = 0.150$, $p = 0.702$). The median value of ΔV_{SUR} was 43.80 (quartiles: 77.06–24.22); $\Delta V_{SUR} \gg 1$ ($F_{[1,60]} = 65.6$, $p < 0.001$).

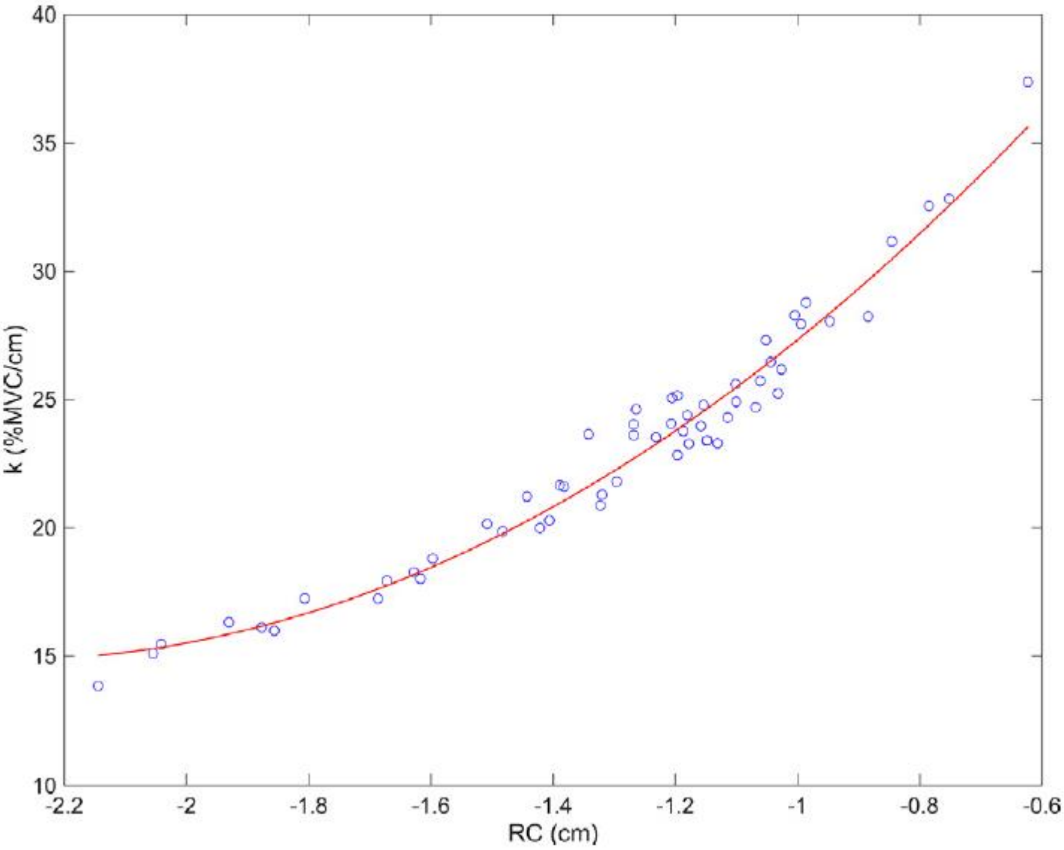

Fig. 5.7: Synergy analysis at the level of referent coordinate (RC) and apparent stiffness (k) reflecting the R-command and C-command, respectively. An illustration of a typical data distribution and hyperbolic regression for the right hand of a representative participant.

5.7.6 *Exploration of analyses across spaces*

We used across-subjects pairwise linear regressions between synergy indices quantified at the three levels of analysis in this dataset. These indices included ΔV_Z quantified for FDS, EDC, and FDS + EDC for the MU-mode space analysis, ΔV_Z for the individual finger force space analysis, and R^2 and ΔV_{SUR} for the analysis in the $\{RC; k\}$ space. Across the eleven between-space analyses, run for the indices computed for the D hand and non-D hand separately, none of the comparisons produced R^2 values approaching significance. On average, $R^2 = 0.00873$, range $\{0.00002; 0.039\}$ ($p > 0.5$).

5.8 Discussion

Our results have provided support for the main two hypotheses formulated in the Introduction. Indeed, force-stabilizing synergies were confirmed within all three spaces, in the space of hypothetical control variables $\{RC; k\}$, in the space of individual finger forces, and in the spaces of groups of motor units (MU-modes). In contrast to earlier studies (Madarshahian and Latash, 2022a; Madarshahian et al., 2022), force-stabilizing synergies were confirmed across all three MU-mode spaces, those defined over MUs in the flexor (FDS), in the extensor (EDC), and across the combined set of MUs (FDS + EDC).

Analysis of synergy indices across the three methods showed no correlations suggesting that these methods reflected processes at different levels of the neural control of the task (see Fig. 1B in the Introduction). In other words, participants who showed higher synergy indices at one of the three levels were equally likely to show higher or lower synergy indices at the other two levels. The lack of correlations suggests that the three methods reflect action of different neural circuits as discussed later. Of course, given the relatively modest number of participants, this result – accepting the null-hypothesis (cf. Corcos et al., 1985) – has to be confirmed in a larger study. The exploratory analysis between the synergy indices quantified for the D and non-D hand failed to show significant hand effects on the synergy index. Analysis in the MU-mode space showed higher overall variance indices in the D hand, but there was no difference in the synergy index. The analysis in the finger force space showed synergy indices nearly twice as large in the non-D hand compared to the Dhand. Although this effect was in the same direction as those reported in earlier studies (Park et al., 2012; de Freitas et al., 2019), the difference between the two hands was under the level of significance.

5.8.1 Hierarchical neural control with spatial referent coordinates

We accept the theory of motor control with spatial RCs for the involved effectors organized into a hierarchy (see Fig. 1 in the Introduction; reviewed in Latash, 2010; Feldman, 2015). Within this framework, performance variables are not prescribed by the central nervous system but emerge as a result of interaction between the time-varying RC values and external force field – an example of parametric control. The mapping from the highest, relatively low-dimensional, control level to lower, higher-dimensional, levels of elements such as extremities, joints, muscles, and MUs represents an example of the problem of motor redundancy (Bernstein, 1947), which has been reformulated as the bliss of abundance (Gelfand and Latash, 1998; Latash, 2012). This view on the apparent excess of elements is readily compatible with the concept of multi-element performance-stabilizing synergies (reviewed in Latash, 2021), which were the object of our study at three levels of task sharing across abundant sets of elemental variables. MUs represent the smallest controllable output elements. Their frequency of firing (f_{MU}) is a function of descending command and length-sensitive reflex input. Fig. 8A illustrates a typical dependence of f_{MU} on muscle length (L) and descending input representing threshold of the stretch reflex for this particular MU, λ_{MU}. MUs within a pool differ in their λ_{MU} and $f_{MU}(L)$ characteristics (Fig. 8B). Earlier studies have shown that MUs within a muscle and across muscles (Madarshahian et al., 2021; Madarshahian and Latash, 2022a; Del Vecchio et al., 2023; Hug et al., 2023; Weinman et al., 2024) form robust groups, which we have addressed as MU-modes. Fig. 8B shows a MU-mode characteristic representing superposition of all the contributing MUs. Within the theory of control with RCs, control of a MU-mode is implemented by specifying its λ_{MU}-mode, which is the smallest λ_{MU} value across all the MUs.

The control of a muscle involves setting λ_{MU}-mode values for the involved MU-modes. Earlier studies and our current study have shown that λ_{MU}-mode values co-vary across trials (cycles or episodes) to stabilize the task-specific performance variable, F_{TOT} in our study. Such force-stabilizing synergies have been described for the sets of MUmodes within the agonist muscle (FDS in our study) and within the antagonist muscle (EDC in our study). Analysis within the spaces of MU-modes defined across both muscles led to two important findings. First, the patterns of the loading factors suggested that the MU-modes (see Madarshahian and Latash, 2022a; Madarshahian et al., 2022) reflected the two basic commands, reciprocal and coactivation (R and C) commands (reviewed in Feldman, 2015). It seems feasible that the composition of the MU-modes reflected different proportions of slow and fast MUs. Second, there was an apparent trade-off between synergies in the spaces of MU-modes defined for individual muscles and those defined across the muscle pair (cf. Gorniak et al., 2007, 2009; discussed in more detail later).

At the next level of the hierarchy, the task can be seen as shared across the four fingers. Analysis of F_{TOT}-stabilizing synergies (Scholz et al., 2000; see also our Fig. 6) has documented such synergies at the levels of finger forces and finger modes (hypothetical variables to fingers accounting for the phenomenon of enslaving, Zatsiorsky et al., 2000; Danion et al., 2003). Within the scheme of control with RCs, control of a finger can be described as a combination of the R and C-commands that define the spatial location and shape of the fingertip force-coordinate characteristic (Fig. 1A in the Introduction), which reflects the contributions of the multiple muscles involved in fingertip force production. In isometric conditions, the R-command defines an *RC* below the surface of contact, i.e., the finger virtually penetrates the surface (cf. Pilon et al., 2007). The C-command defines the slope of the force-coordinate characteristics (apparent stiffness in a linear approximation, Latash and Zatsiorsky, 1993) and translates the spatial difference between the RC and actual fingertip coordinate into force units. The {R; C} pairs to the individual fingers define a {R; C} pair for the hand leading to the production of F_{TOT}, which is the sum of individual finger forces. The presence of two basic commands at the hand control level affords the central nervous system a possibility to organize force-stabilizing synergies documented in earlier studies (Ambike et al., 2016a; Reschechtko and Latash, 2017) and confirmed in our study (see Fig. 7). The mapping between {R; C} pairs at the finger level to the {R; C} pair at the hand level is non-trivial. In particular, so-called ascending synergies were documented for the R-command to the hand but not for the C-command (Reschechtko and Latash, 2018).

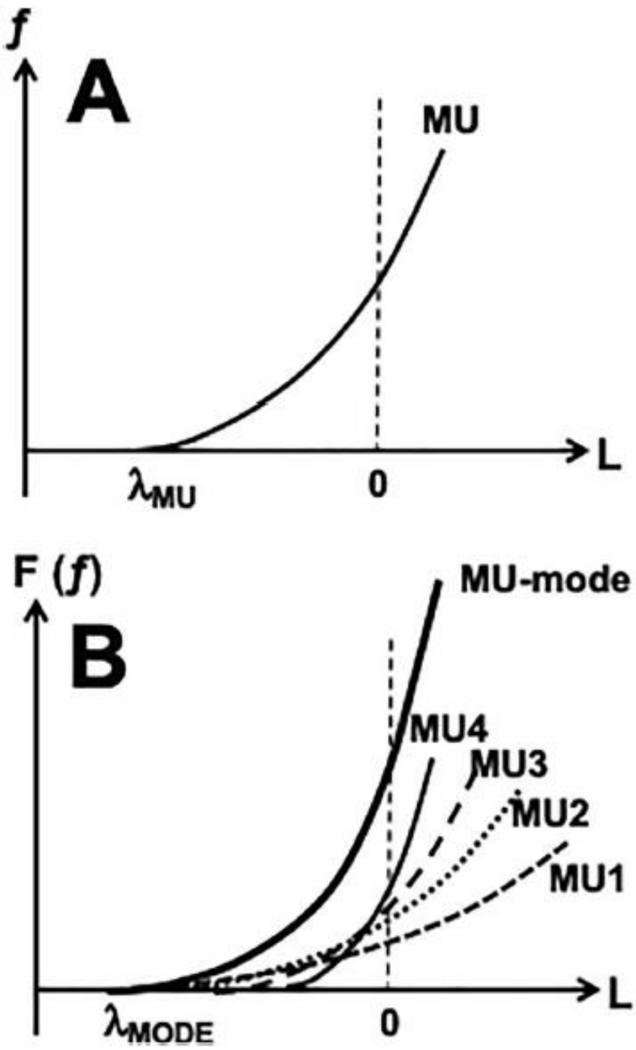

Fig. 5.8: A: The frequency of firing of a motor unit (f_{MU}) changes with muscle length (L) starting from a certain length value corresponding to the threshold of stretch reflex for this particular MU, λ_{MU}. B: MUs within a muscle form robust groups (MU-modes) with the active force–length dependence representing superposition of the contributions to force by all the contributing MUs and starting from a threshold (λM-mode) equal to the lowest λ_{MU} across all the MUs.

5.8.2 *Stability of performance organized at different levels of the hierarchy*

As described in the previous section, the control with RCs within a hierarchy allows organizing synergies stabilizing salient performance variables, such as F_{TOT} in our study, at different levels. On the other hand, there is only one F_{TOT} value in each particular trial, phase, or episode. How do different levels of control contribute to F_{TOT} stability?

This was one of the main questions in our study. Indeed, F_{TOT} stability can be organized at one of the three levels or shared across the levels with each level contributing to the observed stability of performance. Our results have confirmed the contribution of each level of control to the stabilization of F_{TOT}. Moreover, the contributions of the three different levels were not redundant: The indices of synergies did not show significant correlations. How can this be? Within the framework of the UCM hypothesis (Scholz and Schöner, 1999), the apparent excess of elemental variables is used to ensure the stability of a salient performance variable. A number of computational methods have been used to quantify covariation within spaces of elemental variables beneficial for the dynamical stability of performance. The most commonly used method is based on the definition of dynamical stability, which naturally leads to a prediction that variability in the initial state of a system and in external forces leads to larger deviations of an important performance variable from its desired trajectory in less stable directions as compared to more stable directions. As a result, if one computes inter-trial variance at a comparable phase during repeated performance of the same task, larger indices are expected in less stable directions. If the central nervous system is able to stabilize a salient performance variable in a task-specific manner (cf. Schöner, 1995), larger variance is expected along directions that lead to no changes in this variable (spanning the UCM for the variable) compared to directions along which this variable changes (ORT). Based on these logics, the difference between the properly quantified and normalized indices of inter-trial variance within the two spaces, UCM and ORT, has been used to quantify performance-stabilizing synergies, $\Delta V = (V_{UCM} - V_{ORT})/V_{TOTAL}$.

Another method compares deviations within the two spaces when a person tries to perform a quick action leading to a change in a salient performance variable. Deviations along the UCM have been termed motor equivalent (ME) and deviations along the ORT – non-motor equivalent (nME). A number of studies have documented large ME deviations reflecting the relatively low stability along the UCM (Scholz et al., 2007; Mattos et al., 2011), and the difference between ME and nME was used as a synergy index. Correlations between V_{UCM} and ME and between V_{ORT} and nME can be expected based on statistics of folded distributions (Leone et al., 1961) and have been documented experimentally (Falaki et al., 2017; Cuadra et al., 2018). We did not use this method because it may be viewed as redundant with respect to the method of inter-trial variance analysis. In situations when mapping between the spaces of elemental variables and performance variables cannot be linearized, analysis of variance is not possible (cf. Müller and Sternad, 2003). This can happen if the mapping from elemental variables to performance is essentially non-linear as in the mapping between *RC* and *k* values and F_{TOT} in our study. We have used two methods of analysis: Using hyperbolic regression to quantify potential force-stabilizing covariation between *RC* and *k* and using the randomization method (Kudo et al., 2000; Müller and Sternad, 2003) to create surrogate data sets with the same mean and standard deviation values for *RC* and *k* as in the original set but without covariation. In spite of the different methods of analysis and different sets of elemental variables, we documented force-stabilizing synergies for all three major methods. Moreover, such synergies were quantified at the {*RC*; *k*} level of analysis using both randomization method and hyperbolic regression. Also, the inter-trial variance analysis at the level of MU-modes showed synergies for all three sets of MU-modes, those based on MUs within FDS, within EDC, and combined over FDS and EDC. The last result is non-trivial and may be viewed as unexpected. Indeed, earlier studies showed force-stabilizing synergies based on MU-modes defined for each muscle separately but not across the muscles (Madarshahian and Latash, 2022a; Madarshahian et al., 2022).

These results were interpreted as reflections of an inherent trade-off between synergies at two hierarchical levels (cf. Gorniak et al., 2007, 2009): Large V_{UCM} at the higher level translates into large variance of each of the contributing elemental variables, which translates into V_{ORT} at the lower level. It is possible to organize synergies at both levels, but this requires a higher degree of sophistication on the part of the controller to satisfy the inequality $V_{UCM}>V_{ORT}$ at both levels. Our findings of strong intra-muscle synergies likely reflect the strength of autogenic reflex projections. These synergies limit variance in the contribution of both agonist and antagonist MUs to muscle force thus making it less likely to have large V_{UCM} at the level of inter-muscle analysis. This may be the reason for smaller synergy indices in the (FDS + EDC) analysis in our study and lacking synergies in the cited earlier studies.

An earlier study of multi-digit synergies stabilizing various component of the resultant force and moment acting on a grasped handle (Gorniak et al., 2009) considered two levels of analysis: First, the task had to be shared between the thumb and the opposing "virtual finger" (an imagined digit with the mechanical action equal to that of the four fingers combined, Arbib et al., 1985). Second, the virtual finger action had to be shared across the four actual fingers. For some force and moment components, the study showed performance-stabilizing synergies at both levels, while other components were stabilized at the higher level only. We saw signs of a trade-off between the two levels with V_{ORT} values being typically larger in the analysis based on the MU-modes defined using MU sets combined across FDS and EDC as compared to similar within-muscle analyses (see Fig. 5). Nevertheless, the inequality $V_{UCM}>V_{ORT}$ was satisfied at both levels. Note that in the cited earlier studies of MU-mode-based synergies, the synergy indices were similar for the analysis in the spaces of FDS MU-modes and EDC MU-modes, both larger than the synergy indices in the space of (FDS + EDC) MU-modes. In our dataset, the synergy index for FDS was significantly larger than for both EDC and (FDS + EDC). Possibly, subtle differences between the experiments led to participants paying more or less attention to aspects of the task translating into different indices of F_{TOT} stability.

5.8.3 Possible neural mechanisms of force stabilization

There is sufficient evidence to associate two of the three levels of analysis with specific neurophysiological structure and loops. The third level, that of the mechanical variables *RC* and *k* reflecting the R- and C-commands, remains unclear with respect to specific neurophysiological circuitry.

The force-stabilizing synergies in the spaces of MU-modes are likely reflecting action of spinal circuitry including reflex loops. This conclusion has been based, in particular, on studies showing stabilization of unintentional, reflex-induced force changes in the spaces of MU-modes during multi-finger accurate force-production tasks ($V_{UCM} > V_{ORT}$, Madarshahian et al., 2022). Note that analysis of the same data in spaces of finger forces showed no stabilization of the total force (in a sense, $V_{UCM} \approx V_{ORT}$). In contrast, studies of force-stabilizing synergies during multi-finger tasks performed by the dominant and nondominant hands showed effects of hand dominance on the synergy indices in spaces of finger forces (larger synergy indices in the nondominant hand, Park et al., 2012; de Freitas et al., 2019) but not in the spaces of MU-modes (Madarshahian et al., 2022). Since effects of dominance have traditionally been associated with supraspinal effects (reviewed in Sainburg, 2005), these findings corroborate the hypothesis on supraspinal nature of multi-finger synergies and spinal nature of MU-mode-based synergies. We plan to continue the exploration of the hypothetical spinal origin of intra-muscle synergies by studying the tonic vibration reflex in healthy persons and both voluntary actions and reflexes in persons after mild spinal cord injury. Spinal circuitry has been invoked in the interpretation of synergic effects (Latash et al., 2005; Martin et al., 2009, 2019). In particular, effects of recurrent inhibition have been discussed as contributing to stabilization of the output of motoneuronal pools (Uchiyama et al., 2003; Hultborn et al., 2004). Our analysis of MU-mode-based synergies revealed stronger synergy indices in the spaces of MU-modes based on MUs identified within FDS as compared to those indices in the spaces of MU-modes defined using all the MUs combined over the two muscles (FDS + EDC). These effects are compatible with the idea of an inherent trade-off between synergies at different hierarchical levels (Gorniak et al., 2007, 2009) although earlier studies of MUbased synergies showed no such synergies for the (FDS + EDC) analysis (Madarshahian and Latash, 2022a; Madarshahian et al., 2022). The difference may be related to subtle differences between the earlier studies and the current one and task-specific effects of descending input into the pools of Ia-interneurons mediating reciprocal inhibition and, likely, contributing to the (FDS + EDC) synergies. As mentioned in Methods, one of the limitations of our analysis is that it does not distinguish between intermittent recruitment of motor units and modulation of their firing frequency. This makes it difficult to estimate the role of persistent inward currents (PICs) in the intramuscle synergies. PICs are induced, in particular, by synaptic inputs to α-motoneurons that use monoamines, such as serotonin and norepinephrine, as neurotransmitters. The importance of PICs for everyday motor tasks has been supported by a number of studies (Heckman et al., 2005, 2008). PICs tend to reduce the efficacy of other synaptic inputs into the neuron, including those from spinal circuitry assumed to contribute to intra-muscle synergies. Thus, strong PICs may be associated with weaker intra-muscle synergies. One of the common methods to estimate PICs is by quantifying the difference between the MU recruitment and derecruitment thresholds during slow force increase and decrease (Heckman et al., 2005). Hence, we plan to perform a study of the effects of PICs on intra-muscle synergies using slow ramp force production tasks. A number of clinical studies have provided evidence in favor of multi-effector (including multi-muscle and multi-finger) synergies based on supraspinal circuitry, in particular subcortical loops involving the basal ganglia and cerebellum (reviewed in Latash and Huang, 2015). The effects of cortical lesions are more ambiguous. Some studies of patients after mild-to-moderate cortical stroke reported no difference between synergy indices in the ipsilesional and contralesional upper extremities (Reisman and Scholz, 2003; Jo et al., 2016), while other studies reported smaller synergy indices in the contralesional limbs (Gera et al., 2016a,b).

As mentioned earlier, relations of the third level of analysis, that of the $\{RC;\ k\}$-based synergies, to neurophysiological substrate remain unknown. There is no relevant clinical data. Studies suggesting that the primary motor cortex encodes values of *RC* for the agonist and antagonist muscle groups (Raptis et al., 2010; Sangani et al., 2011) raise a possibility of cortical, likely pre-M1, site of $\{RC;\ k\}$-based synergies, but this possibility remains speculative. The presence of multiple neural levels contributing to the stability of a single salient performance variable may be seen as redundant and reflecting the functional importance of dynamical stability during actions in an unpredictable environment.

5.8.4 Experimental estimation of neural commands

Within the theory of control with spatial referent coordinates (*RC*), an action by an effector along a single coordinate can be seen as a consequence of setting values of *RC* for the agonist and antagonist muscles, which translate into the R- and C-commands (see Fig. 1 in the Introduction). Estimating RC experimentally in human studies has been a major methodological challenge. One of the reasons is that any natural human action involves groups of agonist and antagonist muscles, sometimes with mixed action, as, for example, the case for intrinsic hand muscles acting as flexors at the metacarpophalangeal joints and contributing to the extensor mechanism acting at more distal finger joints (Landsmeer and Long, 1965; Long, 1965).

A number of studies have used EMG techniques to define thresh- olds of muscle activation using relatively slow motion of the effector by an external force (Raptis et al., 2010; Mullick et al., 2013; Frenkel-Toledo et al., 2021). Note, however, that *RC* corresponds to the threshold of the first recruited MU across the agonists. EMG methods, however, sample signals from a limited subset of MUs in one muscle (or, rarely, a few muscles) only. Defining the moment of recruitment of the first MU with surface EMG methods is next to impossible, but identifying individual MU action potentials is also unreliable because, typically, only a small subset of the MU pool can be recorded (as in our experiment). Defining *RC* for the agonists and antagonists simultaneously, which is needed to estimate the R- and C-commands, is even more challenging.

Using mechanical methods of measuring force of a muscle or an effector as a function of coordinate (as in Feldman, 1966; Feldman and Orlovsky, 1972; Ambike et al., 2016a,b) potentially avoids this problem, because these methods reflect action of all the MUs and muscles contributing to the action. In human studies, however, these methods are based on a number of assumptions. First, they assume that linear approximation of the effector's force-coordinate behavior is adequate. To justify the assumption of linearity, we accepted only trials with correlation coefficient over 0.9 (as in earlier studies, Ambike et al., 2016a,b; Reschechtko and Latash, 2017). Second, we relied on participant's ability to follow the instruction "not to interfere voluntarily" with force changes induced by the inverse piano episodes. This assumption remains a weakness, but it has been used in many studies, and comparisons of behaviors under this instruction and an instruction "to react" suggest that the participants were indeed able "not to react" (Latash, 1994).

Third, these methods assume that changing the spatial range where both agonist and antagonist are active simultaneously leads to monotonic changes in the slope of the force-coordinate characteristic (k in our study). This assumption has been implicit or explicit in a number of earlier studies (Feldman, 1980, 1986; Ambike et al., 2016a,b) but it has not been confirmed experimentally. In other words, we accepted the intercept of the force-coordinate linear regression as a mechanical reflection of the R-command and the slope (k) as a mechanical reflection of the C-command. Note that we have never assumed that the central nervous system specifies the intercept and slope of the force- coordinate characteristic, only that, under steady force production in isometric conditions, these variables are adequate reflections of the control parameters such as RCs to the opposing muscles or, equivalently, the R- and C-command.

Overall, in our opinion, there seems to be no reliable method of estimating RC commands to the agonist and antagonist muscles applicable across tasks and conditions. All the described methods, so far, have been based on simplifying assumptions and incomplete data sets. Although the method used in our study suffers from a number of similar problems, we see it as a step in the right direction given the consistency of results across subjects, tasks, and studies (see also a recent study by De et al., 2024), including a study that used a similar method to estimate *RC* commands in a whole-body task (Nardon et al., 2022). We hope that a combination of this method based on mechanical variables and improved methods based on electrophysiological variables will soon provide a breakthrough in this important direction of research.

5.8.5 Methodological issues, limitations, and future directions

All the methods of synergy analysis used in this study are based on certain assumptions and include simplifications. The most commonly used method of inter-trial (inter-episode) variance analysis assumes that the individual finger forces do not covary in a task-independent way. This assumption is obviously wrong given the well-documented phenomenon of finger enslaving (Zatsiorsky et al., 2000). In a number of earlier studies, finger forces were transformed into another set of variables, finger modes (Latash et al., 2001; Scholz et al., 2002; see Danion et al., 2003), which assume that the enslaving-specific finger interactions are robust over time and across tasks. A number of recent studies have suggested, however, that enslaving is prone to drifts with time to higher values (Abolins et al., 2020; Abolins and Latash, 2021; Hirose et al., 2020). These results were the main reason we decided to use finger forces, not finger modes, in the analysis of synergies given the relatively long duration of trials in our study. Since enslaving involves positive finger force covariation, analysis of synergies in the finger force space with respect to total force is more conservative because F_{TOT}-stabilizing synergies require predominance of negative finger force covariation.

The analysis of MU-modes and synergies involves a number of steps that are far from 100% obvious. First, the identification of MUs is not perfect. We used the manufacturer's setting of 80% of accuracy, but, as mentioned earlier (Farina and Enoka, 2011), this setting does not guarantee that 80% of MUs are identified correctly. The application of a rather heavy filtering method (Hann filter at 1 s) is conditioned by the fact that the analysis needs at least two action potentials within each window from each MU to avoid gaps in the f_{MU} functions (these cannot be tolerated at future steps of analysis). Since some MUs fire at 4–5 Hz, using smaller filtering windows may become problematic; such manipulations were explored in an earlier study (Madarshahian et al., 2021). Linearization of the relationship between small changes in MU-mode and in F_{TOT} (defining the Jacobian) is another simplification- tion. Our VAF values in the linear regression, however, compare favor- ably with those reported earlier.

Another issue is using sets of MUs in FDS rather than flexor digitorum profundis (FDP), which is the prime mover for the task of force production at the fingertips. This is definitely a drawback, which we could not overcome because of the very weak EMG signal from FDP – a deep muscle. Being aware of this problem, we ran earlier a study of MUs, MU-modes, and synergies using the data from FDS when the subjects performed force-production tasks with the fingertips (as in the current study) and by pressing with the middle phalanges against loops connected to a specially constructed “suspension system” (Madarshahian and Latash, 2022b). Note that during force production by the middle phalanges, FDS was the prime mover (its distal tendons attach at the middle phalanges), while it played a supporting role during force production by the fingertips. All the main outcome variables, including the synergy index values, were similar during the two tasks, which allowed us to conclude that these indices in FDS during fingertip force production were reflective of force-stabilizing synergies. We also did not record EMG signals from the intrinsic hand muscles, which generate flexion action at the metacarpophalangeal joints and extensor action at more distal joints via the extensor mechanism. The problem of recording from only a subset of contributing muscles (and MUs) is inherent to all EMG-based studies. Consistency of results across studies, tasks, and subjects is the main reason we see the findings of the current study as reliable.

Finally, the analysis of $\{RC; k\}$-based synergies involves a number of non-trivial steps. Some of them were covered in the previous section. Here we want to add that, since the UCM was hyperbolic, it could not be linearized even locally, and we had to use different indices of synergy quantification, R^2 of the hyperbolic regression and an index based on the creation of surrogate, covariation-free data sets (cf. Müller and Sternad, 2003). It is unknown how these indices relate to the more traditional ΔV.

Overall, however, we view the current results as reliable given that all the methods had been used in a number of earlier studies, although never applied to the same dataset, and led to consistent findings across subjects and tasks (reviewed in Latash, 2008, 2019). Our main conclusion on the existence of three independent levels of control contributing to stability of performance and likely associated with different neural circuitry is worth further exploration, in particular in patients with dysfunction of some of the implied neural structures and circuits such as patients after stroke, those with Parkinson’s disease and cerebellar disorders, and those after spinal cord injury.

6 GENERAL CONCLUSION

A sedentary lifestyle has become one of the most widespread public health issues in contemporary society. The pathologies associated with it are numerous and range from musculoskeletal disorders such as low back pain (LBP) to neurological and psychological problems. These conditions, which can affect both the entire body and specific body districts, not only compromise the quality of life but also represent an increasing burden on global healthcare systems. Furthermore, many of these pathologies develop slowly and silently, only becoming evident when the damage is already extensive and difficult to reverse.

The aim of this thesis was to explore different forms of motor control analysis, not only at a global level such as for the entire body but also in smaller body areas such as the hand, seeking to understand how these mechanisms can be influenced by sedentary behavior and how, in turn, they may contribute to the onset of musculoskeletal pathologies. The approach was focused on testing innovative strategies for the early diagnosis of motor dysfunctions that could remain imperceptible for a long time, but, if untreated, may evolve into clinically evident disorders. Specifically, the research examined two distinct studies: one on motor control in the context of LBP and another on muscle synergies of the hand, with the goal of providing a clearer picture of how the human body reacts to motor perturbations and how these dysfunctions can be diagnosed and treated more effectively.

The results of the first study on subjects with LBP suggest that alterations in muscle activation patterns are not limited to acute pain moments but often manifest even in the absence of obvious symptoms, including during limited activities or simple postural tasks. This highlights how motor control can be compromised in a subclinical manner, that is, without immediate symptoms, yet creating an environment conducive to the onset of pain or other musculoskeletal issues in the long run. This aspect raises the need for a more timely and accurate diagnosis of motor dysfunctions, using advanced analytical tools that can reveal changes in activation patterns even in the absence of obvious symptoms.

The study of hand muscle synergies, on the other hand, emphasized the importance of understanding how specific body districts, such as the hand, can reflect more complex motor control mechanisms and how they can be monitored to develop targeted therapeutic and rehabilitative strategies. The hand is, in fact, one of the most complex and functional tools of the human body, whose proper management and muscle coordination are essential for performing a myriad of daily activities. Understanding how these motor patterns develop and how they can be altered in neurological or musculoskeletal pathologies opens new possibilities for early diagnosis and personalized treatment.

In general, the research suggests that motor control analysis, through advanced technologies and innovative approaches, could be a valuable tool for diagnosing and managing pathologies related to sedentary behavior. Further exploration of these methodologies, including functional tests, advanced metrics (such as R-index and C-index), and the use of real-time monitoring technologies, could provide a solid foundation for developing personalized rehabilitation interventions that more effectively address the individual needs of patients.

In the context of "silent" pathologies, which do not present immediate symptoms but are nonetheless related to latent motor dysfunctions, this approach could be crucial in preventing the onset of irreversible damage. Pathologies such as LBP, if not treated early, can evolve into chronic disorders, which not only compromise quality of life but also daily functional capacities.

This work represents a first, yet essential, attempt to connect two lines of research in the motor control domain that have traditionally been studied separately: the control of body posture and the control of hand dexterity. The integration of these domains within a shared theoretical and empirical framework aims to shed light on how the central nervous system organizes movement under biomechanical and environmental constraints, while maintaining stability through flexible and adaptive coordinative strategies.

At first glance, full-body postural control and fine manual regulation may seem to demand distinct methodological and conceptual approaches. However, one of the key insights that emerged from this thesis is that the separation between them is, to a large extent, artificial. Manual actions are never truly performed in isolation—they are always embedded within and supported by a constantly modulated postural background. Conversely, postural control is not merely a passive resistance to gravity, but an active, predictive, and goal-directed process often shaped by distal motor intentions.

By adopting a common theoretical lens—specifically, the Referent Coordinate (RC) framework and the Uncontrolled Manifold (UCM) hypothesis—it was possible to examine, across both studies, different manifestations of a shared underlying principle: structured motor variability aimed at stabilizing task-relevant variables. This approach allows the thesis to move beyond the traditional boundaries between motor subdomains, offering instead a reconceptualization of motor control as an integrated system.

Both studies employed indices derived from the referent model (R-index and C-index) to quantify the reciprocal and coactivation commands that underpin motor behavior. These indices provided a common language to analyze and compare motor strategies at different levels, from trunk postural control to fine force coordination among fingers. Notably, these metrics go beyond describing performance; they offer a window into the control parameters actively set by the nervous system. As such, they offer deeper insight into how motor adaptation occurs, particularly in clinical populations.

In the case of chronic low back pain (LBP), results suggest that even asymptomatic individuals may continue to rely on compensatory postural strategies, indicating long-term neural adaptations. This finding aligns with the idea that certain motor strategies, such as increased co-contraction, can become encoded in the motor system as protective responses, persisting even after the initial condition has resolved.

The implications of this are significant. In movement disorders such as Parkinson's disease or multiple sclerosis, increased co-contraction is typically viewed as a pathological sign. However, when similar patterns persist even in states of apparent recovery, as in asymptomatic LBP, they may represent residual defensive strategies, possibly shaped by prior pain experiences or emotional factors (e.g., anxiety, fear of recurrence). This perspective encourages a more nuanced clinical view, in which motor strategies are not merely symptoms but adaptive expressions of a system striving for stability under uncertainty.

This view invites future research to look beyond surface symptoms and investigate how motor commands are structured and retained over time. For instance, co-contraction may not always indicate dysfunction; it could reflect a learned stabilization strategy—one that may benefit from being modulated rather than eliminated.

Another compelling implication is that the same principles underlying trunk instability in LBP might also explain reduced manual dexterity in conditions like focal dystonia or age-related motor decline. This integrative approach opens several promising directions, including simultaneous measurement of posture and fine motor output.

From a methodological standpoint, this work illustrates how the same paradigms (e.g., the task of “releasing an object”) can be applied across different contexts and populations. Originally developed for healthy individuals, the self-triggered load release task has proven to be both simple and robust enough to assess anticipatory balance adjustments in older adults and clinical groups, such as patients with Parkinson’s disease.

Future studies could, for example, track whole-body posture and precise motor execution during real-world tasks (e.g., writing, object manipulation), to observe how proximal and distal strategies dynamically interact. Integration of referent-based indices with neurophysiological techniques (TMS, fMRI, EEG) could further clarify how the brain sets spatial goals and regulates muscle stiffness, and how these mechanisms evolve with learning, under the effect of a pathology, or an emotional state.

In the realm of rehabilitation, the observation that defensive motor strategies can persist post-recovery suggests that motor control cannot be fully understood without addressing cognitive and affective components. Incorporating measures of perceived pain, anxiety, or emotional regulation could lead to a more comprehensive understanding of motor adaptation.

The RC/UCM framework may offer valuable tools for developing individualized rehabilitation protocols aimed not just at restoring strength or range of motion, but at helping patients re-learn functional referent coordinates through active movement exploration.

7 LIMITATION

Both studies present limitations of different kinds. The first study presents both methodological and structural limitations. Although the sample might appear sufficiently large at first glance, a group of 15 participants with low back pain (LBP) may not be adequate, especially considering the heterogeneous and multifactorial nature of the condition. In fact, the experimental group included individuals with clinical diagnoses, but the location of the pathology varied (left, right, or unspecified), and the level of post-rehabilitation recovery was not fully homogeneous.

The non-flexible co-contraction strategy observed in the LBP group has been interpreted as potentially maladaptive; however, it could be either functional or dysfunctional. Longitudinal studies are needed to clarify this issue. Furthermore, the exclusive use of the C and R indices as proxies for central motor control reduces the complexity of postural regulation to just two variables. Dynamic synergies and the role of sensorimotor feedback—visual, vestibular, and proprioceptive—are not addressed. The approach considers muscles in antagonistic pairs and sums the indices, which results in a loss of information about specific muscle patterns and the underlying functional synergies.

The asymmetric effects observed (e.g., higher C-index values during rightward trunk rotation) are speculative; they may result from individual motor habits or slight misalignments in the experimental setup—a possibility acknowledged, but not definitively ruled out, by the authors. A potentially valuable mitigation strategy would have been to include an assessment of functional laterality.

The second study also presents several limitations, many of which are explicitly acknowledged by the authors. First, the Delsys system used to extract motor unit action potentials is frequently subject to criticism. In my personal view, it operates as a kind of "black box", offering little control over parameters or constraints during the extraction process. Moreover, the decomposition algorithm identifies motor unit action potentials only within individual trials, making it impossible to track or compare the same motor units across trials. In practice, the system requires several hours per trial, depending on the number of motor unit firings identified, significantly slowing down the overall data acquisition process.

Although the muscles selected for EMG recording are relatively easy to locate by palpation, many are fusiform in shape and become deeply situated in certain regions. Additionally, the position and nature of the task predominantly engaged the finger flexor muscles over their antagonists. For all these reasons, EMG signal acquisition was challenging and often insufficient for reliable motor unit decomposition. Consequently, the study design included only one (best-quality) trial per limb per participant, further limiting the data pool.

Due to these technical constraints and the resulting modest dataset, increasing the number of participants would likely have helped reduce variability in the results. These represent the primary instrumental and design-related limitations of the study.

A further conceptual limitation lies in the assumption regarding the neural origin of the RC and k signals. The variables referent coordinates (RC) and apparent stiffness (k) are treated as mechanical proxies for neural commands (R- and C-commands), but their true neurophysiological origin remains uncertain.

8 FUTURE DIRECTIONS

The study conducted on subjects with LBP has suggested the need to create protocols and large-scale studies that integrate multiple elements and aspects of the human body, also considering more complex dynamic and functional conditions, such as daily activities that require trunk movements on multiple planes (e.g., combined torsions with flexion or extension). Advanced technologies today, although increasingly precise, often focus on a single aspect. For this reason, it is essential to integrate these technologies and analyze the results as a whole, rather than just sectorally.

Another important aspect that emerged concerns the role of kinesiophobia (fear of movement) and its impact on muscle activation patterns. Although it is commonly analyzed through questionnaires and psychophysical metrics, more precise quantification of movement fear could contribute to the development of more efficient rehabilitation tools and re-education techniques.

Metrics such as the R-index and C-index, used in conditions like Parkinson's disease, have not yet been extended to many other conditions, such as cruciate ligament injuries or multiple sclerosis. The goal would be to verify their applicability in broader clinical contexts, including diverse populations in terms of age, gender, and physical activity levels.

On the other hand, the study of hand-muscle synergies highlighted several interesting aspects. The hand is one of the most important peripheral tools for humans, containing a complex network of muscles. The control of the hand, although often unconsciously perceived, is even more complex than one might think. Its complexity can provide clues about the functioning of various parts of the Central Nervous System, which remains, in some respects, a "black box."

An interesting development would be to extend this analysis to neurological conditions such as stroke or Parkinson's disease, to examine the muscle synergies of the fingers and develop targeted rehabilitation interventions. The use of advanced functional imaging techniques, such as functional magnetic resonance imaging (fMRI) and transcranial magnetic stimulation (TMS), to map the neuroplastic changes induced by rehabilitation, along with simple tasks like force production with different fingers simultaneously, could lead to significant discoveries.

In the more distant future, the development of real-time biofeedback tools and systems based on advanced postural metrics for monitoring and correcting motor control during daily activities and physical exercise could represent a true revolution in the field of physical rehabilitation. These devices, integrating continuous monitoring technologies and personalization, would allow for timely and targeted interventions, optimizing rehabilitation pathways and promoting faster and more lasting recovery. Furthermore, these innovations could extend to other fields, such as the creation and enhancement of robots and robotic limbs, which could be controlled directly by the user, opening the door to new developments in assistive robotics and advanced prosthetics, for greater autonomy and quality of life.

During my doctoral studies, I had the opportunity to grow significantly, both in practical and theoretical terms. At the beginning of the program, my background was primarily theoretical, focusing on human physiology and motor control. Over time, however, I began to develop increasingly technical and computational skills, also driven by my personal interest in technology and DIY projects.

The first project I worked on was related to low back pain. To develop it, I began programming with Arduino, building the magnetic activation system required for the experimental setup. Later, to automate and randomize the trials, I learned how to use MATLAB. This phase of the work was particularly exciting for me and strongly motivated me to further deepen my programming and data analysis skills.

My manual dexterity—the ability to work with tools, assemble structures, and handle screws and bolts—proved to be a constant and valuable asset throughout the project and allowed me to build the entire experimental apparatus myself.

When I traveled to the United States to continue my work, I applied my MATLAB skills to data analysis. However, to collaborate more effectively with colleagues who were using Python and LabVIEW (the interface used for controlling the inverse platform), I also began learning those tools. This enabled me to make a more comprehensive contribution to the project.

In summary, my involvement in the publications included in this thesis has been multifaceted: from the design and construction of the experimental setups to data collection and analysis, and finally to the writing of the scientific articles.

Looking back, I can now recognize both my strengths and the areas in which I can continue to improve. My enthusiasm for technology and hands-on experimentation has been a major advantage, although I have also come to realize that scientific writing requires more time and focus from me than I expected. Nevertheless, I am deeply satisfied with the progress I have made, and most importantly, with the sense of self-awareness and maturity I have gained.

All of these experiences have naturally led me to my current role at the University of Verona, in the Department of Neurosciences, Biomedicine, and Movement Sciences, where I am responsible for the technical management of research laboratories, the development of experimental setups, and data analysis for various research groups. It is a position that fully reflects and leverages the skills and passions I cultivated throughout my doctoral journey.

9 LIST OF TABLES

10 LIST OF FIGURES

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